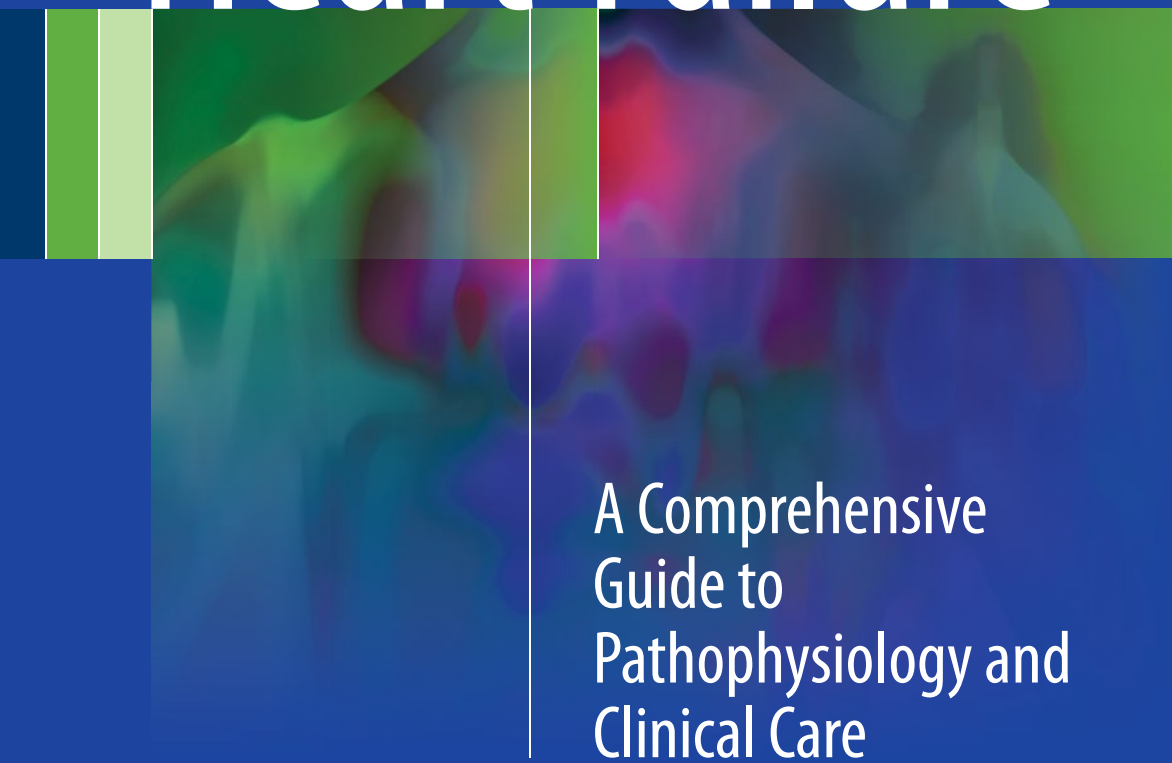
Howard Eisen
Editor

Heart Failure



A Comprehensive Guide to Pathophysiology and Clinical Care

Springer

Heart Failure

Howard Eisen
Editor

Heart Failure

A Comprehensive Guide to Pathophysiology and Clinical Care

Springer

Editor
Howard Eisen
Division of Cardiology
Drexel University College of Medicine
Philadelphia
PA
USA

ISBN 978-1-4471-4218-8 ISBN 978-1-4471-4219-5 (eBook)
DOI 10.1007/978-1-4471-4219-5

Library of Congress Control Number: 2017931583

Printed on acid-free paper

This Springer imprint is published by Springer Nature
The registered company is Springer-Verlag London Ltd.
The registered company address is: 236 Gray's Inn Road, London WC1X 8HB, United Kingdom

Preface

Heart failure has become the leading cause of morbidity, mortality, and hospitalization in the developed world. Much of this is due to the success in prolonging survival in patients with other cardiovascular diseases, such as myocardial infarctions and valvular heart disease. The number of patients with heart failure will almost double in the next 20 years. The understanding of the pathophysiology of heart failure has improved significantly in the past few decades, and this has translated into dramatic improvements in pharmacologic and device therapies that have significantly improved patient outcomes including survival and the quality of life.

Even for patients with the most advanced stages of heart failure, there are now options such as improvements in cardiac transplantation which allow prolonged survival and alternatives to cardiac transplantation in patients who are not candidates for this therapy, which include mechanical circulatory support with a rapidly growing number of new, smaller, more reliable devices and a growing number of patients receiving this therapy.

The goal of this book is to provide an understanding of the etiologies and pathophysiology of heart failure and to provide a context for understanding clinical therapies available for this disease. The use of this book is to provide scientific and clinical background for trainees in cardiovascular disease as well as physicians involved in caring for these patients. As the field continues to evolve, there will be updates to this book to reflect these advancements.

June 7, 2016

Philadelphia, PA, USA — Howard J. Eisen, MD

Acknowledgments

The Editor would like to thank his wife, Dr. Judy Wolf and children, Dr. Jonathan Eisen and Miriam (Mimi) Eisen for their love and support and his colleagues among the faculty and nursing staff and the Cardiology Fellows in the Division of Cardiology at the Drexel University College of Medicine for their support and selfless dedication to providing superlative patient care to the sickest patients. He would also like to thank the authors for their hard work, dedication, and scholarly accomplishments.

Contents

Chapter 1
Molecular Changes in Heart Failure

Raymond C. Givens and P. Christian Schulze

Abbreviations

AKAP	A-kinase anchoring protein
ANF	Atrial natriuretic factor
AT	Angiotensin
βMHC	β-myosin heavy chain
BAD	Bcl-2-antagonist of cell death
BNP	Brain-type natriuretic peptide
cGMP	Cyclic guanine monophosphate
CHF	Congestive heart failure
CRP	C-reactive protein
DAG	Diacylglycerol
DISC	Death-induced signaling complex
ECM	Extracellular matrix
ERAD	Endoplasmic reticulum-associated degradation
ERK	Extracellular-signal-related kinase

R.C. Givens, MD, PhD
Division of Cardiology, Department of Medicine, Columbia University Medical Center, New York, NY, USA
e-mail: rg2751@cumc.columbia.edu

P.C. Schulze, MD, PhD (✉)
Division of Cardiology, Department of Medicine, Columbia University Medical Center, New York, NY, USA

Center for Advanced Cardiac Care, Columbia University Medical Center, Division of Cardiology, 622 West 168th Street, PH 10, Room 203, New York, NY 10032, USA

Geier Clinical Research Center, Center for Advanced Cardiac Care, Division of Cardiology, Columbia University Medical Center, 622 West 168th Street, PH 10, Room 203, New York, NY 10032, USA
e-mail: pcs2121@cumc.columbia.edu

H. Eisen (ed.), *Heart Failure*, DOI 10.1007/978-1-4471-4219-5_1

FAK	Focal adhesion kinase
Gab	Grb2-associated binder
GSK3β	Glycogen synthase kinase 3β
HSP	Heat shock protein
ILK	Integrin-linked kinase
IP_3	Inositol triphosphate
LCAD	Long-chain acyl-CoA dehydrogenase
LTCC	L-type calcium channel
LVAD	Left ventricular assist device
MAPK	Mitogen-activated protein kinases
MCAD	Medium-chain acyl-CoA dehydrogenase
miR	Micro-RNA
MI	Myocardial infarction
MLP	Muscle LIM protein
MMP	Matrix metalloproteinase
mTOR	Molecular target of rapamycin
NF-κB	Nuclear factor kappa-light-chain-enhancer of activated B cells
NFAT	Nuclear factor of activated T cells
NOS	Nitric oxide synthase
NOX	NADPH oxidase
PI3K	Phosphoinositide-3-kinase
PKA	Protein kinase A
PKC	Protein kinase C
PPAR	Peroxisome proliferator-activated receptor
RyR2	Ryanodine receptor type 2
SAC	Stretch-activated ion channel
SERCA	Sarcoplasmic reticulum Ca^{2+} ATPase
SOC	Store-operated Ca^{2+} channel
TAC	Transaortic constriction
TGF-β	Tissue growth factor beta
TIMP	Tissue inhibitor of metalloproteinase
TNF-α	Tumor necrosis factor alpha
TnI	Troponin I
TnT	Troponin T
TRP	Transient receptor potential

Introduction

Over the past three centuries, medical understanding of heart failure has evolved from a simple appreciation of biomechanical and circulatory changes accompanying heart failure to recognition of the complex multiorgan physiology of this syndrome. Within the past few decades, breakthroughs in genetics and molecular

investigation have revealed a vast array of cellular and molecular changes that occur in the heart and systemically as a result of hemodynamic insult. The picture of changes occurring in cardiac hypertrophy and heart failure has become increasingly complex. The goal of this chapter is to summarize the cellular and molecular changes that occur in clinical and experimental heart failure and to highlight established and potential therapeutic targets.

Compensatory Mechanisms

A large variety of myocardial insults can lead to heart failure. In the U.S., atherosclerotic coronary artery disease resulting in myocardial infarction and chronic ischemia as well as chronic arterial hypertension appear to account for the greatest population-level risk [1, 2]. There is also a rising contribution from diabetes and its associated end-organ manifestations including coronary artery disease. In contrast, infectious and valvular heart disease have declined in their impact on heart failure incidence [3].

Regardless of the nature of the initial insult, there appear to be common pathologic responses to cardiac pressure or volume overload. A hallmark finding in the stressed myocardium is hypertrophy of viable cardiomyocytes [4, 5]. The law of LaPlace indicates that the development of cardiac wall thickening due to myocyte hypertrophy is initially protective in that it serves to normalize transmural stress [6, 7]. However, persistent hypertrophy and sustained activation of the molecular pathways responsible for the initial hypertrophic response become physiologically deleterious over time [8].

More than a century of work has clarified that striated muscles such as the myocardium and skeletal muscles respond to an increased workload, e.g. hypertension, by becoming hypertrophic [9–11]. Cardiomyocytes are classically considered to be post-mitotic and, thus, cardiac hypertrophy is thought to result solely from an increase in size of existing cells. The degree to which cardiomyocyte generation from progenitor cells contributes is unclear [12]. The proliferation of non-myocyte cell types such as fibroblasts, smooth muscle cells, mesenchymal cells and the endothelium, however, may contribute significantly to the negative consequences of pathologic hypertrophy, such as myocardial and perivascular fibrosis [13, 14].

The phrase “cardiac remodeling” was originally used to describe gross structural and functional cardiac changes occurring in response to myocardial infarction but has more recently come to describe an expanding list of molecular, cellular, matricellular, metabolic, and electrical alterations resulting from sustained stress [15]. Transaortic constriction (TAC) to produce pressure overload among mice yields significant increases in myocardial thickness and relative cardiac size as early as 2 days later, and increased myocyte size and fibrosis and decreased ejection fraction by as early as 1 week [16, 17]. A pig TAC model reveals increased sarcoplasmic reticulum (SR) Ca^{2+} ATPase (SERCA) expression and activity and increased SR Ca^{2+} uptake within 6 h of TAC [18]. Treatment of rats with the nonselective

β-adrenergic receptor agonist isoproterenol increased expression of the "fetal genes" c-fos and jun-B within 1 h and provoked cardiac hypertrophy by 24 h [19]. The β-adrenergic receptor blocker propranolol prevented early increases in c-fos expression. Analysis of myocardial tissue from this model by electron microscopy revealed mitochondrial swelling and disruption, intra- and extracellular edema, and fibroblast invasion by 96 h.

Persistence of stress upon the myocardium leads to progression of cardiac remodeling associated with the initial hypertrophic responses towards a maladaptive phenotype of systolic dysfunction and cardiac dilation [15]. Neurohormones of the adrenergic and renin-angiotensin-aldosterone systems provide additional cardiac stimuli that are also initially compensatory but with time contribute to adverse cardiac remodeling and multiorgan physiologic derangement. Further progressive cardiac insufficiency results in multiorgan dysfunction and death in the absence of successful intervention.

Cardiomyocyte Changes

The cardiac response to physiologic stress entails complex remodeling of cardiomyocytes and the extracellular matrix. Cardiomyocyte hypertrophy is one of the most appreciable changes in strained and failing myocardium at a microscopic level. However, sustained activation of pro-hypertrophic pathways causes cardiac dysfunction.

The pressure or volume overload caused by a physiologic insult deforms the cardiac microarchitecture. One method by which changes in extracellular mechanical forces are conveyed to the nucleus is through stretch-activated ion channels (SACs). Alterations in mechanical plasma membrane tension are sufficient to activate SACs, which are represented in mammals by transient receptor potential channels (TRPs) that are expressed in cardiomyocytes, vascular smooth muscle cells, and endothelial cells [20, 21]. A representative member, TRPC6, is located on the t-tubule membrane and is triggered to allow the influx of calcium through mechanical stretch and through association with stretch-sensitive receptors [22, 23]. TRPC6 is also activated by diacylglycerol (DAG) independent of protein kinase C (PKC) activity, and by angiotensin II receptor type 1 (AT1R) independent of angiotensin II (AT-II) [24–26]. The SAC-mediated increase in cytoplasmic Ca^{2+} entry activates the protein phosphatase calcineurin A, which can then dephosphorylate nuclear factor of activated T cells (NFAT), allowing it to enter the nucleus and induce expression of pro-hypertrophic genes, discussed below [27, 28]. The promoters of TRPC 1, 3, and 6 display NFAT consensus binding sites and TRPC isoform expression is increased in hypertrophic animal models and failing human hearts [29].

Cellular deformation is also communicated to the nucleus through the integrin family of cell surface receptors that link cytoskeletal and contractile machinery to the extracellular matrix (ECM) through their association with focal adhesion complexes and complex multimolecular structures known as a costameres. The proteins

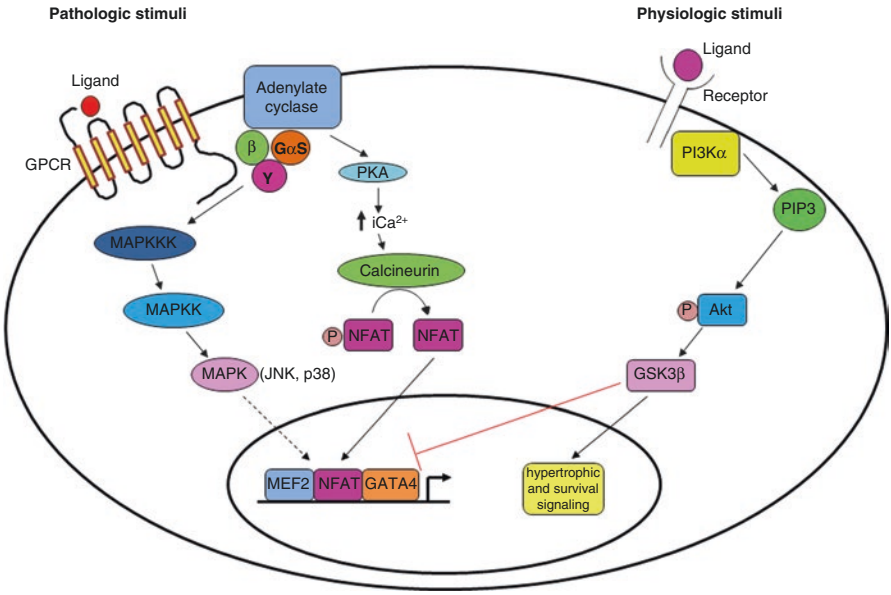


Fig. 1.1 Physiologic and pathologic hypertrophic signaling

that form the costameric complex are localized to Z-discs, which form the lateral boundaries of the sarcomere, the basic contractile unit of the cardiomyocyte [30–32]. Costameres and focal adhesion complexes are linked to multiple hypertrophic signaling pathways [33, 34]. Integrins themselves bind to a large variety of extracellular ligands such as laminin, collagen, and fibronectin [35–37]. Stretch activation of integrin-associated cytoplasmic focal adhesion kinase (FAK) and integrin-linked kinase (ILK) triggers activation of phosphoinositide-3-kinase (PI3K), resulting in downstream activation of Akt and the mitogen-activated protein kinase (MAPK) cascade [38, 39]. Grb2-associated binder (Gab) proteins participate in signaling through Ras, which also triggers MAPK activation and contributes to cardiomyocyte hypertrophy [40] (Fig. 1.1).

Mechanical stretch also activates G-protein-coupled plasma membrane receptors such as AT1R and endothelin A (ETA) in cardiomyocytes and vascular smooth muscle cells, leading to indirect activation of TRP channel opening [24, 41]. Stretching of ventricular cardiomyocytes or treatment with AT-II activates AT1R, inducing activation of extracellular signal-related kinases (ERKs) and Gαq isoforms. Pressure overload in an animal model causes AT1R–dependent cardiac hypertrophy, again even in the absence of AT-II [24]. Gαq proteins activate phospholipase C, leading to an increase in cytosolic inositol triphosphate (IP_3) and DAG [42]. IP_3 activates TRP 3, 6, and 7, and also triggers an IP_3 receptor on the endoplasmic reticulum (ER), leading to Ca^{2+} release from the ER [43]. This Ca^{2+} store depletion activates plasma membrane store-operated Ca^{2+} channels (SOCs), increasing Ca^{2+} influx from extracellular sources [44] (Fig. 1.2).

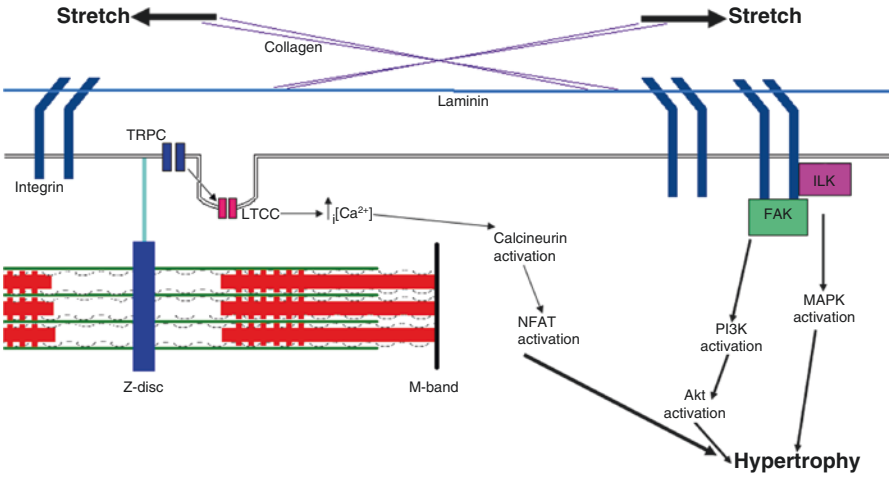


Fig. 1.2 Cardiac mechanotransduction

Increased cytosolic concentrations of Ca^{2+} and DAG activate protein kinase C (PKC) isoforms whose signaling increases expression of early stress-response genes, such as c-fos, c-jun, jun-B, c-myc, egr-1, and heat shock protein (HSP) 70 [45]. Nkx2.5 and GATA-4, also activated by PKC signaling, may participate in PKC down-regulating expression of the sarcoplasmic reticulum (SR) Ca^{2+} ATPase (SERCA), which is responsible for rapid reuptake of Ca^{2+} into the SR [46, 47]. SERCA downregulation explains much of the calcium signaling abnormalities seen in heart failure and has emerged as a potential therapeutic target [48, 49]. Changes in calcium handling associated with cardiac hypertrophy are directly involved in the cell death that characterizes the transition to systolic dysfunction and clinical heart failure [50] (Fig. 1.3).

In experimental models and in limited human data, treatment with the calcineurin inhibitors cyclosporine A or FK506 opposes the hypertrophic phenotype [51–54]. Increased cytosolic and mitochondrial Ca^{2+} concentrations provoke apoptosis [55, 56]. Calcineurin may link hypertrophy to apoptosis by dephosphorylating the pro-apoptotic protein Bcl-2-antagonist of cell death (BAD), promoting its association with Bcl-xl [57].

The actions of GATA-4 and NFAT are opposed by glycogen synthase kinase 3β (GSK3β), which inactivates these proteins through phosphorylation [58]. GSK3β is itself controlled by Akt and PKA, both of which repress GSK3β activity through phosphorylation [59, 60]. Active GSK3β is known to be a negative regulator of hypertrophy [61].

Mechanical stress upon the intact heart activates MAP kinases p38 and ERK 1/2, resulting in phosphorylation of the zinc-finger transcription factor GATA-4. As a result of phosphorylation at serine 105, GATA-4 is activated, thereby allowing its binding to DNA targets such as the BNP promoter [62–64].

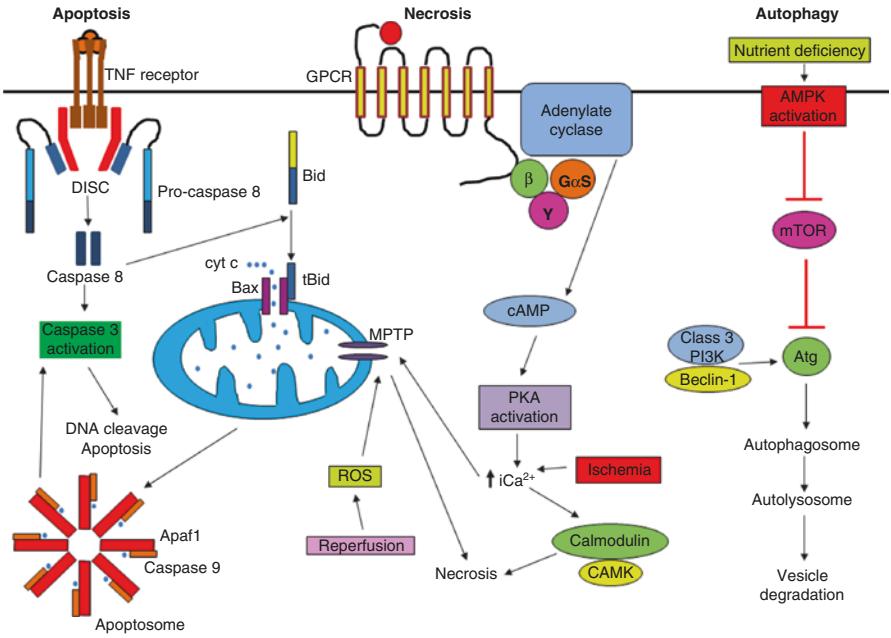


Fig. 1.3 Pathways of cellular death in heart failure

AT1R is induced by pressure overload, and the resulting increase in signaling is prohypertrophic in ways that are dependent and independent of AT-II [24]. AT1R signaling activates TRPC channels, resulting in prohypertrophic signals and derangements in calcium handling [43]. AT-II induces expression of TGF-β1 in cardiac fibroblasts, leading to increased collagen production and fibrosis [65, 66].

At a gross level, cardiac hypertrophy strongly predicts the development of clinical heart failure [67]. The pathologic hypertrophy of pressure or volume overload differs molecularly in important ways from the physiologic hypertrophy that occurs in response to exercise training or pregnancy. Re-expression of the fetal gene program appears to be absent in physiologic hypertrophy [68]. Both physiologic hypertrophy and normal cardiac growth are mediated by insulin-like growth factor 1 (IGF-1), which induces hypertrophy through an Akt pathway. Unlike pathologic hypertrophy mediators, IGF-1 activity is anti-apoptotic and IGF-1 administration in a rat model of ischemic cardiac failure leads to a preservation of systolic function and has beneficial effects on adverse cardiac remodeling [69]. Sustained experimental activation of IGF-1 pathways can, however, eventually cause a transition from physiologic hypertrophy to a more classically pathologic phenotype (Table 1.1).

While most cardiac mass is represented by the cardiomyocytes, several other cell types and extracellular structures are important in the control of cardiac function and demonstrate significant alterations in heart failure. Cardiac mast

Table 1.1 Cellular and molecular changes in physiologic hypertrophy and heart failure

	Normal	Physiologic stimuli	Heart failure
Molecular changes			
"Fetal gene program"	–	–	Increased
Myosin heavy chain isoform	α-MHC	α-MHC	β-MHC
Biomarkers			
BNP	–	Unclear	Elevated
Troponin	Normal	Unknown	May be increased
Cytokine activation	Normal	Normal	Increased TNF-α, IL-6
Catecholamine levels	Normal	Normal	Increased
Cellular changes			
Cell size	Normal	Hypertrophied	Hypertrophied
Fibrosis	Normal	Normal	Increased
Cell death	Normal	Normal	Increased
Capillary density	Normal	Preserved	Decreased
Calcium cycling	Normal	Normal	Increased
Metabolism	Predominately fatty acid oxidation	Predominately fatty acid oxidation	Predominately glucose oxidation
Contractile function	Normal	Normal	Decreased
Excitation-contraction coupling	Normal	Normal	Altered

cells, fibroblasts, conductive tissue, endothelial cell, vascular smooth cells, cardiac progenitor, and resident macrophages contribute cardiac mass and biology. Fibroblasts outnumber cardiomyocytes roughly threefold in the intact heart, multiply in response to mechanical stretch, and contribute to extracellular remodeling.

Diastolic stretch activates NADPH oxidase 2 (NOX2), leading to the production of reactive oxygen species (ROS). ROS may then increase Ca2+ release from sarcoplasmic reticulum by sensitizing ryanodine receptor type 2 channels (RyR2) [70]. NOX2 activity may be critical to induction of cardiomyocyte apoptosis by hypertrophic stimuli such as AngII, as NOX2 inhibition or deletion of the NOX2 cofactor $p47^{phox}$ interferes with AngII-induced apoptosis [71].

Myocyte hypertrophy is generally characterized by the reactivation of a number of genes that are normally expressed during fetal development but eventually become quiescent after birth [72]. This "fetal gene program" includes increased expression of GATA-4, Nkx2.5, and PTX transcription factors, is typical of cell cycle entry. These transcription factors drive the expression of classic fetal genes that are markers and essential mediators of cardiomyocyte hypertrophy, including atrial natriuretic (ANF), brain-type natriuretic peptide (BNP), α-skeletal actin, β-myosin heavy chain (βMHC), and angiotensin-II receptor type 1 (AT1R) [73, 74].

Myocardium-Vascular Mismatch

It has been observed that as cardiac hypertrophy progresses, there is relatively lower concomitant vascularization, such that the number of capillaries per area of myocardium declines [75]. Microvascular dysfunction and decreased coronary flow reserve are observed in experimental and clinic hypertrophy and heart failure even in the absence of coronary atherosclerosis [76, 77]. These changes have been linked to subendocardial ischemia in hypertrophy and may accelerate the transition to heart failure. Treatment of a rabbit TAC model with vascular endothelial growth factor (VEGF) induces MMP-2-dependent angiogenesis, delays the onset of LV dilation, and preserves LV contractility [78].

Fibroblast Proliferation and Fibrosis

The majority of cardiac cellular components are represented by cardiomyocytes, endothelial cells, vascular smooth muscle cells, and fibroblasts. But while cardiomyocytes are the necessary cells for cardiac contraction, they comprise only a third of cardiac cells. The remainder of cardiac mass is mostly comprised of fibroblasts, which are responsible for the production of the extracellular matrix (ECM) that functions as the cardiac mechanical scaffold. Additionally, ECM components contribute to the regulation of cellular growth, tissue differentiation, and angiogenesis. Cardiac fibrosis, which is characterized by the increased extracellular presence of collagens and other ECM components, is a hallmark of advanced hypertrophy and heart failure [79].

Fibroblasts can be activated by increased interstitial fluid flow to produce collagen type III and TGF-β, effects that may be opposed by blockade of the AT1 and TGF-β receptors [80]. Experimental hypertrophic stimuli such as infusion of AngII increase fibroblast production of IL-6, which leads to collagen I production from fibroblasts and may contribute to cardiomyocyte hypertrophy through paracrine signaling [81–84].

Excitation-Contraction Coupling

Cardiac contraction results from Ca^{2+}–dependent interactions of myosin and actin myofilaments. During cell membrane depolarization, Ca^{2+} enters the cardiomyocyte through L-type Ca^{2+} channels (LTCCs) located at transverse tubules, which are in proximity to the sarcoplasmic reticulum (SR) [85]. Ca^{2+} influx triggers a larger release of Ca^{2+} from the SR through ryanodine receptors (RyR2). The SR Ca^{2+}–ATPase (SERCA2A) is responsible for restoring Ca^{2+} to the SR [48]. The

disappearance of SERCA2A during the progression of hypertrophy and heart failure alters the coupling of Ca^{2+} flux to the cardiomyocyte contractile apparatus [86]. In failing human hearts, there is a significant reduction in t-tubule-SR junctional dyads and thus in the co-localization of LTCCs and RyR2, indicating a degree of both physical and biochemical uncoupling of excitation from contraction [87, 88].

Sarcolemmal Proteins

Sufficient myocyte contractile force is dependent upon appropriate excitation-contraction coupling, which requires precise coordination between the entry of extracellular Ca^{2+} into the cytoplasm and the wave of Ca^{2+} release from the sarcoplasmic reticulum (SR) [89]. Transverse tubules (t-tubules) are invaginations of the surface membrane, continuous with the extracellular space, that extend into the interior of cardiac myocytes [36, 90]. T-tubules form a highly organized network that is physically coupled to the SR at Z-discs [91]. This organization is essential for coordination of excitation-contraction coupling. LTCCs are predominately localized to t-tubules and are responsible for the initial cellular Ca^{2+} influx. Ca^{2+} efflux is largely handled by the sodium-calcium exchanger (NCX), found on both tubular and non-tubular sarcolemmal [92]. The relative importance of Ca^{2+} efflux through these different domains is unclear. A population of β adrenergic receptors is localized to t-tubules, where they appear to modulate LTCC function and localize cAMP signaling [93]. In rodent heart failure models, this localization is lost, with β2 receptors redistributing from t-tubules to the cell crest, leading to diffusion of cAMP signaling [94].

Hypertrophied and failing hearts demonstrate misshapen and dilated t-tubules and tubular disorganization and disappearance, which has been called t-tubule remodeling [87]. The degree of tubular remodeling is associated with the severity of heart failure [95]. As L-type calcium channels are primarily localized to T-tubules, there is also a decline in inward calcium currents in failing myocytes [96]. In a rodent model, T-tubule disruption can be reversed after mechanical unloading with heterotopic abdominal heart transplantation [97].

Myocardial Metabolism in Heart Failure

Myocardial metabolism depends to large parts (>70 % at baseline) on the utilization of fatty acids for oxidative metabolism and ATP generation. The complete oxidation of one molecule of palmitic acid as an example for the most prevalent circulating and nutritionally derived saturated fatty acid generates 129 ATP molecules. In contrast, complete oxidation of glucose results in generation of 36 ATP molecules. Therefore, oxidation of fatty acids is a more energy efficient process compared to the oxidation of glucose (Fig. 1.4).

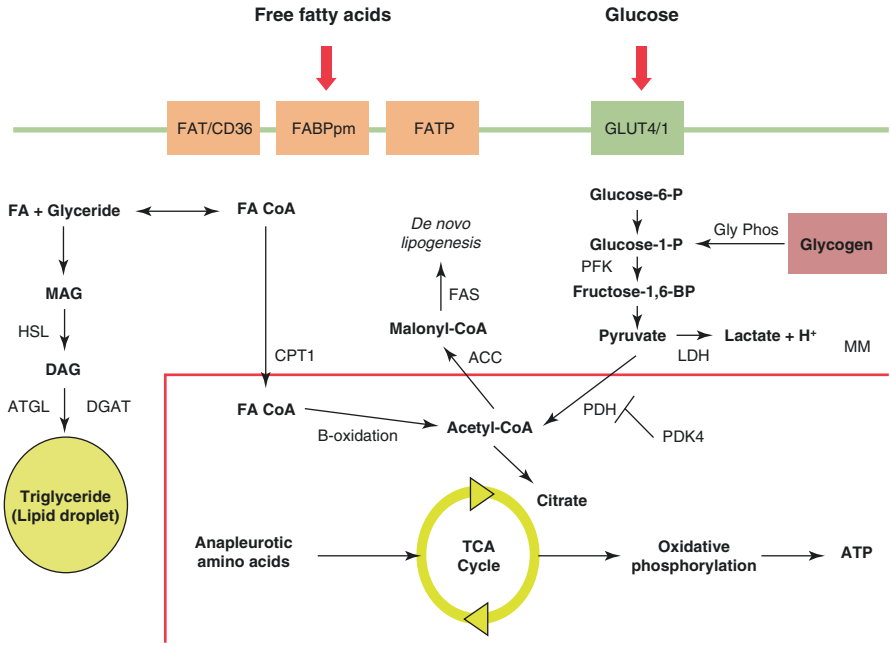


Fig. 1.4 Cardiac metabolism

The reversion to the fetal gene expression in cardiac hypertrophy and heart failure encompasses not only structural and contractile genes but also metabolic substrate utilization. During fetal development, cardiac metabolism depends primarily upon glycolysis, but the heart transitions toward fatty acid oxidation in the postnatal period [98]. While lipid metabolism may increase early in experimental hypertrophy, expression levels of fatty acid oxidation enzymes are decreased in the failing heart [99, 100]. An important determinant of fatty acid utilization and metabolism is the activity of PPARα, which targets binding sites in the promoters for the genes encoding carnitine palmitoyl transferase-I (CPT-I) and long-chain and medium-chain acyl-COA dehydrogenases (LCAD and MCAD) and activates their transcription [101]. In the hypertrophied heart, the relative shift from fatty acid to glucose utilization occurs in concert with decreased PPARα activity and expression [102]. Of note, further changes in myocardial gene expression result in a preferential generation of ATP through anaerobic metabolism, namely glycolytic breakdown of glucose to pyruvate and lactase. This is best known for myocardial metabolism in circumstances of ischemia and has been shown to produce only 8 molecules of ATP during glycolysis resulting in a severe energy (ATP)-depleted state of the failing myocardium. Reversibility of cardiac metabolism after cardiac recompensation requires up to 5 days until ATP stores reach levels known from stable heart failure patients.

Part of the repression of PPARα activity in cardiac hypertrophy may be explained by sequestration of this nuclear transcription factor in the cytoplasm by the MAP

kinase kinase MEK1 [103]. The repression of PPARα expression and activity may be involved in the progression of pathological hypertrophy. Administration of PPARα ligands such as conjugated linoleic acid opposes cardiac hypertrophy in spontaneously hypertensive rat strain [104].

Ectopic accumulation of lipids in non-adipose tissues leads to lipotoxicity. In animal models and in human heart failure patients, fatty acid utilization declines and cardiac metabolism shifts back toward the fetal phenotype of glucose dependence [99, 105]. Recent work has demonstrated the myocardial accumulation of toxic lipid intermediates such as ceramide and diacylglycerol in the failing myocardium with depletion of stores of neutral lipids including triglycerides and fatty acids. Mechanical support with a left ventricular assist device (LVAD) may reverse some of the cardiac and systemic metabolic abnormalities observed in heart failure [106].

Myocardial Inflammation in Heart Failure

The progression of cardiac hypertrophy and heart failure are linked to inflammation in several ways. Elevated serum levels of TNF-α and IL-6 are seen among heart failure patients and correlate with NYHA heart failure class, the degree of cardiac cachexia, and overall prognosis [107–110]. Myocardial tissue from patients with severe heart failure obtained at the time of heart transplantation revealed an increased presence of macrophages and T lymphocytes and more endothelial activation, as indicated by the presence of intercellular adhesion molecule-1 (ICAM-1) [111].

Experimental pressure overload induces cardiac expression of proinflammatory cytokines TNF-α and IL-6, which further contribute to cardiac hypertrophy and heart failure [112–114]. TNF-α binding to its receptor TNFR1 leads to formation of the death inducing signaling complex (DISC), downstream caspase activation, and resulting apoptotic cell death. Upregulation of IL-6 expression through an α1 adrenergic receptor-A kinase anchoring protein (AKAP)-inhibitor of IκB kinase β (IKKβ) may lead to autocrine and paracrine increases in fetal and hypertrophic gene transcription through the IL-6 receptor [115]. Patients who respond clinically to cardiac resynchronization therapy show decreased serum levels of IL-6, as well as IL-8, TNF-α, and TGF-β; among non-responders, TGF-β levels increase [116, 117].

Cell Death

The processes outlined above contribute to apoptosis, necrosis, and autophagy, which together account for a significant increase in myocardial cell death and partly account for the transition from compensated hypertrophy to decompensated heart failure. All of the types of cell death can occur simultaneously and in

close proximity to each other in failing human hearts [118]. Autophagy is the packaging of intracellular components into double-membrane autophagosomes that are then degraded by lysosomes. Autophagy can be induced by nutrient depletion, hypoxia, oxidative stress, organelle damage, and protein aggregation through pathways that are dependent upon and independent of molecular target of rapamycin (mTOR). Under conditions of ischemia, autophagy appears to be instrumental in maintaining cardiac function. With reperfusion, the continued activities of autophagic processes may lead to cell loss and resulting cardiac dysfunction. One of the pathways responsible for autophagy is AMPK. A mouse model with dominant-negative AMPK in cardiac myocytes showed decreased autophagy in response to ischemia, leading to worse cardiac function in response to myocardial infarction [119]. Some lines of evidence suggest that autophagy facilitates the development of heart failure. Mice with cardiac overexpression of beclin 1, required for autophagosome formation, have increased cardiac autophagy, ventricular dilation, cardiac fibrosis, and mortality compared to non-transgenic mice in response to transaortic constriction (TAC). Mice heterozygous for a disrupted *beclin 1* gene have less cardiac autophagy and better preservation of systolic function [120]. Autophagy is repressed by mTOR, a member of the PI3K-related kinase family. Mice with a conditional cardiac knockout of raptor, an essential component of mTOR complex 1, develop severe cardiac dilation, increased autophagy, and a transition from oxidation of fatty acids to glucose utilization in response to TAC; these mice do not develop a classic initial hypertrophic response [121] (Fig. 1.3).

Increased cardiomyocyte apoptosis has been confirmed in multiple animal models of heart failure and in myocardial samples from heart failure patients [122, 123]. Important contributors to cardiomyocyte apoptosis include cytokines that are produced as part of the initial hypertrophic gene expression cascade. Serum TNF-α levels are increased among heart failure patients and are associated with worsening functional class [108, 124–126]. TNF-α expression is increased in mechanically stretched cardiomyocytes in culture and in pressure-overloaded cardiac tissue after aortic banding, correlating with apoptotic index [127, 128]. The apoptotic response is attenuated in TNF-α-knockout mice [127]. Infusion of animal models with TNF-α or cardiac-specific overexpression of TNF-α increases myocyte apoptosis and causes worsening of systolic function [129]. TNF-α binds to its receptor TNFR1, prompting formation of the death inducing signaling complex (DISC), recruitment of FADD, and activation of caspase 8, which then cleaves caspase 3, leading to activation caspase activated DNAse (CAD) and resulting DNA cleavage and apoptotic cell death [130, 131].

Cardiomyocyte necrosis due to oncotic cell death results from cellular ATP depletion, causing inactivation of ATP-dependent ion pumps and thus dissipation of energy-dependent osmotic gradients [132, 133]. Cellular swelling results and intracellular contents are released into the extracellular space. Oxygen deprivation may be a cause of ATP depletion. Decreased oxygen tension can result from coronary ischemia. Additionally, there may chronic hypoxia due to mismatch between myocyte size and vascular density in the hypertrophied heart. In advanced

cardiac hypertrophy, the increased size of myocytes outpaces the production of new capillaries, leading to a relative decrease in capillary density and creating increased oxygen diffusion distance to myocytes [75]. There is also an increase in coronary vascular resistance [134].

Cellular necrosis has traditionally been considered to be an accidental and unregulated process but, in at least some cases, appears to be governed by sophisticated regulatory pathways. A plasma membrane pathway, involving some of the same molecular machinery utilized by TNF-α to promote apoptosis, has been identified [135]. The actions of TNF-α at the plasma membrane can promote either cellular survival or death, with necrosis prevailing when survival and apoptotic pathways are inhibited [136]. TNF-α binds to TNF-α receptor I (TNFRI), leading to the recruitment of a multimolecular complex that ultimately activates NF-κB, promoting cellular survival [137]. This complex can subsequently recruit Fas-associated protein with death domain (FADD), resulting in a second complex that can promote necrosis [138, 139].

The coordinated effects of metabolic derangements, cardiomyocyte death, and interstitial fibrosis cause a shift from compensated hypertrophy to decompensated heart failure. PPARγ coactivator-1 (PGC-1) isoforms α and β are both suppressed in response to experimental pressure overload, and the loss of these activities appears central to the hypertrophy-heart failure transition [140, 141]. In addition to regulating the expression of nuclear genes responsible for fatty acid import and oxidation, PGC-1 isoforms also activate the expression of transcription factors that target the mitochondrial genome, controlling the expression of oxidative phosphorylation genes and mitochondrial biogenesis [140, 142]. Cardiac PGC-1α overexpression causes unchecked mitochondrial proliferation, disrupting normal contractile structure and leading to a dilated cardiomyopathy [143]. PGC-1β-knockout mice demonstrate more cardiac fibrosis, higher levels of reactive oxygen species, and greater reduction in ejection fraction after trans-aortic banding than do wild-type mice [141].

Extracellular Matrix Changes in Heart Failure

Extracellular matrix turnover, largely catalyzed by matrix metalloproteinases (MMPs), is central to myocardial remodeling. Myocardial levels of collagenase-3 and membrane-type MMPs are increased in heart failure. Circulating levels of MMP-2 and MMP-9 are found in heart failure patients. Peroxynitrite, formed by the reaction of superoxide anion with nitric oxide, activates MMPs. Conversely, MMP inhibition lessens to effects of peroxynitrite on contractile dysfunction in isolated cardiomyocytes [144]. Animal models demonstrate the ability of pharmacologic MMP inhibition to favorably affect post-MI remodeling. Genetic deletion of tissue inhibitors of metalloproteinases (TIMPs) causes acceleration of post-MI remodeling.

Vascular Changes and Endothelial Dysfunction

Normal endothelium functions as a structural barrier between blood and the vascular wall and as a regulator of vascular tone and coagulation by balancing opposing factors [145]. One of its most important roles is the production of nitric oxide (NO) by nitric oxide synthase (NOS) isoforms. NO produces vascular smooth muscle relaxation through stimulation of guanylate cyclase production of cyclic guanosine monophosphate (cGMP). The oxidative stress that characterizes heart failure inhibits NOS production of NO. Decreased NO availability then contributes to vasoconstriction and increased after load. Vasoconstriction as well may cause a relative hypoperfusion of the hypertrophied myocardium, further contributing to ventricular dysfunction.

Impaired Nitric Oxide Coupling

In heart failure, there appears to be increased NOS production of reactive oxygen species (ROS) such as superoxide anion instead of NO, a development that has been termed NOS uncoupling. The simultaneous decline in NO and increase in ROS lead to a decline in vasodilation and myocardial relaxation [146]. The reaction of ROS with NO leads to the formation of peroxynitrite. Infusion of peroxynitrite into intact rat hearts causes production of pro-MMP-2, a transient vasodilation that is then followed by a sustained vasoconstriction, and progressive mechanical cardiac dysfunction, changes that are prevented by treatment with an MMP inhibitor and by quenching peroxynitrite with glutathione [147].

Biomarkers of Myocardial Remodelling

As proposed by Braunwald, biomarkers of heart failure may be classified into those that reflect myocyte injury, myocardial stretch, oxidative stress, neurohormonal activation, ECM remodeling, inflammation, renal dysfunction, and others that don't fit neatly into these categories [148].

B-type natriuretic peptide (BNP), most recently more commonly used in clinical practice, and atrial natriuretic peptide (ANP) are the major examples of biomarkers reflecting myocardial stretch. The value of natriuretic peptides in guiding heart failure management has been established by clinical studies [149]. Further, plasma levels of the soluble form of ST2, which is a myocardial receptor for IL-33 in its membrane-bound form, are increased in response to myocardial stretch, and predict the occurrence of heart failure among patients with an ST-segment elevation myocardial infarction (STEMI), and death among patients with established heart failure [150, 151].

Circulating cardiac troponins (Tn) I and T are the major clinical markers of myocardial injury and necrosis. Elevated serum troponin levels can be found among individuals with essential hypertension and cardiac hypertrophy [152–155]. Conventional serum TnI levels correlate with LV wall thickness among patients with hypertrophic cardiomyopathy (HCM) [156]. In a separate study, increasing high-sensitivity TnT (hs-TnT) levels correlated with worsening functional status, outflow obstruction, and with left ventricular wall thickness among HCM patients [157]. Serum TnI predicted the development of heart failure among a community-based sample of elderly men, independently of its association with blood pressure, body mass index, smoking, and history of myocardial infarction [158]. High-sensitivity TnT level associates with risk of death among patients with nonischemic dilated cardiomyopathy [159].

The serum ratio of pro-collagen type I amino-terminal propeptide (PINP) to collagen type I cross-linked carboxyterminal telopeptide (CITP), respective markers of collagen synthesis and breakdown, may predict collagen accumulation [160]. ECM turnover depends upon the activity of matrix metalloproteinase (MMP) isoforms, which belong to a large family of zinc-dependent proteases. Their activities are inhibited by tissue inhibitors of metalloproteinases. A study of patients with heart failure with preserved ejection fraction showed significant differences in levels of MMP-2, TIMP-4, and pro-collagen type III amino-terminal propeptide (PIIINP) compared to patients with LVH but not heart failure and with controls; in levels of MMP-3 and MMP-8 compared to patients with LVH alone; and in levels of MMP-7, MMP-9, TIMP-1, TIMP-2, CITP, and osteopontin. A model consisting of PIIINP, MMP-2, MMP-8, and TIMP-4 and adjusted for clinical covariates demonstrated an improved ability to distinguish patients with heart failure with preserved ejection fraction compared to a model consisting of clinical covariates alone [161].

Serum C-reactive protein (CRP) levels are elevated among heart failure patients compared to people without heart failure. Furthermore, higher CRP levels are associated with more severe heart failure and with a higher risk of death [162]. Higher levels of CRP and IL-6 predict the onset of CHF among patients with and without metabolic syndrome [163–165]. In one study of patients with severe heart failure, serum levels of TNF-α and IL-6 and soluble receptors differed significantly between survivors and nonsurvivors, higher levels predicting lower likelihood of survival [166]. Serum levels of TNF-α and of its soluble receptors (types I and II) were elevated among heart failure compared to age-matched healthy controls, and levels of the type-II soluble receptor (sTNFRII) independently predicted death [110]. Among patients with severe heart failure in a separate study, levels of IL-6, TNF-α, and IL-1β and of the soluble receptors for TNF-α and IL-2 were associated with risk of death in univariate analyses; IL-6 levels independently predicted a combined endpoint of death, new heart failure episodes, and need for heart transplantation [167]. Galectins are a family of β-galactoside-binding proteins that regulate inflammation [168]. Higher galectin-3 levels are associated with worse heart failure functional classification and with worse outcome [169, 170].

Neuregulin-1 (NRG1) is produced by coronary endothelial cells and bind to ErbB4 receptors on cardiomyocytes, prompting its interaction with HER2/neu

(ErbB2) and triggering of downstream effectors such as focal adhesion kinase (FAK) that are involved in sarcomere organization and cell survival [171]. Antagonism of HER2 with the monoclonal antibody trastuzumab in addition to chemotherapy increased the risk of cardiac fourfold compared to chemotherapy alone, despite an overall oncologic and survival benefit [172]. NRG-1β levels increase with heart failure class and predict transplant-free survival [173]. In a small clinical trial, daily infusion with a recombinant human NRG-1 for 11 days produced beneficial acute hemodynamic effects (significant reductions in pulmonary capillary wedge pressure, systemic vascular resistance, and serum levels of norepinephrine and aldosterone; and increased cardiac output) and a sustained 12 % increase in LV ejection fraction at 3 months [174].

Cardiac Non-coding RNA

Micro-RNAs (miRs) are noncoding molecules, 18 to 25 nucleotides in length, that silence expression of specific genes by binding to complementary segments of messenger RNA, targeting them for degradation and/or inhibiting their translation [175]. Studies comparing human heart failure and animal models have found concordance in the upregulation of mir-24, -195, 199a, and 214 in response to cardiac stress [176].

MiRs have been found to circulate stably in blood [177]. MiR-423-5p is increased in the failing human heart; plasma levels distinguish heart failure patients from healthy controls and patients with dyspnea not due to heart failure and correlated with N-terminal-pro-BNP [178]. A small clinical study demonstrated that a combination of serum levels of miR-423-5p, -320a, -22, and -92b could differentiate between heart failure patients and controls, although the interpretation is limited by significant differences between the groups in drug treatment and the prevalences of diabetes and chronic kidney disease [179]. In a separate study, miR-423-5p showed no significant differences among patients with transposition of the great arteries and a failing systemic right ventricle after atrial repair and sex- and age-matched health controls [180]. The logarithm of plasma miR-126 concentration negatively with log[BNP], declined with worsening NYHA class, and increased with clinical improvement [181]. Plasma levels of miR-499 were elevated after acute MI and viral myocarditis and during acute heart failure [182].

Conclusion

Much progress has been made in the past half-century in the understanding of the molecular changes preceding and accompanying heart failure. Continued investigation is hoped to identify new targets for prevention, diagnosis, and therapy. Studies of in vitro systems have been invaluable in unraveling the molecular and cellular

mechanisms at play in heart failure. But the major breakthroughs in this area and in biomedical science generally have issued from the creation of genetically manipulated animal models. The availability of human genome sequences and our deepening understanding of inter-individual genetic variability will illuminate new discoveries in heart failure risk and treatment. Epigenetic elements, such as microRNAs, especially those that circulate in plasma may prove to be both markers and mediators of heart failure risk, progression, and response to treatment. The explosion of data resulting from all of these efforts will require advances in bioinformatics and in systems biology.

References

1. He J, Ogden LG, Bazzano LA, Vupputuri S, Loria C, Whelton PK. Risk factors for congestive heart failure in US men and women: NHANES I epidemiologic follow-up study. Arch Intern Med. 2001;161:996–1002.
2. Rich MW. Epidemiology, pathophysiology, and etiology of congestive heart failure in older adults. J Am Geriatr Soc. 1997;45:968–74.
3. Kannel WB, Ho K, Thom T. Changing epidemiological features of cardiac failure. Br Heart J. 1994;72:S3–9.
4. Savinova OV, Gerdes AM. Myocyte changes in heart failure. Heart Fail Clin. 2012;8:1–6.
5. Ruwhof C, van der Laarse A. Mechanical stress-induced cardiac hypertrophy: mechanisms and signal transduction pathways. Cardiovasc Res. 2000;47:23–37.
6. Tallarida RJ, Rusy BF, Loughnane MH. Left ventricular wall acceleration and the law of Laplace. Cardiovasc Res. 1970;4:217–23.
7. Lorell BH, Carabello BA. Left ventricular hypertrophy: pathogenesis, detection, and prognosis. Circulation. 2000;102:470–9.
8. Packer M. Neurohormonal interactions and adaptations in congestive heart failure. Circulation. 1988;77:721–30.
9. Cotton TF. Cardiac hypertrophy. Can Med Assoc J. 1914;4:709–14.
10. Stein BR, Barnes AR. Severity and duration of hypertension in relation to amount of cardiac hypertrophy. Am J Med Sci. 1948;216:661–4.
11. Hill JA, Olson EN. Cardiac plasticity. N Engl J Med. 2008;358:1370–80.
12. Laflamme MA, Murry CE. Heart regeneration. Nature. 2011;473:326–35.
13. Adler CP, Costabel U. Cell number in human heart in atrophy, hypertrophy, and under the influence of cytostatics. Recent Adv Stud Cardiac Struct Metab. 1975;6:343–55.
14. Booz GW, Baker KM. Molecular signalling mechanisms controlling growth and function of cardiac fibroblasts. Cardiovasc Res. 1995;30:537–43.
15. McKay RG, Pfeffer MA, Pasternak RC, et al. Left ventricular remodeling after myocardial infarction: a corollary to infarct expansion. Circulation. 1986;74:693–702.
16. Souders CA, Borg TK, Banerjee I, Baudino TA. Pressure overload induces early morphological changes in the heart. Am J Pathol. 2012;181:1226–35.
17. Voelkl J, Lin Y, Alesutan I, et al. Sgk1 sensitivity of Na(+)/H(+) exchanger activity and cardiac remodeling following pressure overload. Basic Res Cardiol. 2012;107:236.
18. Nediani C, Formigli L, Perna AM, et al. Early changes induced in the left ventricle by pressure overload. An experimental study on swine heart. J Mol Cell Cardiol. 2000;32:131–42.
19. Brand T, Sharma HS, Schaper W. Expression of nuclear proto-oncogenes in isoproterenol-induced cardiac hypertrophy. J Mol Cell Cardiol. 1993;25:1325–37.
20. Sharif-Naeini R, Folgering JH, Bichet D, et al. Sensing pressure in the cardiovascular system: Gq-coupled mechanoreceptors and TRP channels. J Mol Cell Cardiol. 2010;48:83–9.

21. Inoue R, Jian Z, Kawarabayashi Y. Mechanosensitive TRP channels in cardiovascular pathophysiology. Pharmacol Ther. 2009;123:371–85.
22. Dyachenko V, Husse B, Rueckschloss U, Isenberg G. Mechanical deformation of ventricular myocytes modulates both TRPC6 and Kir2.3 channels. Cell Calcium. 2009;45:38–54.
23. Spassova MA, Hewavitharana T, Xu W, Soboloff J, Gill DL. A common mechanism underlies stretch activation and receptor activation of TRPC6 channels. Proc Natl Acad Sci U S A. 2006;103:16586–91.
24. Zou Y, Akazawa H, Qin Y, et al. Mechanical stress activates angiotensin II type 1 receptor without the involvement of angiotensin II. Nat Cell Biol. 2004;6:499–506.
25. Hofmann T, Obukhov AG, Schaefer M, Harteneck C, Gudermann T, Schultz G. Direct activation of human TRPC6 and TRPC3 channels by diacylglycerol. Nature. 1999;397:259–63.
26. Lemonnier L, Trebak M, Putney Jr JW. Complex regulation of the TRPC3, 6 and 7 channel subfamily by diacylglycerol and phosphatidylinositol-4,5-bisphosphate. Cell Calcium. 2008;43:506–14.
27. Molkentin JD, Lu JR, Antos CL, et al. A calcineurin-dependent transcriptional pathway for cardiac hypertrophy. Cell. 1998;93:215–28.
28. Bush EW, Hood DB, Papst PJ, et al. Canonical transient receptor potential channels promote cardiomyocyte hypertrophy through activation of calcineurin signaling. J Biol Chem. 2006;281:33487–96.
29. Kuwahara K, Wang Y, McAnally J, et al. TRPC6 fulfills a calcineurin signaling circuit during pathologic cardiac remodeling. J Clin Invest. 2006;116:3114–26.
30. Srivastava D, Yu S. Stretching to meet needs: integrin-linked kinase and the cardiac pump. Genes Dev. 2006;20:2327–31.
31. Frank D, Frey N. Cardiac Z-disc signaling network. J Biol Chem. 2011;286:9897–904.
32. Pyle WG, Solaro RJ. At the crossroads of myocardial signaling: the role of Z-discs in intracellular signaling and cardiac function. Circ Res. 2004;94:296–305.
33. Torsoni AS, Constancio SS, Nadruz Jr W, Hanks SK, Franchini KG. Focal adhesion kinase is activated and mediates the early hypertrophic response to stretch in cardiac myocytes. Circ Res. 2003;93:140–7.
34. Hoshijima M. Mechanical stress-strain sensors embedded in cardiac cytoskeleton: Z disk, titin, and associated structures. Am J Physiol Heart Circ Physiol. 2006;290:H1313–25.
35. Laser M, Willey CD, Jiang W, et al. Integrin activation and focal complex formation in cardiac hypertrophy. J Biol Chem. 2000;275:35624–30.
36. Kostin S, Scholz D, Shimada T, et al. The internal and external protein scaffold of the T-tubular system in cardiomyocytes. Cell Tissue Res. 1998;294:449–60.
37. Ahmed N, Riley C, Rice G, Quinn M. Role of integrin receptors for fibronectin, collagen and laminin in the regulation of ovarian carcinoma functions in response to a matrix microenvironment. Clin Exp Metastasis. 2005;22:391–402.
38. Taylor JM, Rovin JD, Parsons JT. A role for focal adhesion kinase in phenylephrine-induced hypertrophy of rat ventricular cardiomyocytes. J Biol Chem. 2000;275:19250–7.
39. Hauselmann SP, Rosc-Schluter BI, Lorenz V, et al. beta1-Integrin is up-regulated via Rac1-dependent reactive oxygen species as part of the hypertrophic cardiomyocyte response. Free Radic Biol Med. 2011;51:609–18.
40. Wei BR, Martin PL, Hoover SB, et al. Capacity for resolution of Ras-MAPK-initiated early pathogenic myocardial hypertrophy modeled in mice. Comp Med. 2011;61:109–18.
41. Mederos Y, Schnitzler M, Storch U, Meibers S, et al. Gq-coupled receptors as mechanosensors mediating myogenic vasoconstriction. EMBO J. 2008;27:3092–103.
42. Gresset A, Sondek J, Harden TK. The phospholipase C isozymes and their regulation. Subcell Biochem. 2012;58:61–94.
43. Seth M, Zhang ZS, Mao L, et al. TRPC1 channels are critical for hypertrophic signaling in the heart. Circ Res. 2009;105:1023–30.
44. Freichel M, Schweig U, Stauffenberger S, Freise D, Schorb W, Flockerzi V. Store-operated cation channels in the heart and cells of the cardiovascular system. Cell Physiol Biochem. 1999;9:270–83.

45. Rockman HA, Ross RS, Harris AN, et al. Segregation of atrial-specific and inducible expression of an atrial natriuretic factor transgene in an in vivo murine model of cardiac hypertrophy. Proc Natl Acad Sci U S A. 1991;88:8277–81.
46. Wang J, Paradis P, Aries A, et al. Convergence of protein kinase C and JAK-STAT signaling on transcription factor GATA-4. Mol Cell Biol. 2005;25:9829–44.
47. Prasad AM, Inesi G. Regulation and rate limiting mechanisms of Ca2+ ATPase (SERCA2) expression in cardiac myocytes. Mol Cell Biochem. 2012;361:85–96.
48. Zarain-Herzberg A, Fragoso-Medina J, Estrada-Aviles R. Calcium-regulated transcriptional pathways in the normal and pathologic heart. IUBMB Life. 2011;63:847–55.
49. Jessup M, Greenberg B, Mancini D, et al. Calcium Upregulation by Percutaneous Administration of Gene Therapy in Cardiac Disease (CUPID): a phase 2 trial of intracoronary gene therapy of sarcoplasmic reticulum Ca2+−ATPase in patients with advanced heart failure. Circulation. 2011;124:304–13.
50. Ling H, Zhang T, Pereira L, et al. Requirement for Ca2+/calmodulin-dependent kinase II in the transition from pressure overload-induced cardiac hypertrophy to heart failure in mice. J Clin Invest. 2009;119:1230–40.
51. Dhandapany PS, Fabris F, Tonk R, et al. Cyclosporine attenuates cardiomyocyte hypertrophy induced by RAF1 mutants in Noonan and LEOPARD syndromes. J Mol Cell Cardiol. 2011;51:4–15.
52. Paoletti E, Marsano L, Bellino D, Cassottana P, Cannella G. Effect of everolimus on left ventricular hypertrophy of de novo kidney transplant recipients: a 1 year, randomized, controlled trial. Transplantation. 2012;93:503–8.
53. Di Marco GS, Reuter S, Kentrup D, et al. Cardioprotective effect of calcineurin inhibition in an animal model of renal disease. Eur Heart J. 2011;32:1935–45.
54. Hisamitsu T, Nakamura TY, Wakabayashi S. Na(+)/H(+) exchanger 1 directly binds to calcineurin A and activates downstream NFAT signaling, leading to cardiomyocyte hypertrophy. Mol Cell Biol. 2012;32:3265–80.
55. Joiner ML, Koval OM, Li J, et al. CaMKII determines mitochondrial stress responses in heart. Nature. 2012;491:269–73.
56. Yang Y, Zhu WZ, Joiner ML, et al. Calmodulin kinase II inhibition protects against myocardial cell apoptosis in vivo. Am J Physiol Heart Circ Physiol. 2006;291:H3065–75.
57. Wang HG, Pathan N, Ethell IM, et al. Ca2+−induced apoptosis through calcineurin dephosphorylation of BAD. Science. 1999;284:339–43.
58. Antos CL, McKinsey TA, Frey N, et al. Activated glycogen synthase-3 beta suppresses cardiac hypertrophy in vivo. Proc Natl Acad Sci U S A. 2002;99:907–12.
59. Stuenaes JT, Bolling A, Ingvaldsen A, et al. Beta-adrenoceptor stimulation potentiates insulin-stimulated PKB phosphorylation in rat cardiomyocytes via cAMP and PKA. Br J Pharmacol. 2010;160:116–29.
60. Webb IG, Nishino Y, Clark JE, et al. Constitutive glycogen synthase kinase-3alpha/beta activity protects against chronic beta-adrenergic remodelling of the heart. Cardiovasc Res. 2010;87:494–503.
61. Hardt SE, Sadoshima J. Negative regulators of cardiac hypertrophy. Cardiovasc Res. 2004;63:500–9.
62. Tenhunen O, Sarman B, Kerkela R, et al. Mitogen-activated protein kinases p38 and ERK 1/2 mediate the wall stress-induced activation of GATA-4 binding in adult heart. J Biol Chem. 2004;279:24852–60.
63. Kerkela R, Pikkarainen S, Majalahti-Palviainen T, Tokola H, Ruskoaho H. Distinct roles of mitogen-activated protein kinase pathways in GATA-4 transcription factor-mediated regulation of B-type natriuretic peptide gene. J Biol Chem. 2002;277:13752–60.
64. Liang Q, Wiese RJ, Bueno OF, Dai YS, Markham BE, Molkentin JD. The transcription factor GATA4 is activated by extracellular signal-regulated kinase 1- and 2-mediated phosphorylation of serine 105 in cardiomyocytes. Mol Cell Biol. 2001;21:7460–9.
65. Gao X, He X, Luo B, Peng L, Lin J, Zuo Z. Angiotensin II increases collagen I expression via transforming growth factor-beta1 and extracellular signal-regulated kinase in cardiac fibroblasts. Eur J Pharmacol. 2009;606:115–20.

66. Shivakumar K, Dostal DE, Boheler K, Baker KM, Lakatta EG. Differential response of cardiac fibroblasts from young adult and senescent rats to ANG II. Am J Physiol Heart Circ Physiol. 2003;284:H1454–9.
67. Katz AM. The cardiomyopathy of overload: a hypothesis. J Cardiovasc Pharmacol. 1991;18(Suppl 2):S68–71.
68. Eghbali M, Deva R, Alioua A, et al. Molecular and functional signature of heart hypertrophy during pregnancy. Circ Res. 2005;96:1208–16.
69. Duerr RL, Huang S, Miraliakbar HR, Clark R, Chien KR, Ross Jr J. Insulin-like growth factor-1 enhances ventricular hypertrophy and function during the onset of experimental cardiac failure. J Clin Invest. 1995;95:619–27.
70. Prosser BL, Ward CW, Lederer WJ. X-ROS signaling: rapid mechano-chemo transduction in heart. Science. 2011;333:1440–5.
71. Maejima Y, Kuroda J, Matsushima S, Ago T, Sadoshima J. Regulation of myocardial growth and death by NADPH oxidase. J Mol Cell Cardiol. 2011;50:408–16.
72. Rajabi M, Kassiotis C, Razeghi P, Taegtmeyer H. Return to the fetal gene program protects the stressed heart: a strong hypothesis. Heart Fail Rev. 2007;12:331–43.
73. Frank D, Kuhn C, Brors B, et al. Gene expression pattern in biomechanically stretched cardiomyocytes: evidence for a stretch-specific gene program. Hypertension. 2008;51:309–18.
74. Kuwahara K, Nishikimi T, Nakao K. Transcriptional regulation of the fetal cardiac gene program. J Pharmacol Sci. 2012;119:198–203.
75. Anversa P, Capasso JM. Loss of intermediate-sized coronary arteries and capillary proliferation after left ventricular failure in rats. Am J Physiol. 1991;260:H1552–60.
76. Laguens R, Alvarez P, Vigliano C, et al. Coronary microcirculation remodeling in patients with idiopathic dilated cardiomyopathy. Cardiology. 2011;119:191–6.
77. Camici PG, Olivotto I, Rimoldi OE. The coronary circulation and blood flow in left ventricular hypertrophy. J Mol Cell Cardiol. 2012;52:857–64.
78. Friehs I, Margossian RE, Moran AM, Cao-Danh H, Moses MA, del Nido PJ. Vascular endothelial growth factor delays onset of failure in pressure-overload hypertrophy through matrix metalloproteinase activation and angiogenesis. Basic Res Cardiol. 2006;101:204–13.
79. Weber KT, Janicki JS, Shroff SG, Pick R, Chen RM, Bashey RI. Collagen remodeling of the pressure-overloaded, hypertrophied nonhuman primate myocardium. Circ Res. 1988;62:757–65.
80. Galie PA, Russell MW, Westfall MV, Stegemann JP. Interstitial fluid flow and cyclic strain differentially regulate cardiac fibroblast activation via AT1R and TGF-beta1. Exp Cell Res. 2012;318:75–84.
81. Ma F, Li Y, Jia L, et al. Macrophage-stimulated cardiac fibroblast production of IL-6 is essential for TGF beta/Smad activation and cardiac fibrosis induced by angiotensin II. PLoS One. 2012;7:e35144.
82. Fredj S, Bescond J, Louault C, Delwail A, Lecron JC, Potreau D. Role of interleukin-6 in cardiomyocyte/cardiac fibroblast interactions during myocyte hypertrophy and fibroblast proliferation. J Cell Physiol. 2005;204:428–36.
83. Melendez GC, McLarty JL, Levick SP, Du Y, Janicki JS, Brower GL. Interleukin 6 mediates myocardial fibrosis, concentric hypertrophy, and diastolic dysfunction in rats. Hypertension. 2010;56:225–31.
84. Martin ML, Blaxall BC. Cardiac intercellular communication: are myocytes and fibroblasts fair-weather friends? J Cardiovasc Transl Res. 2012;5:768–82.
85. Ibrahim M, Gorelik J, Yacoub MH, Terracciano CM. The structure and function of cardiac t-tubules in health and disease. Proc Biol Sci/The Royal Society. 2011;278:2714–23.
86. Ribadeau Dumas A, Wisnewsky C, Boheler KR, Ter Keurs H, Fiszman MY, Schwartz K. The sarco(endo)plasmic reticulum Ca(2+)-ATPase gene is regulated at the transcriptional level during compensated left ventricular hypertrophy in the rat. C R Acad Sci III. 1997;320:963–9.
87. Crossman DJ, Ruygrok PN, Soeller C, Cannell MB. Changes in the organization of excitation-contraction coupling structures in failing human heart. PLoS One. 2011;6:e17901.

88. Zhang HB, Li RC, Xu M, et al. Ultrastructural uncoupling between T-tubules and sarcoplasmic reticulum in human heart failure. Cardiovasc Res. 2013;98:269–76.
89. Guo A, Zhang C, Wei S, Chen B, Song LS. Emerging mechanisms of T-tubule remodeling in heart failure. Cardiovasc Res. 2013;98:204–15.
90. Brette F, Orchard C. T-tubule function in mammalian cardiac myocytes. Circ Res. 2003;92:1182–92.
91. Kee AJ, Gunning PW, Hardeman EC. Diverse roles of the actin cytoskeleton in striated muscle. J Musc Res Cell Motil. 2009;30:187–97.
92. Yang Z, Pascarel C, Steele DS, Komukai K, Brette F, Orchard CH. Na+−Ca2+ exchange activity is localized in the T-tubules of rat ventricular myocytes. Circ Res. 2002;91:315–22.
93. Laflamme MA, Becker PL. G(s) and adenylyl cyclase in transverse tubules of heart: implications for cAMP-dependent signaling. Am J Physiol. 1999;277:H1841–8.
94. Nikolaev VO, Moshkov A, Lyon AR, et al. Beta2-adrenergic receptor redistribution in heart failure changes cAMP compartmentation. Science. 2010;327:1653–7.
95. Wei S, Guo A, Chen B, et al. T-tubule remodeling during transition from hypertrophy to heart failure. Circ Res. 2010;107:520–31.
96. He J, Conklin MW, Foell JD, et al. Reduction in density of transverse tubules and L-type Ca(2+) channels in canine tachycardia-induced heart failure. Cardiovasc Res. 2001;49:298–307.
97. Ibrahim M, Navaratnarajah M, Siedlecka U, et al. Mechanical unloading reverses transverse tubule remodelling and normalizes local Ca(2+)-induced Ca(2+)release in a rodent model of heart failure. Eur J Heart Fail. 2012;14:571–80.
98. Jolley RL, Cheldelin VH, Newburgh RW. Glucose catabolism in fetal and adult heart. J Biol Chem. 1958;233:1289–94.
99. Sack MN, Rader TA, Park S, Bastin J, McCune SA, Kelly DP. Fatty acid oxidation enzyme gene expression is downregulated in the failing heart. Circulation. 1996;94:2837–42.
100. Abdalla S, Fu X, Elzahwy SS, Klaetschke K, Streichert T, Quitterer U. Up-regulation of the cardiac lipid metabolism at the onset of heart failure. Cardiovasc Hematol Agents Med Chem. 2011;9:190–206.
101. Meng RS, Pei ZH, Yin R, et al. Adenosine monophosphate-activated protein kinase inhibits cardiac hypertrophy through reactivating peroxisome proliferator-activated receptor-alpha signaling pathway. Eur J Pharmacol. 2009;620:63–70.
102. Karbowska J, Kochan Z, Smolenski RT. Peroxisome proliferator-activated receptor alpha is downregulated in the failing human heart. Cell Mol Biol Lett. 2003;8:49–53.
103. el Azzouzi H, Leptidis S, Bourajjaj M, van Bilsen M, da Costa Martins PA, De Windt LJ. MEK1 inhibits cardiac PPARalpha activity by direct interaction and prevents its nuclear localization. PLoS One. 2012;7:e36799.
104. Alibin CP, Kopilas MA, Anderson HD. Suppression of cardiac myocyte hypertrophy by conjugated linoleic acid: role of peroxisome proliferator-activated receptors alpha and gamma. J Biol Chem. 2008;283:10707–15.
105. Tuunanen H, Engblom E, Naum A, et al. Decreased myocardial free fatty acid uptake in patients with idiopathic dilated cardiomyopathy: evidence of relationship with insulin resistance and left ventricular dysfunction. J Card Fail. 2006;12:644–52.
106. Chokshi A, Drosatos K, Cheema FH, et al. Ventricular assist device implantation corrects myocardial lipotoxicity, reverses insulin resistance, and normalizes cardiac metabolism in patients with advanced heart failure. Circulation. 2012;125:2844–53.
107. Levine B, Kalman J, Mayer L, Fillit HM, Packer M. Elevated circulating levels of tumor necrosis factor in severe chronic heart failure. N Engl J Med. 1990;323:236–41.
108. Testa M, Yeh M, Lee P, et al. Circulating levels of cytokines and their endogenous modulators in patients with mild to severe congestive heart failure due to coronary artery disease or hypertension. J Am Coll Cardiol. 1996;28:964–71.
109. Kell R, Haunstetter A, Dengler TJ, Zugck C, Kubler W, Haass M. Do cytokines enable risk stratification to be improved in NYHA functional class III patients? Comparison with other potential predictors of prognosis. Eur Heart J. 2002;23:70–8.

110. Ferrari R, Bachetti T, Confortini R, et al. Tumor necrosis factor soluble receptors in patients with various degrees of congestive heart failure. Circulation. 1995;92:1479–86.
111. Devaux B, Scholz D, Hirche A, Klovekorn WP, Schaper J. Upregulation of cell adhesion molecules and the presence of low grade inflammation in human chronic heart failure. Eur Heart J. 1997;18:470–9.
112. Baumgarten G, Knuefermann P, Kalra D, et al. Load-dependent and -independent regulation of proinflammatory cytokine and cytokine receptor gene expression in the adult mammalian heart. Circulation. 2002;105:2192–7.
113. Yokoyama T, Nakano M, Bednarczyk JL, McIntyre BW, Entman M, Mann DL. Tumor necrosis factor-alpha provokes a hypertrophic growth response in adult cardiac myocytes. Circulation. 1997;95:1247–52.
114. Bozkurt B, Kribbs SB, Clubb Jr FJ, et al. Pathophysiologically relevant concentrations of tumor necrosis factor-alpha promote progressive left ventricular dysfunction and remodeling in rats. Circulation. 1998;97:1382–91.
115. del Vescovo CD, Cotecchia S, Diviani D. A-kinase-anchoring protein-Lbc anchors IkappaB kinase beta to support interleukin-6-mediated cardiomyocyte hypertrophy. Mol Cell Biol. 2013;33:14–27.
116. Stanciu AE, Vatasescu RG, Stanciu MM, Iorgulescu C, Vasile AI, Dorobantu M. Cardiac resynchronization therapy in patients with chronic heart failure is associated with anti-inflammatory and anti-remodeling effects. Clin Biochem. 2013;46:230–4.
117. Osmancik P, Herman D, Stros P, Linkova H, Vondrak K, Paskova E. Changes and prognostic impact of apoptotic and inflammatory cytokines in patients treated with cardiac resynchronization therapy. Cardiology. 2013;124:190–8.
118. Kostin S, Pool L, Elsasser A, et al. Myocytes die by multiple mechanisms in failing human hearts. Circ Res. 2003;92:715–24.
119. Russell 3rd RR, Li J, Coven DL, et al. AMP-activated protein kinase mediates ischemic glucose uptake and prevents postischemic cardiac dysfunction, apoptosis, and injury. The J Clin Invest. 2004;114:495–503.
120. Zhu H, Tannous P, Johnstone JL, et al. Cardiac autophagy is a maladaptive response to hemodynamic stress. J Clin Invest. 2007;117:1782–93.
121. Shende P, Plaisance I, Morandi C, et al. Cardiac raptor ablation impairs adaptive hypertrophy, alters metabolic gene expression, and causes heart failure in mice. Circulation. 2011;123:1073–82.
122. Sharov VG, Sabbah HN, Shimoyama H, Goussev AV, Lesch M, Goldstein S. Evidence of cardiocyte apoptosis in myocardium of dogs with chronic heart failure. Am J Pathol. 1996;148:141–9.
123. Narula J, Haider N, Virmani R, et al. Apoptosis in myocytes in end-stage heart failure. N Engl J Med. 1996;335:1182–9.
124. Dutka DP, Elborn JS, Delamere F, Shale DJ, Morris GK. Tumour necrosis factor alpha in severe congestive cardiac failure. Br Heart J. factor in chronic heart failure with cachexia. Int J Cardiol. 1997;58:257–61.
125. Zhao SP, Zeng LH. Elevated plasma levels of tumor necrosis factor in chronic heart failure with cachexia. Int J Cardiol. 1997;58:257–61.
126. Nozaki N, Yamaguchi S, Shirakabe M, Nakamura H, Tomoike H. Soluble tumor necrosis factor receptors are elevated in relation to severity of congestive heart failure. Jpn Circ J. 1997;61:657–64.
127. Sun M, Chen M, Dawood F, et al. Tumor necrosis factor-alpha mediates cardiac remodeling and ventricular dysfunction after pressure overload state. Circulation. 2007;115:1398–407.
128. Stamm C, Friehs I, Cowan DB, et al. Inhibition of tumor necrosis factor-alpha improves postischemic recovery of hypertrophied hearts. Circulation. 2001;104:I350–5.
129. Haudek SB, Taffet GE, Schneider MD, Mann DL. TNF provokes cardiomyocyte apoptosis and cardiac remodeling through activation of multiple cell death pathways. J Clin Invest. 2007;117:2692–701.

130. Crow MT, Mani K, Nam YJ, Kitsis RN. The mitochondrial death pathway and cardiac myocyte apoptosis. Circ Res. 2004;95:957–70.
131. Al-Lamki RS, Brookes AP, Wang J, et al. TNF receptors differentially signal and are differentially expressed and regulated in the human heart. Am J Transplant. 2009;9:2679–96.
132. Majno G, Joris I. Apoptosis, oncosis, and necrosis. An overview of cell death. Am J Pathol. 1995;146:3–15.
133. Weerasinghe P, Buja LM. Oncosis: an important non-apoptotic mode of cell death. Exp Mol Pathol. 2012;93:302–8.
134. Tomanek RJ, Palmer PJ, Peiffer GL, Schreiber KL, Eastham CL, Marcus ML. Morphometry of canine coronary arteries, arterioles, and capillaries during hypertension and left ventricular hypertrophy. Circ Res. 1986;58:38–46.
135. Micheau O, Tschopp J. Induction of TNF receptor I-mediated apoptosis via two sequential signaling complexes. Cell. 2003;114:181–90.
136. Whelan RS, Kaplinskiy V, Kitsis RN. Cell death in the pathogenesis of heart disease: mechanisms and significance. Ann Rev Physiol. 2010;72:19–44.
137. Ea CK, Deng L, Xia ZP, Pineda G, Chen ZJ. Activation of IKK by TNFalpha requires site-specific ubiquitination of RIP1 and polyubiquitin binding by NEMO. Mol Cell. 2006;22:245–57.
138. He S, Wang L, Miao L, et al. Receptor interacting protein kinase-3 determines cellular necrotic response to TNF-alpha. Cell. 2009;137:1100–11.
139. Holler N, Zaru R, Micheau O, et al. Fas triggers an alternative, caspase-8-independent cell death pathway using the kinase RIP as effector molecule. Nat Immunol. 2000;1:489–95.
140. Riehle C, Abel ED. PGC-1 proteins and heart failure. Trends Cardiovasc Med. 2012;22:98–105.
141. Riehle C, Wende AR, Zaha VG, et al. PGC-1beta deficiency accelerates the transition to heart failure in pressure overload hypertrophy. Circ Res. 2011;109:783–93.
142. Kelly DP, Scarpulla RC. Transcriptional regulatory circuits controlling mitochondrial biogenesis and function. Genes Dev. 2004;18:357–68.
143. Lehman JJ, Barger PM, Kovacs A, Saffitz JE, Medeiros DM, Kelly DP. Peroxisome proliferator-activated receptor gamma coactivator-1 promotes cardiac mitochondrial biogenesis. J Clin Invest. 2000;106:847–56.
144. Leon H, Baczko I, Sawicki G, Light PE, Schulz R. Inhibition of matrix metalloproteinases prevents peroxynitrite-induced contractile dysfunction in the isolated cardiac myocyte. Br J Pharmacol. 2008;153:676–83.
145. Marti CN, Gheorghiade M, Kalogeropoulos AP, Georgiopoulou VV, Quyyumi AA, Butler J. Endothelial dysfunction, arterial stiffness, and heart failure. J Am Coll Cardiol. 2012;60:1455–69.
146. Silberman GA, Fan TH, Liu H, et al. Uncoupled cardiac nitric oxide synthase mediates diastolic dysfunction. Circulation. 2010;121:519–28.
147. Wang W, Sawicki G, Schulz R. Peroxynitrite-induced myocardial injury is mediated through matrix metalloproteinase-2. Cardiovasc Res. 2002;53:165–74.
148. Braunwald E. Biomarkers in heart failure. Preface. Heart Fail Clin. 2009;5:xiii–xiv.
149. Maisel AS, Krishnaswamy P, Nowak RM, et al. Rapid measurement of B-type natriuretic peptide in the emergency diagnosis of heart failure. N Engl J Med. 2002;347:161–7.
150. Shimpo M, Morrow DA, Weinberg EO, et al. Serum levels of the interleukin-1 receptor family member ST2 predict mortality and clinical outcome in acute myocardial infarction. Circulation. 2004;109:2186–90.
151. Dhillon OS, Narayan HK, Khan SQ, et al. Pre-discharge risk stratification in unselected STEMI: Is there a role for ST2 or its natural ligand IL-33 when compared with contemporary risk markers? Int J Cardiol. 2013;167:2182–8.
152. Mishra RK, Li Y, Defilippi C, et al. Association of cardiac troponin T with left ventricular structure and function in CKD. Am J Kidney Dis. 2013;61(5):701–9.

153. Lowbeer C, Gustafsson SA, Seeberger A, Bouvier F, Hulting J. Serum cardiac troponin T in patients hospitalized with heart failure is associated with left ventricular hypertrophy and systolic dysfunction. Scand J Clin Lab Invest. 2004;64:667–76.
154. Sato Y, Yamamoto E, Sawa T, et al. High-sensitivity cardiac troponin T in essential hypertension. J Cardiol. 2011;58:226–31.
155. Negishi K, Kobayashi M, Ochiai I, et al. Association between fibroblast growth factor 23 and left ventricular hypertrophy in maintenance hemodialysis patients. Comparison with B-type natriuretic peptide and cardiac troponin T. Circ J. 2010;74:2734–40.
156. Kubo T, Kitaoka H, Okawa M, et al. Serum cardiac troponin I is related to increased left ventricular wall thickness, left ventricular dysfunction, and male gender in hypertrophic cardiomyopathy. Clin Cardiol. 2010;33:E1–7.
157. Moreno V, Hernandez-Romero D, Vilchez JA, et al. Serum levels of high-sensitivity troponin T: a novel marker for cardiac remodeling in hypertrophic cardiomyopathy. J Card Fail. 2010;16:950–6.
158. Sundstrom J, Ingelsson E, Berglund L, et al. Cardiac troponin-I and risk of heart failure: a community-based cohort study. Eur Heart J. 2009;30:773–81.
159. Kawahara C, Tsutamoto T, Nishiyama K, et al. Prognostic role of high-sensitivity cardiac troponin T in patients with nonischemic dilated cardiomyopathy. Circ J. 2011;75:656–61.
160. Biolo A, Fisch M, Balog J, et al. Episodes of acute heart failure syndrome are associated with increased levels of troponin and extracellular matrix markers. Circ Heart Fail. 2010;3:44–50.
161. Zile MR, Desantis SM, Baicu CF, et al. Plasma biomarkers that reflect determinants of matrix composition identify the presence of left ventricular hypertrophy and diastolic heart failure. Circ Heart Fail. 2011;4:246–56.
162. Anand IS, Latini R, Florea VG, et al. C-reactive protein in heart failure: prognostic value and the effect of valsartan. Circulation. 2005;112:1428–34.
163. Suzuki T, Katz R, Jenny NS, et al. Metabolic syndrome, inflammation, and incident heart failure in the elderly: the cardiovascular health study. Circ Heart Fail. 2008;1:242–8.
164. Bahrami H, Bluemke DA, Kronmal R, et al. Novel metabolic risk factors for incident heart failure and their relationship with obesity: the MESA (Multi-Ethnic Study of Atherosclerosis) study. J Am Coll Cardiol. 2008;51:1775–83.
165. Barac A, Wang H, Shara NM, et al. Markers of inflammation, metabolic risk factors, and incident heart failure in American Indians: the strong heart study. J Clin Hypertens. 2012;14:13–9.
166. Deswal A, Petersen NJ, Feldman AM, Young JB, White BG, Mann DL. Cytokines and cytokine receptors in advanced heart failure: an analysis of the cytokine database from the Vesnarinone trial (VEST). Circulation. 2001;103:2055–9.
167. Orus J, Roig E, Perez-Villa F, et al. Prognostic value of serum cytokines in patients with congestive heart failure. J Heart Lung Transplant. 2000;19:419–25.
168. Liu FT, Yang RY, Hsu DK. Galectins in acute and chronic inflammation. Ann N Y Acad Sci. 2012;1253:80–91.
169. Ueland T, Aukrust P, Broch K, et al. Galectin-3 in heart failure: high levels are associated with all-cause mortality. Int J Cardiol. 2011;150:361–4.
170. Anand IS, Rector TS, Kuskowski M, Adourian A, Muntendam P, Cohn JN. Baseline and serial measurements of galectin-3 in patients with heart failure: relationship to prognosis and effect of treatment with valsartan in the Val-HeFT. Eur J Heart Fail. 2013;15:511–8.
171. Pentassuglia L, Sawyer DB. ErbB/integrin signaling interactions in regulation of myocardial cell-cell and cell-matrix interactions. Biochim Biophys Acta. 2013;1833(4):909–16.
172. Slamon DJ, Leyland-Jones B, Shak S, et al. Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. N Engl J Med. 2001;344:783–92.
173. Ky B, Kimmel SE, Safa RN, et al. Neuregulin-1 beta is associated with disease severity and adverse outcomes in chronic heart failure. Circulation. 2009;120:310–7.

174. Jabbour A, Hayward CS, Keogh AM, et al. Parenteral administration of recombinant human neuregulin-1 to patients with stable chronic heart failure produces favourable acute and chronic haemodynamic responses. Eur J Heart Fail. 2011;13:83–92.
175. Mann DL. MicroRNAs and the failing heart. N Engl J Med. 2007;356:2644–5.
176. van Rooij E, Sutherland LB, Liu N, et al. A signature pattern of stress-responsive microRNAs that can evoke cardiac hypertrophy and heart failure. Pro Nat Acad Sci USA. 2006;103:18255–60.
177. Mitchell PS, Parkin RK, Kroh EM, et al. Circulating microRNAs as stable blood-based markers for cancer detection. Pro Natl Acad Sci U S A. 2008;105:10513–8.
178. Tijsen AJ, Creemers EE, Moerland PD, et al. MiR423-5p as a circulating biomarker for heart failure. Circ Res. 2010;106:1035–9.
179. Goren Y, Kushnir M, Zafrir B, Tabak S, Lewis BS, Amir O. Serum levels of microRNAs in patients with heart failure. Eur J Heart Fail. 2012;14:147–54.
180. Tutarel O, Dangwal S, Bretthauer J, et al. Circulating miR-423_5p fails as a biomarker for systemic ventricular function in adults after atrial repair for transposition of the great arteries. Int J Cardiol. 2013;167:63–6.
181. Fukushima Y, Nakanishi M, Nonogi H, Goto Y, Iwai N. Assessment of plasma miRNAs in congestive heart failure. Circ J. 2011;75:336–40.
182. Corsten MF, Dennert R, Jochems S, et al. Circulating MicroRNA-208b and MicroRNA-499 reflect myocardial damage in cardiovascular disease. Circ Cardiovasc Genet. 2010;3: 499–506.

Chapter 2
Hemodynamics and Heart Failure

Gary S. Ledley, Shahzad Ahmed, Haile Jones, Steven J. Rough, and Peter Kurnik

Introduction

Every year in the United States, there are approximately 550,000 newly diagnosed heart failure patients. Five million patients suffer from chronic heart failure. Acute heart failure exacerbation is the leading cause for hospitalization in Medicare patients over the age of 65. A fundamental understanding in the definition, etiology, pathophysiology and hemodynamics has led to advances in treatments.

G.S. Ledley, MD
Drexel University College of Medicine, Department of Internal Medicine, Division of Cardiology, Mail Stop 470 245 North 15th Street, Philadelphia, PA 19102, USA
e-mail: gledley@drexelmed.edu

S. Ahmed, MD
Hahnemann University Hospital, Drexel University College of Medicine, Division of Cardiology, Mail Stop 470 245 North 15th Street, Philadelphia, PA 19102, USA
e-mail: shahzad.ahmed@drexelmed.edu

H. Jones, MD
Interventional Cardiology, Halifax Regional Cardiology, 306 Becker Drive, Roanoke Rapids, NC 27870, USA

S.J. Rough, MD
Interventional Cardiology, Sweetwater Medical & Cardiovascular Institute, 1615 Sweetwater Road Suite D, National City, CA 91950, USA

P. Kurnik, MS, MD (✉)
Division of Cardiology, Diagnostic and Interventional Cardiology, Drexel University College of Medicine, Mail Stop 470 245 North 15th Street, Philadelphia, PA 19102, USA
e-mail: pkurnik@drexelmed.edu

H. Eisen (ed.), *Heart Failure*, DOI 10.1007/978-1-4471-4219-5_2

Definition

The complete definition of heart failure is not confined solely to the heart, but involves a complex interplay between the heart and other organs. Definitions in heart failure have mainly focused on impaired pump function and clinical manifestations of venous congestion. Katz [1] states "*heart failure is a clinical syndrome in which heart disease reduces cardiac output, increases venous pressures, and is accompanied by molecular and other abnormalities that cause progressive deterioration of the failing heart*".

Etiology

The end result of heart failure is caused by a multitude of disease abnormalities. Damage to the heart varies in its clinical presentation, systemic effects on the body, in treatment and prognosis. Ischemic heart disease, pulmonary hypertension, systemic hypertension, primary heart muscle abnormalities and valvular abnormalities are a few of the causes of heart failure (Table 2.1) [2].

Clinical Presentation

Heart failure can be classified as acute or chronic, compensated or decompensated, and combinations of these variables. History and physical examination skills are paramount to diagnosis in patients presenting with heart failure and their correlation

Table 2.1 Common etiologies of heart failure

Coronary heart disease	Acute coronary syndromes
Hypertension	Often associated with left ventricular hypertrophy and preserved ejection fraction
Cardiomyopathies	Familial/genetic or non-familial/non-genetic (including acquired, e.g. myocarditis)
	Hypertrophic (HCM), dilated (DCM), restrictive (RCM), arrhythmogenic right ventricular (ARVC), unclassified
Drugs	β-Blockers, calcium antagonists, antiarrhythmics, cytotoxic agents
Toxins	Alcohol, medication, cocaine, trace elements (mercury, cobalt, arsenic)
Endocrine	Diabetes mellitus, hypo/hyperthyroidism, Cushing syndrome, adrenal insufficiency, excessive growth hormone, phaeochromocytoma
Nutritional	Deficiency of thiamine, selenium, carnitine. Obesity, cachexia
Infiltrative	Sarcoidosis, amyloidosis, haemochromatosis, connective tissue disease
Others	Chagas' disease, HIV infection, peripartum cardiomyopathy, end-stage renal failure

Reprinted from Dickstein et al. [2], © 2008, by permission of Oxford University Press

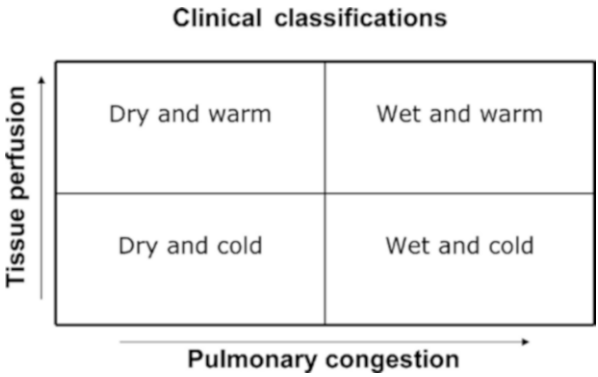


Fig. 2.1 Correlation of hemodynamic profile and invasive hemodynamic findings (Reprinted from Dickstein et al. [2], © 2008, by permission of Oxford University Press)

to invasive hemodynamic alterations. Since the results from the Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness (ESCAPE) trial, the routine use of the invasive pulmonary artery catheter has largely fallen out of favor. Although the trial demonstrated no changes in primary endpoint with the routine utilization of right heart catheterization, there were correlations in the accuracy of jugular venous pressure (JVP) and right atrial pressure. An elevation of left ventricular filling pressures was associated with the findings of orthopnea and increased JVP. Discharge assessment of fluid status via elevated JVP and orthopnea ("wet") or decreased cardiac output with reduced perfusion ("cold") correlated with a 50 % increase in risk of death or re-hospitalization at 6 months [3, 4]. Invasive pulmonary artery catheter hemodynamic assessment is utilized to aid in the understanding and diagnosis of pathophysiology in patients that do not respond to typical initial treatments (Fig. 2.1) [2]. Recognition of these hemodynamic characteristics can lead to alteration in therapeutic decision making.

Acute Decompensated Heart Failure

A decrease in EF due to ischemia or infarction results in primary pump failure. Acutely depressed LV function results in depressed cardiac output and venous congestion.

As the heart suffers a decrease in pump capacity there is an increase in the pressures of the venous system. The increase in venous pressure is a result of the inability of the heart to adequately accept the blood returning to the heart. Right and left atrial pressures increase. These hemodynamic alterations from a decrease in cardiac output occur within a few seconds. With the inability of a low cardiac output to provide adequate systemic perfusion, there is a response in the compensatory mechanism that results in an increase in sympathetic nervous tone.

Sympathetic stimulation results from a complex system of neurohormonal feedback. A decrease in pump function results in lower systemic arterial pressure that in turn activates the baroreceptor reflex mechanism. Ischemic heart responses,

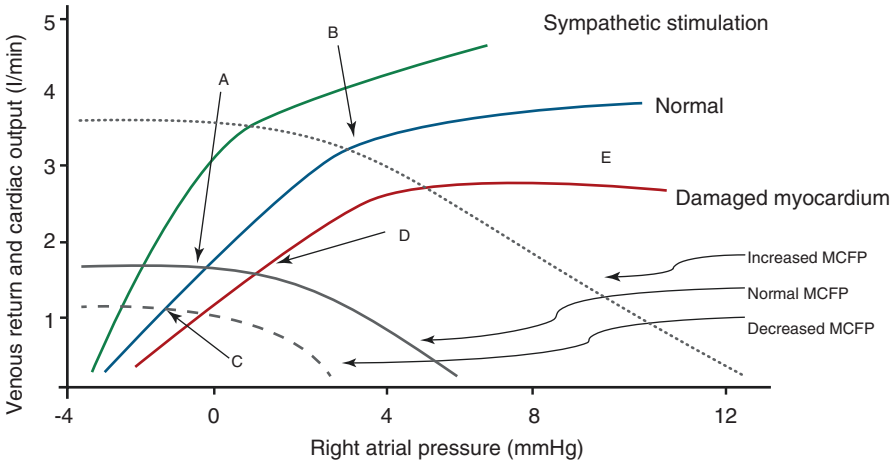


Fig. 2.2 Cardiac output and right atrial pressure relationship with varying myocardial functional states (Reprinted from Guyton [5], © 1955, with permission from The American Physiological Society)

intracardiac reflexes, and other components of this feedback system contribute to sympathetic nervous system activation. Parasympathetic inhibition and sympathetic stimulation occurs within a few seconds to compensate for the acute fall in cardiac output. As sympathetic simulation occurs, the target and main effects are to the peripheral vasculature and the heart. An increase in cardiac function occurs with sympathetic stimulation to increase the recruitment of cardiac reserves within the normal and the remaining partially functional damaged myocardium. If there is diffuse damage to the ventricular myocardium during an ischemic insult, there is strengthening in the remaining functional myocytes via sympathetic stimulation. If there is no function of a portion of the ventricle, sympathetic stimulation results in the stimulation of the remaining normal myocardium. The normal myocardium attempts to compensate for the shortcomings of the damaged myocardium.

In addition to increasing myocardial muscle function, sympathetic stimulation leads to changes in the peripheral vasculature. This increase in tone in the peripheral vessels, leads to an increase in venous return. The mean systemic filling pressures are elevated increasing the flow from the venous system to the heart. The increased flow leads to increased filling of the damaged heart that in turn leads to increase in priming the heart to aid in pump function. Less than a minute in needed for the sympathetic nervous system to be completely activated (Fig. 2.2) [5, 6].

Chronic Heart Failure

The ischemic insult is followed by no, partial, or full recovery over weeks to months. In addition to ventricular myocardial recovery, fluid retention via renal mechanisms also occurs to compensate for this new cardiac pump status and alters the normal

Table 2.2 Normal hemodynamic parameters

Normal hemodynamic parameters		Pressure (mmHg)
Right atrium	*a*-wave / *v*-wave / mean	1–7 / 1–7 / 0–5
Right ventricle	Systolic / end diastolic	17–32 / 1–7
Pulmonary artery	Systolic / end diastolic	17–32 / 1–7
Left atrium	*a*-wave / *v*-wave / mean	4–12 / 4–15 / 4–15
Left ventricle	Systolic / end diastolic	90–140 / 5–12
Aorta	Systolic / end diastolic / mean	90–140 / 60–90 / 70–105

Reprinted with permission from Leopold and Faxon [7], © 2015, McGraw-Hill Education

physiologic hemodynamics found in invasive assessments (Table 2.2) [7]. Renal function is extremely sensitive to alterations in perfusion. A low cardiac output state can lead to a decline in renal function manifested to the point of anuria. The decrease in urine output can persist until there is normalization in systemic blood pressure and cardiac output.

Blood volume is altered via renal mechanisms to affect cardiac function. Initially, moderate retention of fluid results in an increase in blood volume that is beneficial to the diminished pumping function of the heart. The increase in fluid retention increases venous return, thereby increasing blood flow to the heart.

As the damaged heart receives the increased venous return, there is a gain of cardiac function. If cardiac output becomes too low, the kidneys respond with the inability to excrete adequate amounts of sodium and water. Excess fluid retention is no longer beneficial to myocardial function, and only serves to increase cardiac workload in the damaged heart and manifests as edema.

Extravasation of fluid from the pulmonary vasculature leading to hypoxia from pulmonary edema, and systemic edema develops in various organs and contributes to their dysfunction. Myocardial functional recovery can range from full to none. After partial recovery there is fluid retention that occurs to establish a new hemodynamic state. The increase in blood volume results in an increase in venous return that provides assistance in the pumping function of the heart. The elevated venous pressure persists as the cardiac output improves. As this new steady state is established and this resting cardiac output improves, the sympathetic tone progressively abates over several weeks following an acute ischemic insult. Altered renal function that results in fluid retention persists in this new hemodynamic state. As the pumping function of the heart compensates, the sympathetic tone begins to gradually decrease transitioning from an acute phase to a chronic heart failure state.

Compensated and De-compensated Chronic Heart Failure

As partial recovery of the ventricular myocardial function occurs, the resting pump output from the heart normalizes with the help of an increase in atrial pressure. This increased filling pressure helps in recruitment of myocardium and improved output

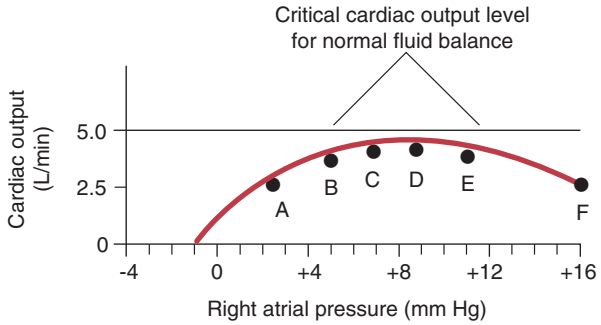


Fig. 2.3 The rise and fall of cardiac output as right atrial pressure increases. Further increase in RAP leads to a decline in cardiac output (Reprinted from Hall [8], © 2016, with permission from Elsevier)

in the resting state. As a patient begins to exercise, the already maximized heart lacks reserve and symptoms of heart failure return. The lack of cardiac reserve is a common occurrence in heart failure patients as they achieve a resting compensated state and attempt to demand more cardiac output with exercise or systemically stressed state.

In severe cardiac failure, de-compensation occurs as a consequence of the inability of the heart to provide additional cardiac output when there are increased systemic demands. Neither sympathetic stimulation nor fluid retention can increase cardiac output to normal. Fluid retention results as the heart is unable to provide sufficient blood flow to the kidneys to excrete sodium and water.

Correlation of cardiac output on the ***y*** axis and the atrial filling pressures on the ***x*** axis is represented in Fig. 2.3 [8]. As a poorly functional ventricle responds to gradually increasing filling pressures, the cardiac output rises. After a certain point of maximal myocardial stretch, cardiac output falls and higher filling pressures no longer provide additional aid in cardiac function. A progressive increase in fluid retention increases filling pressures beyond the ideal ventricular size and dilatation with overstretching ensues. As progressive increases in fluid retention occur, the mean systemic filling pressures are translated to the heart, which then leads to the gradual rise and fall of cardiac output.

If the cardiac output never reaches a point of providing sufficient perfusion, specifically to the kidney, then cardiac failure is imminent, leading to systemic edema and pulmonary edema, hypoxia, pump failure and eventually death.

Pathophysiology

The Frank-Starling mechanism or Starling's Law of the heart dictates that with increasing volume in the heart there is an increase in myocardial performance that includes an increased stroke volume (Fig. 2.4) [9]. This is a manifestation of the

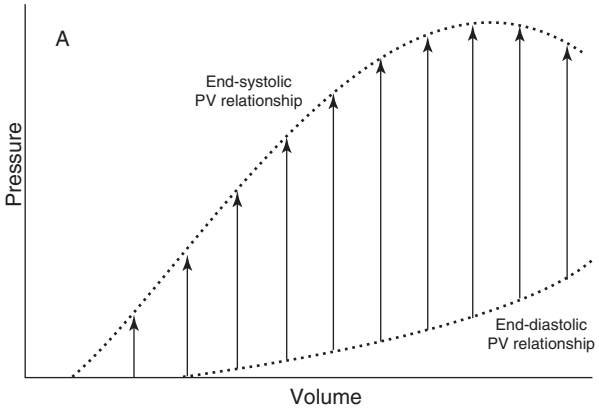


Fig. 2.4 Pressure-volume relationship within the left ventricle. As end diastolic volume increases, resulting end diastolic and systolic pressures increase (Reprinted with permission from Katz [9], © 2011, with permission from Wolters Kluwer Health)

sarcomere length-tension relationship. As the ventricle fills with blood there is distention of cardiac myocytes and less sarcomere overlap. As the myocytes are "stretched", the heart is able to increase the volume of blood it ejects. After the optimal point of overlap, the ventricle can be overstretched leading to a decrease in the amount of volume ejected from the heart. The ascending portion of the Starling curve illustrates how the increase in preload leads to the increase in cardiac output. Ventricular over filling can be detrimental. End diastolic pressures rise, and the overly "stretched" myocardium transitions to the descending portion of the Starling curve and a decrease in stroke volume and systolic pressure.

Valvular Heart Failure

Normal valvular function provides a mechanism for unidirectional flow without resistance. The limitation of blood flow during diastole or systole is cause by a stenosis in the atrio-ventricular or ventricular-arterial valves respectively.

Valvular Stenosis

Aortic stenosis and pulmonic stenosis result in a decrease in cardiac output due to increased resistance to emptying of the ventricle. This increase in resistance to cardiac output results in a measurable pressure gradient across the valve which can be measured via a dual lumen pigtail catheter, separate aortic root and left ventricular catheters, or arterial sheath and left ventricular catheter. In aortic stenosis with

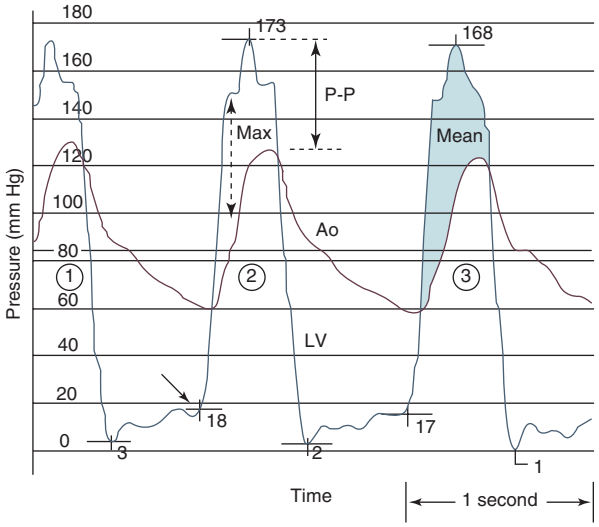


Fig. 2.5 Transaortic pressure gradient. The gradient between the left ventricle (LV) and the aorta (Ao) in aortic stenosis can be described by three invasive measures. The mean gradient (beat #3) represents the area under the left ventricular–aortic pressure curve. The peak-to-peak (P-P) gradient (beat #2) is the difference between the maximum aortic pressure and the maximum left ventricular systolic pressure. The maximum (*Max*) gradient (beat #2) is the maximum difference that can be measured between the left ventricle and aorta during systole (Reprinted with permission from Shavelle [10], © 2014, with permission from Elsevier)

preserved left ventricular function, as the severity in aortic valvular stenosis increases, there is an increase in the LV chamber pressure generation. Aortic and left ventricular pressure tracings are used to measure peak to peak, maximum, and mean pressure gradients (Fig. 2.5) [10]. With the advent of increased diagnostic accuracy of echocardiography, the utilization of direct hemodynamic measurement is most strongly indicated when there is a discrepancy between clinical and echocardiographic findings.

After analysis of hemodynamic tracings, the Gorlin formula is utilized in the calculation of aortic valve area. Special circumstances with decreased systolic function, "low-output, low gradient aortic stenosis", are a subset of patients that pose diagnostic dilemmas.

Differentiation of *pseudo* aortic stenosis from true aortic stenosis in the setting of decreased cardiac output is crucial in effective management of the patient. Three particular scenarios are made apparent during dobutamine infusion with simultaneous aortic and left ventricular hemodynamic tracings obtained.

Illustrated in Fig. 2.6 is the potential findings during dobutamine challenge in patients with "low-output, low gradient" aortic stenosis [10, 11].

The far left clinical scenario both cardiac output and aortic valve mean gradient increase as a result of dobutamine infusion, thus true aortic stenosis. The middle scenario finds an increase in cardiac output with no dramatic increase in aortic valve

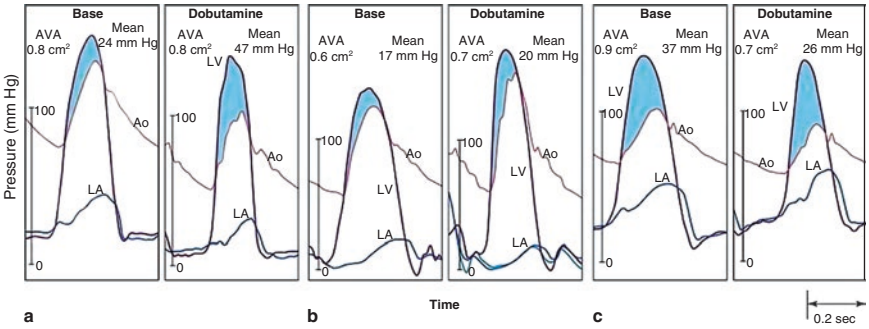


Fig. 2.6 Differentiation of three invasive measurement scenarios as a result of dobutamine infusion in "low-output, low gradient" aortic stenosis (Reprinted with permission from Nishimura et al. [11], © 2002, with permission from Wolters Kluwer Health. And reprinted with permission from Shavelle [10], © 2014, with permission from Elsevier)

pressure gradient, a finding of mild aortic stenosis. In the right most clinical scenario, there was no change in the aortic valve pressure gradient as a result of dobutamine infusion, truly severe aortic stenosis.

In addition to valvular stenosis that limits cardiac output, is valvular stenosis that limits cardiac filling. Mitral and tricuspid valvular stenosis affects the ability to provide adequate chamber preload. Hemodynamic findings result in an elevation in PCWP but inaccurately reflect LVEDP. PCWP in mitral stenosis is reflection of left atrial pressure but not left ventricular end diastolic pressure. Mitral stenosis results in a pressure gradient between the left atrium and the left ventricle. The classic finding on hemodynamic tracings is the elevation of pulmonary pressures, prominent "a" and "v" waves on PCWP (Figs. 2.7a, b) [12]. Simultaneous tracings within the left ventricle reveal an evident pressure gradient between PCWP and LVEDP.

One must take into account the temporal delay as the pressure of the fluid column is transmitted to the right heart catheter from the left atrium through the pulmonary vascular bed. It is therefore ideal to obtain a direct measurement of left atrial pressure via septal puncture with simultaneous left ventricular hemodynamic tracings (Fig. 2.7c) [13].

Valvular Regurgitation

Aortic valvular regurgitation results in an increase in LV diastolic pressures. Acute aortic regurgitation results in the acute volume overload of the left ventricular chamber, this in turn leads to pulmonary edema, premature closure of the mitral valve and can also result in systemic shock (Fig. 2.8) [12].

Chronic aortic regurgitation results in a wide pulse pressure, high systolic and low diastolic pressures. In chronic, compensated aortic valve regurgitation, the left ventricle and systemic hemodynamics have had time to adjust, thus resulting in a

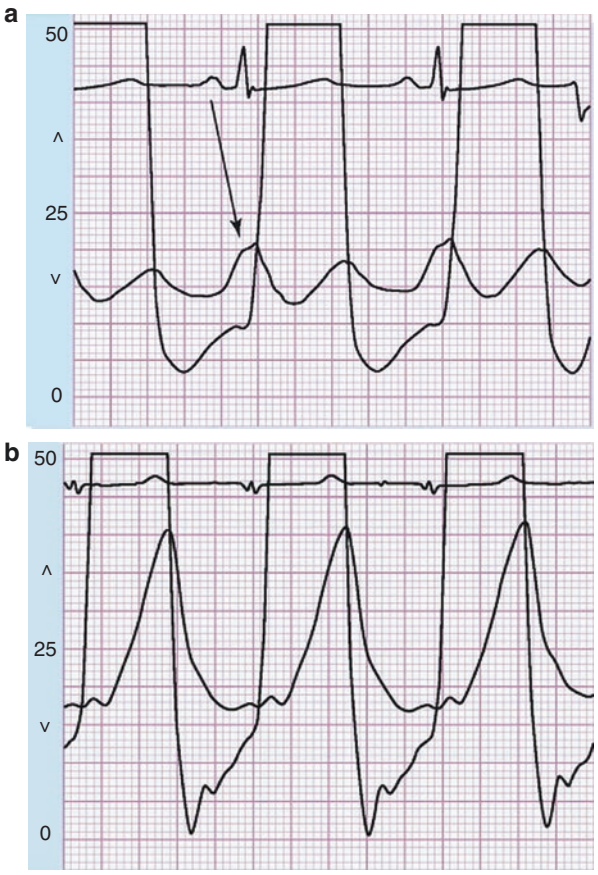


Fig. 2.7 (**a**) The "a" wave on a left atrial (shown here) or pulmonary capillary wedge pressure is accentuated in mitral stenosis (Reprinted with permission from Ragosta [12], © 2010, with permission from Elsevier) (**b**) The "v" wave may also be markedly increased in patients with mitral stenosis. This patient with mitral stenosis has no mitral regurgitation and normal systolic function (Reprinted with permission from Ragosta [12], © 2010, with permission from Elsevier) (**c**) Measurement of the transmitral gradient by cardiac catheterization is frequently made with a simultaneous pulmonary artery wedge pressure (PAWP) and left ventricular (LV) pressure. However, as a result of the delay in transmission of the change in pressure contour and a phase shift, the gradient using a pulmonary artery wedge pressure will frequently overestimate the true transmitral gradient. *Left*, Simultaneous left ventricular and pulmonary artery wedge pressure in a patient with mitral stenosis. The measured mean gradient is 15 mmHg. *Right*, In the same patient, the transmitral gradient is measured with a left ventricular and direct left atrial (LA) pressure. The true mean transmitral gradient is only 6 mmHg (Reprinted with permission Nishimura and Carabello [13], © 2012, with permission from Wolters Kluwer Health)

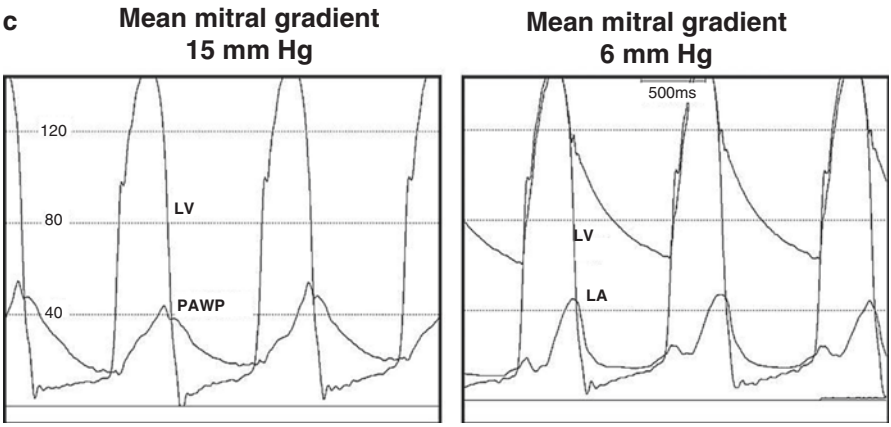


Fig. 2.7 (continued)

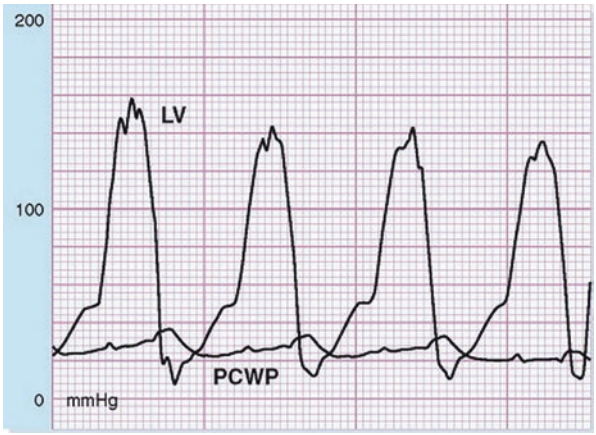


Fig. 2.8 Acute severe aortic valvular regurgitation resulting in LVEDP > PCWP (Reprinted with permission from Ragosta [12], © 2010, with permission from Elsevier)

normal early LVEDP. As the cardiac cycle approaches the end of the diastolic filling period, the LVEDP approaches the level of diastolic pressure. The rise of LVEDP to meet diastolic pressure is known as diastasis (Fig. 2.9) [10].

Similarly, chronicity of mitral valvular regurgitation determines the findings on hemodynamic tracings. Acute mitral valvular regurgitation results in pulmonary edema and prominent "*v*" waves on PA and PCWP hemodynamic tracing illustrated with simultaneous Aortic hemodynamic tracings (Fig. 2.10) [14].

Chronic valvular regurgitation may not manifest with the classic finding of prominent "v" waves on PCWP and pulmonary artery tracings as in acute mitral regurgitation. The presence of prominent of "v" waves is determined by the compliance of the left atrium in addition to its size and pressure. Given this, chronic mitral regurgitation and may manifest as normal physiologic "v" waves on hemodynamic tracings.

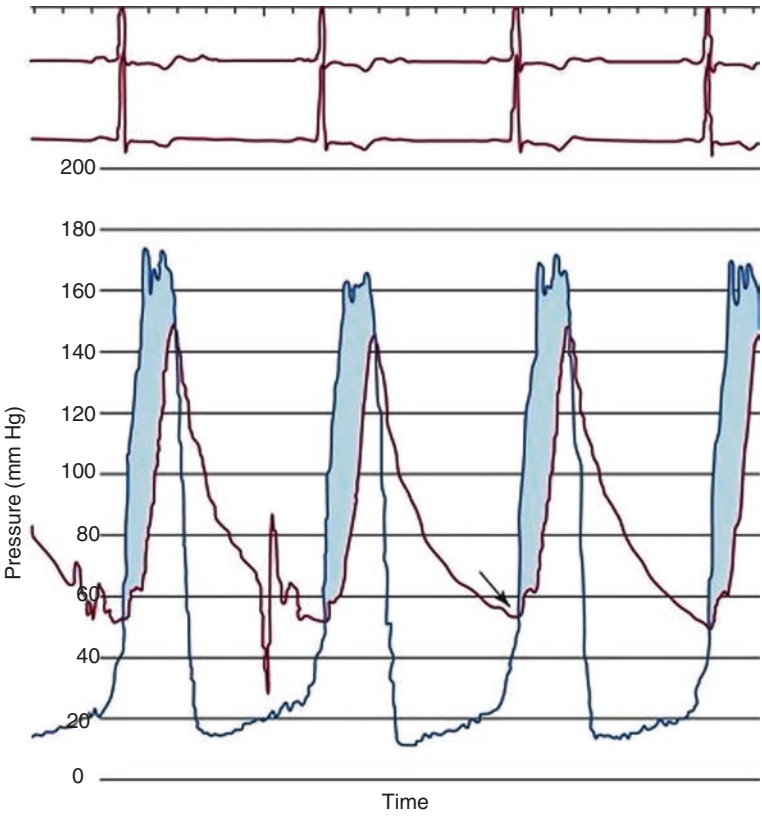


Fig. 2.9 Hemodynamics in severe aortic regurgitation. Simultaneous aortic and left ventricular pressures in a patient with mild aortic stenosis and severe aortic regurgitation. Note that the pulse pressure is wide (approximately 100 mmHg) and the aortic diastolic pressure (*arrow*) is low (Reprinted with permission from Shavelle [10], © 2014, with permission from Elsevier)

Unilateral Heart Failure

There are unique clinical presentations of unilateral heart failure that alter the hemodynamics related to the affected ventricle, specifically left sided heart failure in absence of right sided heart failure and vice versa.

Left sided heart failure in isolation, with normally functioning right sided ventricle leads to an increase in mean pulmonary artery pressures. In the setting of inadequate left ventricular pump function, the blood accumulates in the pulmonary vasculature and the backup in volume shifts from the systemic arterial circulation to the pulmonary vasculature. Pulmonary vasculature capillary pressures rise as a consequence of increased volume. Fluid accumulation in the pulmonary bed gradually rises to a point where the capillary network can no longer tolerate the additional fluid and begins to leak out into the interstitium. With the rise in pulmonary

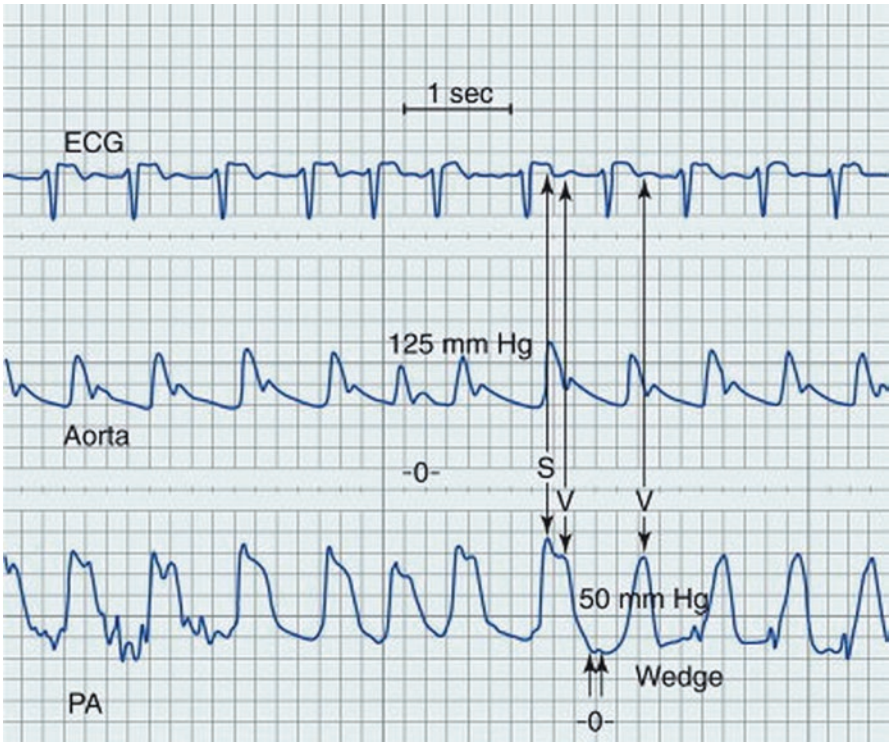


Fig. 2.10 Acute severe mitral regurgitation. Electrocardiogram (ECG), aortic (Aorta), pulmonary artery (PA) pressure (*left*), and pulmonary capillary wedge (wedge) pressure (*right*) tracings in a patient with acute severe mitral regurgitation. A prominent v wave is present in both the pulmonary artery and wedge pressure tracings. The pulmonary artery pressure is bifid because of the presence of both the pulmonary artery systolic wave (S) and the v wave. The large v wave can cause the wedge tracing to be confused with a pulmonary artery tracing (Reprinted from Sharkey [14], © 1987, with permission from Elsevier)

pressures beyond the ability of the capillary bed to hold in the fluid via osmotic mechanisms, pulmonary edema is manifested clinically as rales and dyspnea. The clinical presentation of severe pulmonary edema in the setting of acute myocardial infarction and cardiogenic shock can be dramatic resulting in profound hypoxia in less than an hour.

Isolated right ventricular failure results in a gradual increase in systemic venous pressures and a loss of preload to the left ventricular side. Right and left ventricular interdependence is a key concept in understanding the pathophysiologic alterations in hemodynamics of isolated right ventricular dysfunction. In acute right ventricular infarction, the systolic function of the pump is compromised. As right sided ventricular dysfunction occurs, right sided chamber dilatation along with a fall in systolic pressures occurs. The diastolic filling pressure of the ventricle rises and demonstrates a characteristic prominent "y" descent manifested as a dip and plateau on hemodynamic tracings (Fig. 2.11) [15].

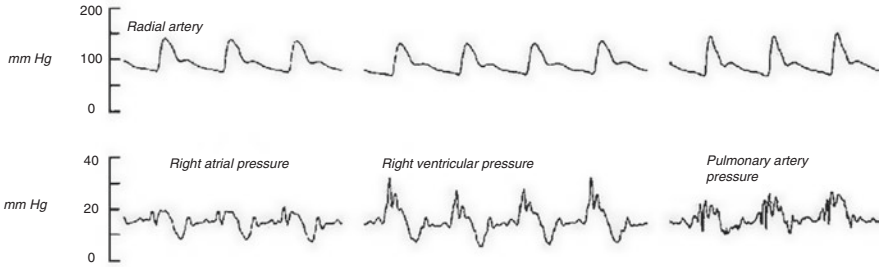


Fig. 2.11 Right ventricular infarction hemodynamic tracings (Reprinted from Lorell et al. [15], © 1979, with permission from Elsevier)

The depressed ventricular function leads to an increase in right atrial filling pressures and a backup into venous system. Acute right ventricular chamber dilatation encroaches upon the left ventricular chamber filling. As the shared space within the pericardium is fixed, acute RV dilation results in a decrease in LV chamber filling. The enhancement of the right and left interdependence is manifested dramatically as hypotension, clear lung fields, prominent JVD all mimicking the syndrome of pericardial constriction. Experimental models of isolated RV infarct have demonstrated the inability to induce hypotension in animals where the pericardium is surgically absent. Without acute reperfusion and hemodynamic support RV infarction can be life threatening.

Constrictive Pericarditis and Restrictive Cardiomyopathy

Restrictive cardiomyopathy is a rare form of cardiomyopathy in which the ventricle becomes abnormally rigid and lacks the flexibility to adequately expand as it fills with blood. This leads to venous congestion and heart failure.

It has distinct morphologic features allowing it to be separated from other cardiomyopathies. For example with restriction the left ventricle is usually normal in size and function unlike dilated or hypertrophic cardiomyopathies. A syndrome that poses a diagnostic dilemma with restrictive cardiomyopathy is constrictive pericarditis. They both exhibit normal ventricular size and function as well as some similar hemodynamic abnormalities.

It is extremely important for the clinician to be able to distinguish between constrictive pericarditis and restrictive cardiomyopathy since they require markedly different treatment. In some cases, invasive cardiac catheterization may be necessary to help differentiate the two. In addition the hemodynamic features of restrictive cardiomyopathy and constrictive pericarditis can be similar to tamponade and right ventricle infarction. This section will discuss the hemodynamics of these entities and how the hemodynamics can be used and differentiate between them.

Constrictive Pericarditis

Constrictive pericarditis is the end-stage of an inflammatory process affecting the pericardium, resulting in scarring and subsequent loss of the normal elasticity of the pericardial sac. In the developed world idiopathic or viral illness is the most common cause followed by post-surgical and radiation therapy (Table 2.3) [16–19].

Pathophysiology

The pericardium is a fluid filled fibro-elastic sac that surrounds the heart. It functions to keep the heart contained in the chest cavity and stretches to accommodate physiologic changes in cardiac volume [20, 21]

In constrictive pericarditis, the total cardiac volume is fixed as a result of the non-compliant shell around the heart. The abnormal pericardium prohibits outward ventricular expansion, which is necessary to accommodate venous return. As a result, an adaptive process occurs in which the inter-ventricular septum bulges inward either into the left or right ventricle in order to accommodate myocardial blood flow into the adjacent ventricle. This maladaptive process will allow filling in one ventricle while compromising blood flow into the other. This is known as ventricular interdependence, since the amount of blood flow into one ventricle is dependent on the amount of blood flow into the other.

Ventricular interdependence is the result of the rigid pericardium, which prevents the normal reduction in intra-thoracic pressure during inspiration from being transmitted to the heart chambers. As a result during inspiration pulmonary venous pressure will decrease while left ventricular pressure remains constant. This ultimately leads to a reduction in the gradient driving filling into the LV. Reduction in LV volume allows RV filling to occur. As the RV fills, the inter-ventricular septum will

Table 2.3 Causes of constrictive pericarditis

Idiopathic
Irradiation
Postsurgical
Infectious
Neoplastic
Autoimmune(connective tissue) disorders
Uremia
Post trauma
Sarcoid
Methylsergide therapy
Implantable defibrillator patches

Reprinted from LeWinter and Hopkins [19], © 2015, with permission from Elsevier

shift toward the left further reducing LV filling. This septal shift occurs because outward expansion is not possible due to the constraining effects of the rigid pericardium.

During expiration the opposite sequence will occur. Pulmonary venous pressures will rise resulting in an increased trans-pulmonary gradient into the LV. As LV fillings increases the inter-ventricular septum will bulge to the right resulting in decrease flow into the RV (Fig. 2.12) [19].

With constrictive pericarditis, early diastolic filling is preserved since it is a myocardial process and not dependent upon a functioning pericardium. In fact, early filling occurs even more rapidly than normal due to elevated atrial pressures and increased suctioning form the ventricle. However; in early to mid-diastole, ventricular filling will cease abruptly due to the non-compliant pericardium. Consequently, almost all filling occurs in early diastole and systemic venous congestion results causing peripheral edema, hepatic congestion, and ascites.

Typical constrictive physiology will be evident on right atrial and left ventricle pressure recording at the time of cardiac catheterization. During early diastole the ventricular pressure initially decreases rapidly causing a steep y descent on the right atrial pressure waveform. In mid to late diastole flow abruptly ceases which is evident as a plateau after the initial downward dip (Fig. 2.13) [19, 22].

In patients with constriction right and left heart pressure recording should be performed simultaneously. Typical measurements will reveal elevated and equal RA, RV diastolic, LV diastolic, and pulmonary wedge pressures. The fillings pressures are typically elevated at approximately 20 mmHg with no more than a 3–5 mmHg difference. The RA pressure will show a preserved x descent and prominent y descent. Both

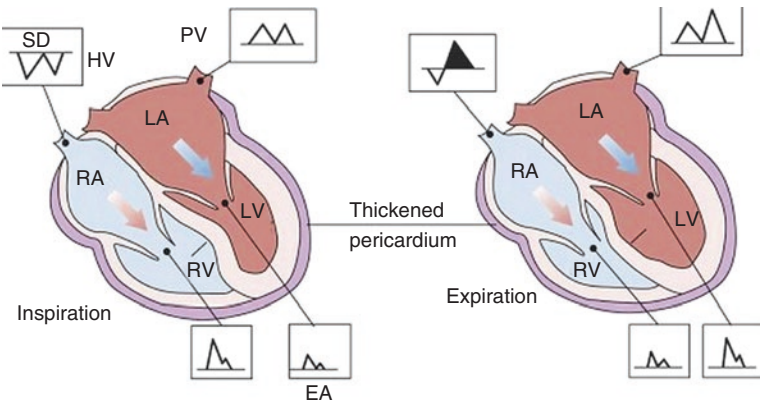


Fig. 2.12 Schematic representation of transvalvular and central venous flow velocities in constrictive pericarditis. During inspiration the decrease in LV filling results in a leftward septal shift that allows augmented flow into the right ventricle. The opposite occurs during expiration. *D* diastole, *EA* mitral inflow, *HV* hepatic vein, *LA* left atrium, *LV* left ventricle, *PV* pulmonary venous flow, *RA* right atrium, *RV* right ventricle, *S* systole (Reprinted from LeWinter and Hopkins [19], © 2015, with permission from Elsevier)

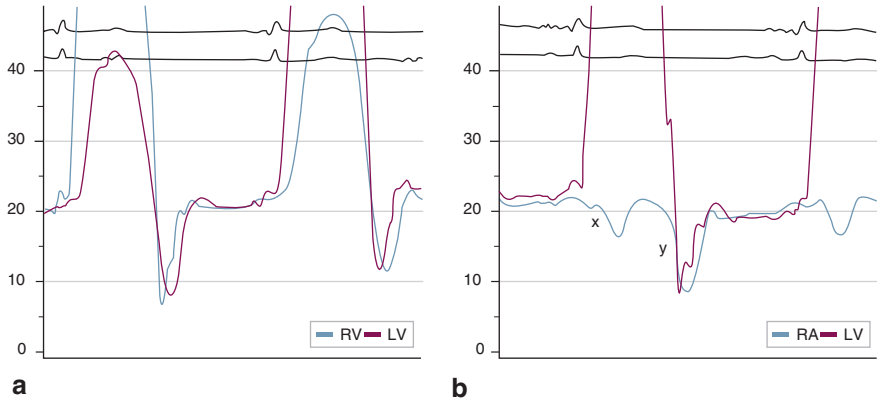


Fig. 2.13 Pressure recording in a patient with constrictive pericarditis. (**a**) Simultaneous LV and RV pressure tracing with the "dip-and-plateau waveform" or "square root sign" seen on right or left ventricular pressure waveform tracings. The black arrow represents the rapid descent, and the white arrow represents the plateau portion. (**b**) Right atrial pressure with prominent Y descent (Reprinted from Vaitkus et al. [22], © 1996, with permission from Wolters Kluwer Health, Inc. and Reprinted from LeWinter and Hopkins [19], © 2015, with permission from Elsevier)

RV and LV pressure tracings will show a early diastole dip followed by a plateau in mid to late diastole. Pulmonary hypertension is not usually a feature of constriction. The PA pressures are typically between 35-40 mmHg. If hypovolemia is present rapid volume challenge of 1000 cc may help to reveal typical hemodynamic features, which can be masked when fillings pressures are low [21, 23].

Clinical Presentation

Constrictive pericarditis can present with a myriad of symptoms, thus making a diagnosis solely on the basis of the clinical history is difficult. The usual presentation consists of predominantly right heart failure. Dyspnea is the most common presenting symptom and occurs in virtually all patients. Fatigue and orthopnea are common. Lower extremity edema and abdominal swelling are also common. Constrictive can mimic and be mistaken for other causes of right heart failure as well as end-stage liver disease. However it is important to note that in primary liver disease jugular venous pressures are not elevated.

The vast majority of patients with constriction have elevated jugular venous pressure. Elevated JVP has been reported in as many as 93 % of patients with surgically confirmed constrictive pericarditis. A pericardial knock, which corresponds with the sudden cessation of ventricular filling occurs in approximately half the cases. Kussmaul's sign, which is the lack of an inspiratory decline in JVP, can be present in patients with constrictive pericarditis, however it is nonspecific [17].

Table 2.4 Causes of restrictive cardiomyopathy

Hemochromatosis
Amyloidosis (most common cause in the United States)
Sarcoidosis
Scleroderma
Carcinoid heart disease
Glycogen storage disease of the heart
Radiation
Metastatic malignancy
Anthracycline toxicity

Restrictive Cardiomyopathy

Restrictive cardiomyopathy may be caused by various local and systemic disorders that may be categorized into 4 groups. They includes idiopathic, infiltrative, treatment-induced, and malignancy (Table 2.4) [24].

Clinical Presentation

Affected patients have signs and symptoms of pulmonary and systemic congestion resulting in dyspnea, peripheral edema, palpitations and fatigue. In advanced cases hepatosplenomegaly, ascites, and anasarca can occur from marked elevation in venous pressures.

Jugular venous pressure is generally elevated. Kussmaul's sign, which is the lack of an inspiratory decline in JVP, can be present. Also a prominent y descent may appear; however, it may not be obvious in patients with mild disease. The cardiovascular examination is often indistinguishable from that of constrictive pericarditis [25, 26].

Constrictive Pericarditis Versus Restrictive Cardiomyopathy

The history, physical examination, and radiographic findings may suggest a particular diagnosis. For example constrictive pericarditis may be suggested in patients with prior radiation or cardiothoracic surgery. Restrictive cardiomyopathy is more likely in a patient with a predisposing systemic disease such as amyloidosis. However, in many instances their clinical presentation and course overlap, making the ability to distinguish between the two syndromes difficult.

In some cases, invasive cardiac catheterization may be necessary to help differentiate (Table 2.5) [19].

Table 2.5 Hemodynamic features of constrictive vs restrictive cardiomyopathy

	Constriction	Restriction
Prominent Y descent	Present	Variable
Filling pressures >25 mmHg	Rare	Common
Pulmonary systolic pressure >60 mmHg	No	Common
Square root sign	Present	Variable
Respiratory variation in LV and RV pressure	Discordant	Concordant

Reprinted from LeWinter and Hopkins [19], © 2015, with permission from Elsevier

In both conditions, RV and LV diastolic pressure will be elevated. However in restrictive cardiomyopathy, the difference between diastolic pressures of the LV and RV normally exceed 3–5 mmHg. In constriction those pressures usually are within 3-5 mmHg of each other. Pulmonary hypertension is rare in constriction but common in restriction. The absolute level of diastolic pressure in restriction commonly exceeds 25 mmHg whereas in constriction pressure rarely exceeds 20 mmHg. [27].

One of the most sensitive ways to differentiate constrictive pericarditis from restriction is through the respiratory effects observed between the RV and LV systolic pressures. With constriction there is discordance between RV and LV systolic pressure with respiration due to ventricular interdependence. However, with restriction ventricular interdependence does not exist because the pericardium is normal. Thus in restriction RV and LV systolic pressure move concordantly with each other during the respiratory cycle (Fig. 2.14) [27].

Constriction Versus RV Infarction and Tamponade

Compressive hemodynamic effects resulting in diastolic dysfunction may be seen in other conditions besides constrictive pericarditis. In fact, any condition that causes elevated intra-pericardial pressure, i.e. from pericardial tamponade to abrupt chamber dilatation with RV infraction, will lead to increased intra-pericardial pressure and constrictive physiology. All three conditions including RV infarction may show elevation and equalization of diastolic filling pressures in the RA, RV, and PCW, as well as the LV [14, 15].

However, only constriction will exhibit dissociation between intra-thoracic and intra-cardiac pressures during the respiratory cycle (Fig. 2.15) [28]. Normally with inspiration the negative pressure created within the intra-thoracic cavity results in a simultaneous decrease in pulmonary and ventricular pressures. In constriction the rigid pericardium acts to isolate the heart leaving it unaffected from these physiologic changes. As a result only patients with constriction will exhibit dissociation between intra-thoracic and intra-cardiac pressures, which distinguishes it from RV infarction and tamponade where the LV and wedge pressures will rise and fall concordantly.

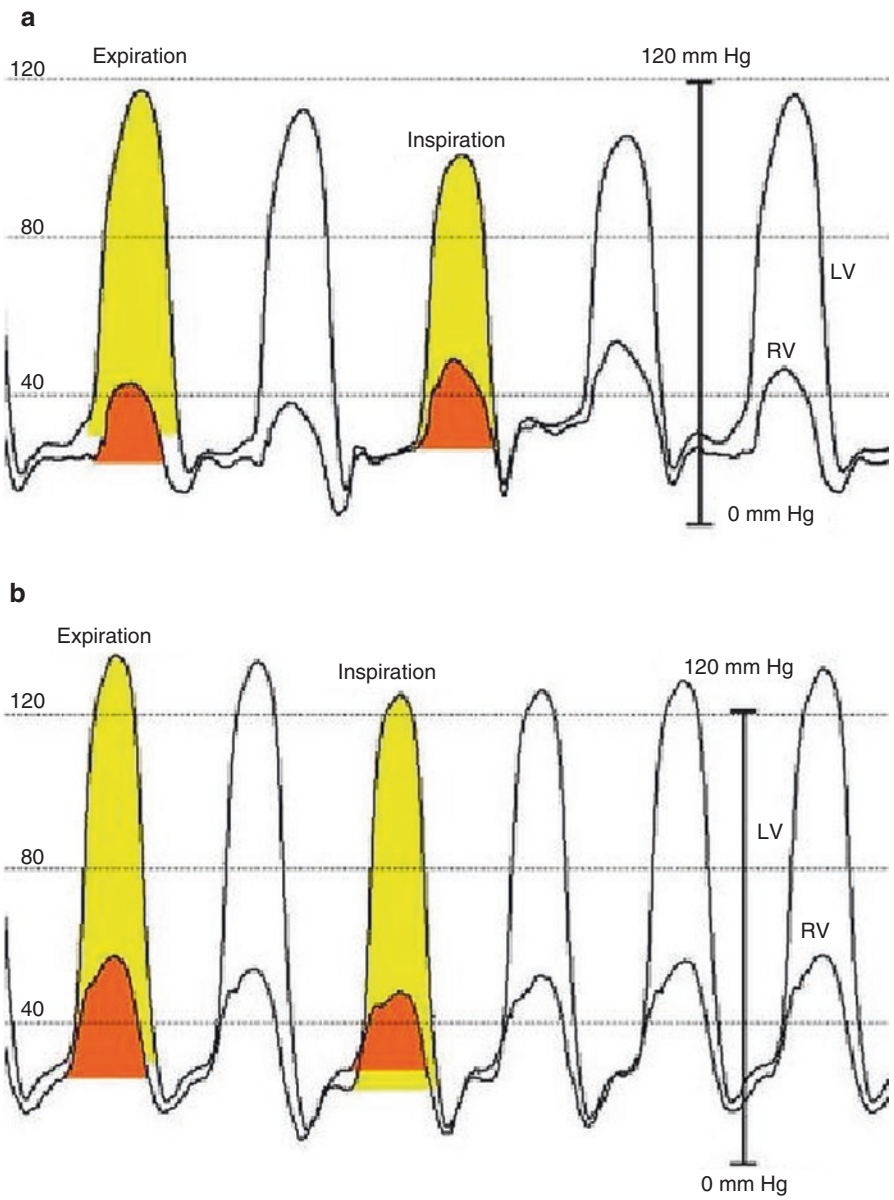


Fig. 2.14 LV and RV Pressure Recording From 2 Patients. During Expiration and Inspiration (**a**) With constrictive pericarditis LV and RV systolic pressure are discordant with respiration. During inspiration there is an increase in the RV pressure and a decrease in LV pressure. The opposite occurs during expiration (**b**) With restriction LV and RV systolic pressures are concordant during respiration. During inspiration there is a decrease in the RV pressure and a decrease in LV pressure. The opposite occurs during expiration (Reprinted from Talreja et al. [27], © 2008, with permission from Elsevier)

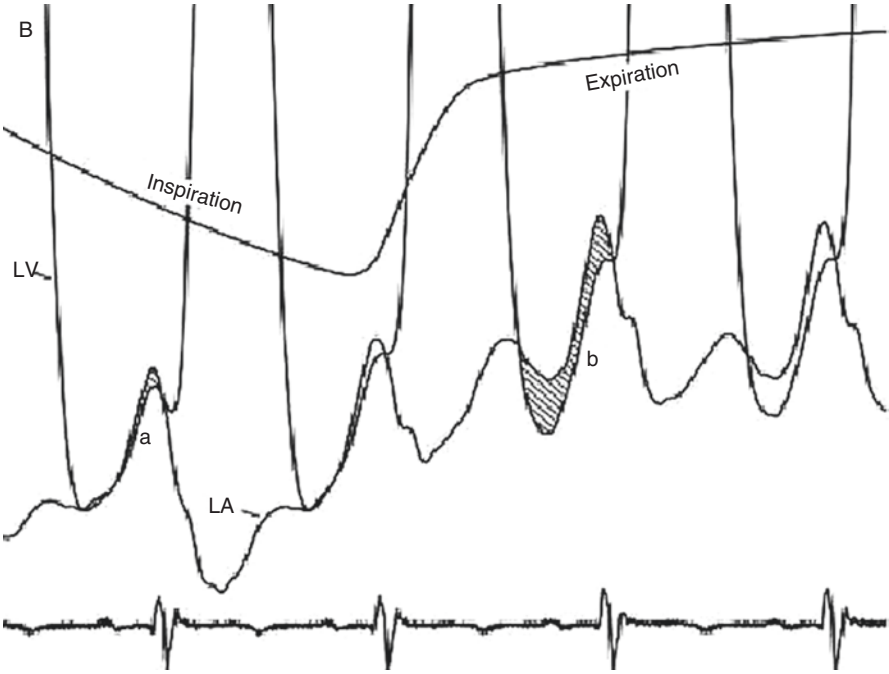


Fig. 2.15 Simultaneous pressure recording of LV and PCWP. There is significant respiratory change suggesting dissociation of intra-thoracic and intra-cardiac pressures (Reprinted from Doshi et al. [28], © 2015, with permission from Elsevier)

References

1. Katz AM. Heart failure: pathophysiology, molecular biology, and clinical management. 2 ed. Philadelphia: Lippincott Williams & Wilkins; 2009.
2. Dickstein K, Cohen-Solal A, Filippatos G, McMurray JJV, Ponikowski P, Poole-Wilson PA, ESC Committee for Practice Guidelines, et al. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2008: the Task Force for the diagnosis and treatment of acute and chronic heart failure 2008 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association of the ESC (HFA) and endorsed by the European Society of Intensive Care Medicine (ESICM). Eur Heart J. 2008;29(19):2388–442.
3. Drazner MH, Hellkamp AS, Leier CV, Shah MR, Miller LW, Russell SD, et al. Value of clinician assessment of hemodynamics in advanced heart failure: the ESCAPE trial. Circ Heart Fail. 2008;1(3):170–7.
4. Mehra MR. Optimizing outcomes in the patient with acute decompensated heart failure. Am Heart J. 2006;151(3):571–9.
5. Guyton AC. Determination of cardiac output by equating venous return curves with cardiac response curves. Physiol Rev. 1955;35(1):123–9.
6. Henderson WR, Griesdale DEG, Walley KR, Sheel AW. Clinical review: guyton--the role of mean circulatory filling pressure and right atrial pressure in controlling cardiac output. Crit Care. 2010;14(6):243.
7. Leopold JA, Faxon DP. Diagnostic cardiac catheterization and coronary angiography. In: Kasper D, Fauci A, Hauser S, Longo D, Jameson J, Loscalzo J, editors. Harrison's principles of internal medicine. 18 ed. New York: McGraw-Hill; 2015.

8. Hall JE.Guyton and hall textbook of medical Physiology. Published December 31, 2015.13th Edition. Philadelphia: Elsevier; 2016. Chapter 22, p. 271–81.
9. Katz AM. Physiology of the heart. 5th ed. Philadelphia: Lippincott Williams & Wilkins; 2011. Chapter 11, p. 307–10.
10. Shavelle DM. Evaluation of valvular heart disease by cardiac catheterization and angiocardiography. In: Otto CM, Bonow RO, editors. Valvular heart disease: a companion to Braunwald's heart disease. Philadelphia: Saunders Elsevier; © 2014. Chapter 7, p. 91–106.
11. Nishimura RA, Grantham JA, Connolly HM, Schaff HV, Higano ST, Holmes DR. Lowoutput, lowgradient aortic stenosis in patients with depressed left ventricular systolic function: the clinical utility of the dobutamine challenge in the catheterization laboratory. Circulation. 2002;106(7):809–13.
12. Ragosta M. Cardiac catheterization: an atlas and DVD. 1 ed. Philadelphia: Saunders Elsevier; 2010. p. 58–74.
13. Nishimura RA, Carabello BA. Hemodynamics in the cardiac catheterization laboratory of the 21st century. Circulation. 2012;125(17):2138–50.
14. Sharkey SW. Beyond the wedge: clinical physiology and the Swan-Ganz catheter. Am J Med. 1987;83(1):111–22.
15. Lorell B, Leinbach RC, Pohost GM, Gold HK, Dinsmore RE, Hutter AM, et al. Right ventricular infarction clinical diagnosis and differentiation from cardiac tamponade and pericardial constriction. Am J Cardiol. 1979;43(3):465–71.
16. Cameron J, Oesterle SN, Baldwin JC, Hancock EW. The etiologic spectrum of constrictive pericarditis. Am Heart J. 1987;113(2 Pt 1):354–60.
17. Ling LH, Oh JK, Schaff HV, et al. Constrictive pericarditis in the modern era: evolving clinical spectrum and impact on outcome after pericardiectomy. Circulation. 1999;100(13):1380–6.
18. Bertog SC, Thambidorai SK, Parakh K, et al. Constrictive pericarditis: etiology and cause-specific survival after pericardiectomy. J Am Coll Cardiol. 2004;43(8):1445–52.
19. LeWinter MM, Hopkins WE. Pericardial diseases Chapter 71. In: Mann DL, Zipes DP, Libby P, Bonow RO, editors. Braunwald's heart disease: a textbook of cardiovascular medicine, 2-Volume Set, 10th ed. Philadelphia: Elsevier; 2015. p. 1636–1557.
20. LeWinter MM, Myhre EESP, Slinker BK. Influence of the pericardium and ventricular interaction on diastolic function. In: Gaasch WH, LeWinter MM, editors. Heart failure and left ventricular diastolic function. Philadelphia: Lea & Febiger; 1993. p. 103–17.
21. Talreja DR, Edwards WD, Danielson GK, et al. Constrictive pericarditis in 26 patients with histologically normal pericardial thickness. Circulation. 2003;108(15):1852–7 Epub 2003 Sep 29.
22. Vaitkus PT, Cooper KA, Shuman WP, Hardin NJ. Images in cardiovascular medicine constrictive pericarditis. Circulation. 1996;93(4):834–5.
23. Bush CA, Stang JM, Wooley CF, Kilman JW. Occult constrictive pericardial disease. Diagnosis by rapid volume expansion and correction by pericardiectomy. Circulation. 1977;56(6):924–30.
24. Davies MJ, Mann JM. Systemic pathology. In: The Cardiovascular System. Vol 10. 1995:1409; Wald DS, Gray HH. Restrictive cardiomyopathy in systemic amyloidosis. QJM. 2003;96(5):380–2.
25. Kushwaha SS, Fallon JT, Fuster V. Restrictive cardiomyopathy. N Engl J Med. 1997;336(4):267–76.
26. Benotti JR, Grossman W, Cohn PF. Clinical profile of restrictive cardiomyopathy. Circulation. 1980;61(6):1206–12.
27. Talreja DR, Nishimura RA, Oh JK, Holmes DR. Constrictive pericarditis in the modern era: novel criteria for diagnosis in the cardiac catheterization laboratory. J Am Coll Cardiol. 2008;51(3):315–9.
28. Doshi S, Ramakrishnan S, Gupta SK. Invasive hemodynamics of constrictive pericarditis. Indian Heart J. 2015;67(2):175–82.

Chapter 3
Imaging and Heart Failure

Gustavo Jardim Volpe and Joao A.C. Lima

Abbreviations

2D–Echo	Two-dimensional Echocardiography
3D–Echo	Two-dimensional Echocardiography
CAD	Coronary artery disease
CCT	Cardiac computed tomography
CMR	Cardiac magnetic resonance
CRT	Cardiac resynchronization therapy
EF	Ejection fraction
HF	Heart Failure
LA	Left atria
LV	Left ventricle
LVEF	Left ventricular ejection fraction
MRI	Magnetic resonance imaging
PET	Positron emission tomography
RV	Right ventricle
RVG	Radionucleotide ventriculography
SPECT	Single-photon emission computed tomography
ST	Speckle tracking
TDI	Tissue Doppler Imaging

G.J. Volpe, MD, PhD (✉)
Hospital das Clínicas de Ribeirão Preto, Universidade de São Paulo, Campus Universitário, s/n, Ribeirão Preto, SP 14048-900, Brazil
e-mail: gustavovolpe@usp.br

J.A.C. Lima, MD, MBA
Department of Medicine, Division of Cardiology, The Johns Hopkins Hospital, 600 North Wolfe Street/Blalock 524, Baltimore, MD 21287, USA
e-mail: jlima@jhmi.edu

H. Eisen (ed.), *Heart Failure*, DOI 10.1007/978-1-4471-4219-5_3

Introduction

Imaging techniques have a key role in the heart failure (HF). For the correct diagnosis and clinical conduction of any patient with signals of impaired cardiac function, the heart function should be assessed at least once. Moreover, some studies are fundamental for the differential diagnosis and the identification of some reversible conditions such as the ischemic heart disease can be the difference between success or failure in the treatment of HF [1, 2]. From the simple nineteenth century chest X-ray until the present cutting-edge magnetic resonance imaging (MRI) sequences, there has been a long way. Attempts to perform a detailed evaluation of all available modalities is beyond the scope of this chapter; the focus will instead be on clinical use and differential diagnosis of HF.

Chest Radiography

The use of chest X-ray in patients with heart disease goes back to the end of the nineteenth century. This modality is still a useful diagnostic test for evaluation of a patient with dyspnea. It is low cost, fast, and requires a minimal amount of radiation. As a first-line exam, the chest x-ray can help differentiate HF from primary pulmonary disease [2]. Cardiomegaly (cardiac-to-thoracic width ratio more than 50 %), Kerley B-lines, cephalization of the pulmonary vessels, and pleural effusion are the most suggestive findings of HF. Variations in the cardiac area shape and size can also reveal signs of valvular disease or congenital abnormalities. However, none of the findings can either alone or in association establish or exclude the definitive diagnosis of impaired cardiac function. In a systematic review, Badget et al. concluded that blood vessel redistribution and cardiomegaly are the best radiographic findings for diagnosis or increased preload and reduced ejection fraction, respectively, but neither can adequately exclude or confirm left ventricular dysfunction [3]. Similarly, Knudsen et al. evaluated 880 patients from seven different sites presenting with acute dyspnea to the emergency department and found that—of all the signs in the chest x-ray abnormalities—only cardiomegaly had a sensitivity greater than 50 % for the diagnosis of HF [4].

In clinical follow-up, chest radiography can be important to identify signs of decompensated HF. In this sense, pleural effusions, pulmonary congestion, and cephalization of the pulmonary vessels can be signals of volume overload—mainly if there is a previous examination without these findings. The differentiation between pneumonia and pulmonary congestion is often tricky, so once more the interpretation of the exam within the clinical ends up being very important.

Finally, the chest x-ray is an important exam in the first approach to a patient with suspected HF and in the follow-up, but the findings should be interpreted carefully.

Echocardiography

Echocardiography comprehends all the cardiac ultrasound imaging techniques, including two- and three-dimensional echocardiography (2D- and 3D–Echo), color flow Doppler, pulsed and continuous wave Doppler, and tissue Doppler imaging (TDI). Regardless of the fast improvement in cardiovascular imaging and the development of new techniques such as cardiac MRI, echocardiography is still the method of choice in patients with suspected HF. It is a reliable, reproducible, and low-cost exam that allows good evaluation of the anatomy and function of the heart. Nonetheless, in recent years echocardiography has been considered an extension of the physical exam due to the great reduction in the unit size.

In the initial evaluation of a patient with suspected HF, 2D–Echo with Doppler flow study is the most useful complementary exam. It evaluates the ventricle volumes and function, valves and pericardial abnormalities, and atrial volumes to answer three fundamental questions that could account for the clinical presentation: (1) Is the left ventricular ejection fraction (LVEF) preserved or reduced, (2) Is the structure of the left ventricle (LV) normal or abnormal, and (3) Are there other structural abnormalities such as valvular, pericardial, or right ventricular (RV) abnormalities [5]? All this information should be provided with numerical estimates when available and with evaluation of the chambers' geometry and regional LV wall motion (Table 3.1). The biplane method of discs (modified Simpson's rule) is the method of choice to measure LV volumes and, therefore, the LVEF by the American Society of Echocardiography (ASE) [6]. The methods based in the M-mode measurements (Teichholz, for example) and the visual subjective assessment of LVEF are subject to variations and poor reproducibility when there is regional LV dysfunction; therefore, their use is discouraged. Although the lack of correlation of ejection fraction (EF) and the LV dimensions to HF symptoms or myocardial capacity [7], they are closely related to morbidity and mortality [8, 9]. The LV mass and the left atrial (LA) volumes are other important parameters in the evaluation of the patient with HF, not only for their role in the differential diagnosis, but also for their relationship with adverse events in those patients [10–12].

Evaluation of the diastolic function is also fundamental in the diagnosis of the type of HF— mainly in patients with symptoms and preserved LVEF. A variety of echocardiographic techniques can determine the left atrial pressure and left ventricular end-diastolic pressure, but none of them alone is sufficiently accurate or reproducible to make a definitive diagnosis of LV diastolic dysfunction [2]. We can have good prognostic information from those measures [13], but the association of the relevant 2D–Echo and Doppler data are recommended for the diagnostic evaluation. Depending on the association of findings, the function could be graded according to severity in "abnormal relaxation," "pseudonormal," and "restrictive." Mild diastolic dysfunction—"abnormal relaxation"—can be detected via decrease in early diastolic flow velocity and greater reliance on atrial contraction to fill the LV. Moderate diastolic dysfunction—"pseudonormal"—reflects an increasing left atrial pressure at the onset of diastole and an increase in early diastolic flow velocity

Table 3.1 Reference values for left ventricular function and dimension by 2D echocardiography [6]

	Women				Men			
	Normal	Mildly abnormal	Moderately abnormal	Severely abnormal	Normal	Mildly abnormal	Moderately abnormal	Severely abnormal
Mass (g)	66–150	151–171	172–182	≥ 183	96–200	201–227	228–254	≥255
Mass/BSA (g/m^2)	44–88	89–100	101–112	≥113	50–102	103–116	117–130	≥131
EDV/BSA (ml/m^2)	35–75	76–86	87–96	≥97	35–75	76–86	87–96	≥97
ESV/BSA (ml/m^2)	12–30	31–36	37–42	≥43	12–30	31–36	37–42	≥43
EDD (cm)	3.9–5.3	5.4–5.7	5.8–6.1	≥6.2	4.2–5.9	6.0–6.3	6.4–6.8	≥6.9
EF (%)	≥55	45–54	30–44	<30	≥55	45–54	30–44	<30

2D two-dimensional, *BSA* body surface area, *EDV* end diastolic volume, *ESV* end systolic volume, *EDD* end diastolic diameter, *EF* ejection fraction

to a level near that of normal filing. Severe diastolic dysfunction—"restrictive filling"—occurs when left atrial pressure is further elevated, with quick early diastolic flow and rapid equalization between LV and LA pressures in early diastole [14]. This characterization can be done based in the information from the mitral inflow Doppler, Tissue Doppler of mitral annular motion and the pulmonary venous flow [15] and it is related to adverse outcomes [16].

The cardiac dyssynchrony assessment is other potential use of echocardiography. From clinical and experimental studies, we can subdivide dyssynchrony into three levels: atrioventricular, interventricular and intra-(left) ventricular. Of those, the last one seems to be the best to predict cardiac resynchronization therapy (CRT) response [17]. The most commonly used techniques include M-mode echocardiography, TDI, strain imaging, and the 3D–Echo. Several small and single-center studies show good correlations between markers of dyssynchrony and response to CRT, but the largest prospective and multicenter study designed for this evaluation—the PROSPECT (Predictors of Response to CRT)—has shown modest results [17, 18]. In this sense, the guidelines for CRT treatment indication do not include any dyssynchrony evaluation by imaging. Nevertheless, recent improvements in the acquisition and analysis of the echo images contributed to better reproducibility of the parameters, so perhaps new studies can cast more light in this issue.

Some new echocardiographic techniques like the 3D–Echo and the "speckle tracking" (ST) are opening new horizons in cardiac non-invasive evaluation. Development of new matrix array transducers that acquire full volume data in real time allow the 3D–echo to get rid of off-line image reconstructions, and therefore made this modality more suitable for the clinical use (Fig. 3.1). The great advantage is the calculation of volumes and diameters of the heart without geometric assumptions. Some studies have shown that 3D–Echo is highly accurate and reproducible for assessing LV volumes and mass when compared to cardiac MRI [19, 20]. The ST is also one of the most promising new techniques, because it can measure the global and regional strains without a dependence of angle acquisition, different of what happens with the TDI. This modality relies on algorithms that can identify multiple unique patterns of echocardiographic pixel intensity and then automatically track them along the cardiac cycle, providing their movement in plane (strain) and by the time (strain rate) (Fig. 3.2). Several small studies have shown correlations with strain parameters by ST and tissue alteration, such as fibrosis, and with markers of subtle myocardial disease [21]. For both 3D–Echo and ST, however, we still need information from randomized trials and epidemiologic studies.

Cardiac Magnetic Resonance Imaging

Cardiac Magnetic Resonance (CMR) is considered one of the most useful techniques in the evaluation of suspected HF. It can provide all the anatomical and functional parameters that echocardiography can provide—with additional high spatial resolution and tissue characterization. Furthermore, CMR is regarded as the

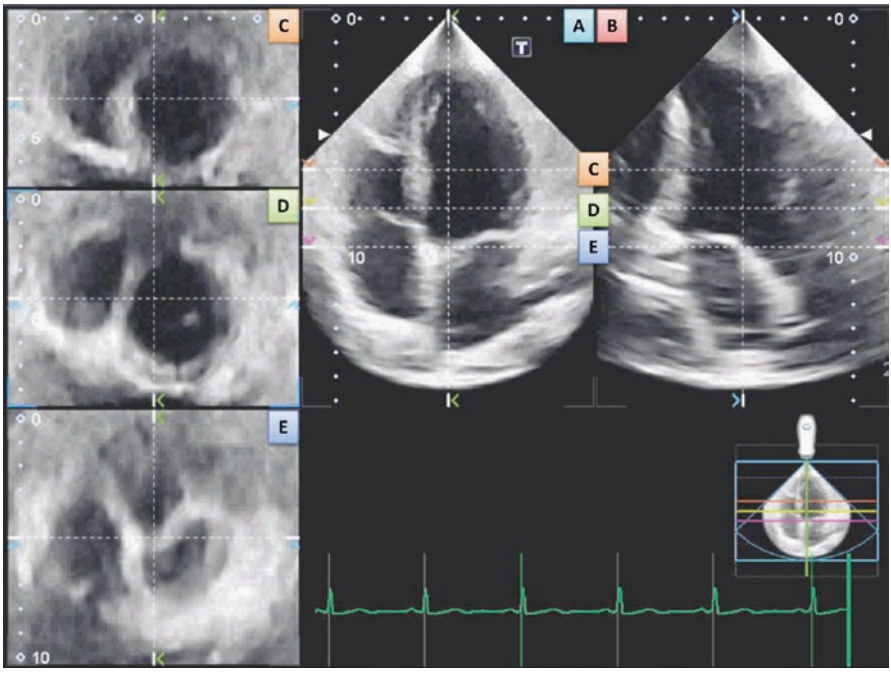


Fig. 3.1 Example of a 3D echocardiography acquisition. With full volume data acquisition in real time, it is possible to obtain cines of various planes at the same time. (**a**) 4 chamber view; (**b**) 2 chamber view; (**c–e**) short axis views. It is remarkable to notice the ability to observe more than one plane at the same time

gold standard with respect to accuracy and reproducibility of volumes, mass, and wall motion [2]. Its ability to have good image quality in most exams makes it the exam of choice for functional evaluation when 2D–Echo is non-diagnostic.

A general CMR exam comprises a complete segmentation of the heart, with a vertical and horizontal long axis of the LV (2 and 3 chamber views), a stack of 8–12 slices in the short axis and the left ventricle outflow track (3 chamber view) (Fig. 3.3).

All the volumes and LV mass are usually calculated using the modified Simpson's rule in the short axis stack, with the big advantage of the absence of geometrical assumptions for those calculations (Table 3.2). This fact is especially important given the chamber dilatation and remodeling that often accompany HF. Nowadays, the most commonly used sequence for cine imaging is a balanced steady-state free precession (SSFP) with retrospective ECG gating [22], which has good spatial resolution and contrast between the ventricular wall, the blood and adjacent structures. The disadvantage of this sequence is the necessity of repeatedly breath-holds, which can be difficult to achieve in HF patients. Because of that, the use of real time acquisition of cine imaging is becoming more available. This sequence provides diagnostic images (with lower spatial resolution when compared to SSFP) acquired in 3–4 s, with no breath-hold required [23, 24], and can be considered a good option in

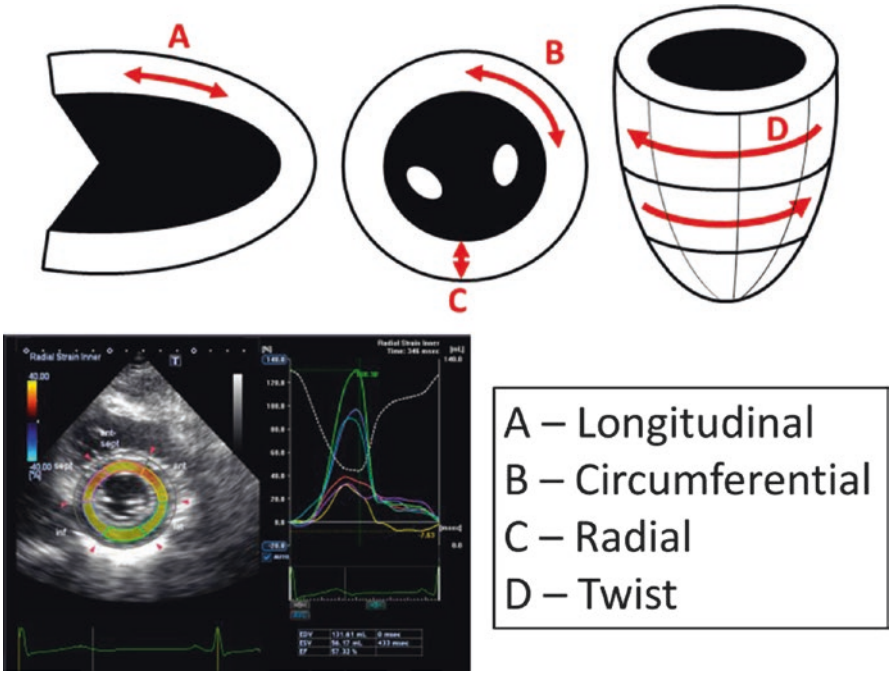


Fig. 3.2 Representation of the strain parameters obtained from "speckle tracking" technique by echocardiography. (**a**) Longitudinal strain demonstrates the shortening of the wall segment as the base moves towards the base in systole; (**b**) Circumferential strain reflects the reduction in circumference of the heart in systole (This is the most stable strain parameter); (**c**) Radial strain reflects the thickening of a wall segment in systole; (**d**) Twist is the difference in degrees between apical and basal rotation. In the inferior left there is an example of a radial strain acquisition with the curves

patients who cannot perform this maneuver. Completing the function assessment, phase-contrast images can be obtained for the measurement of valve flow, intracardiac flow, and even myocardial tissue motion [24]. This sequence relies on phase shifting related to the motion (or flow) of the blood (or myocardium) when compared to the stationary structures, which provides a detailed pixel map where intensity is directly related to the velocity and the sign (positive or negative) indicates the direction (Fig. 3.4). Myocardial tagging is a powerful tool to evaluate the global and regional myocardial function with detailed and comprehensive examination of intra-myocardial motion and deformation; therefore, it is the reference technique for evaluating the tissue strains [25]. Besides the good sensibility to the detection of subtle abnormalities, the role of the tagging sequences in regular clinical use remains uncertain [24].

In addition to the function analysis, tissue characterization has a key role in the evaluation of HF patient not only for the diagnosis, but also because of the prognostic information related to its findings. In this sense, several T1- and T2-weighted sequences with or without gadolinium use can be performed to provide information about the composition and perfusion of the myocardial tissue. T2- and T2*-weighted

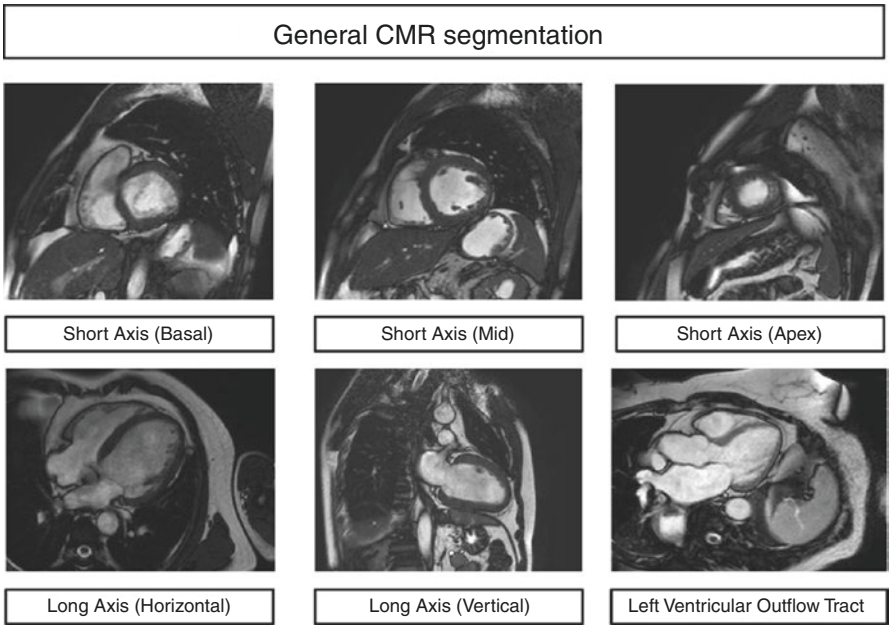


Fig. 3.3 General cardiac magnetic resonance (CMR) imaging segmentation. A CMR exam comprehends a complete segmentation of the heart, with a vertical and horizontal long axis of the LV (2 and 3 chamber views), a stack of 8–12 slices in the short axis (here with an example of basal, mid and apex) and the left ventricle outflow track (3 chamber view)

Table 3.2 Reference values for left and right ventricular function and dimension by cardiac MRI in adults [42]

	Women		Men	
	<35 years	≥35 years	<35 years	≥35 years
Left ventricle				
Mass (g)	52–132	54–130	89–173	74–166
Mass/BSA (g/m^2)	35–71	34–70	47–87	42–78
EDV/BSA (ml/m^2)	62–98	51–95	68–112	53–97
ESV/BSA (ml/m^2)	13–37	11–35	16–44	10–34
EF (%)	57–81	57–81	57–77	59–83
Right ventricle				
EDV/BSA (ml/m^2)	67–111	42–118	74–134	67–111
ESV/BSA (ml/m^2)	25–45	6–54	26–62	20–48
EF (%)	55–67	50–78	47–67	49–73

Reference values based in SSFP cine images analyzed with Argus software (Siemens, The Netherlands) from short axis. These values may vary depending on image sequence, acquisition technique and contouring

BSA body surface area, *EDV* end diastolic volume, *ESV* end systolic volume, *EF* ejection fraction

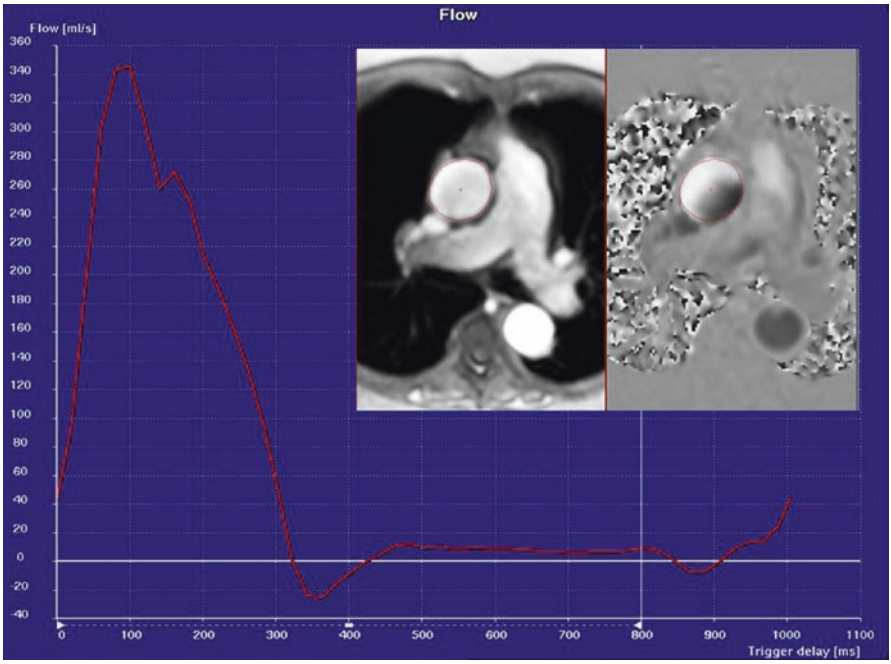


Fig. 3.4 Flow quantification of the ascending aorta with phase contrast imaging by Cardiac magnetic resonance imaging. In this example, the ROI (*red*) is placed in the ascending aorta and can observed in the ECG-gated cine phase contrast magnitude (*left*) and phase (*right*) images during early diastole. On phase images, the bright signal intensity corresponds to cephalad flow and the black signal to caudal flow. A plot of mean flow through the cardiac cycle in the ascending aorta can be then generated

images are generally performed without contrast to bring information about the intrinsic tissue composition, such as water and iron content, and when associated with other techniques can even provide information about the lipid content [27–29]. T1-weighted images are generally used in association with contrast to show its dynamics since the gadolinium makes the T1 times shorter. Late gadolinium enhancement and perfusion images rely on this effect to generate the images. The association of those findings makes the evaluation even more powerful.

Stress perfusion imaging with CMR is an accurate exam to investigate coronary arterial disease. It can be performed using pharmacologic or even physical stress, but the first modality is far more common due the convenience. Dipyridamole or adenosine are used to generate coronary vasodilatation; the first pass of the contrast shows areas of delayed perfusion (darker) that can be related to coronary narrowing. The Dobutamine stress test relies on wall motion abnormalities, the same as the stress echocardiography. Both MRI tests are robust and highly reproducible for the diagnosis of coronary artery disease (CAD) [30, 31].

LGE techniques could be considered one of the most important improvements in the CMR imaging and is widely accepted for the assessment of myocardial replacement fibrosis [30, 32, 33]. Right after the infusion, the gadolinium contrast rapidly diffuses across the capillary membranes, but not in the intracellular space. After 8–12 min, an equilibrium state is reached and the volume of distribution of the contrast is higher in fibrotic areas and therefore marking these areas bright white with a T1-weighted sequence. For increase the image contrast, an inversion-recovery preparation pulse is set in this sequence to null the signal of viable areas. It is a valuable tool in the evaluation of the patient with heart failure, since the several patterns of involvement can suggest the diagnosis of some specific pathology. The hyperenhancement pattern considered "ischemic" always involves the subendocardium (or can be transmural) and should be located in a region consistent with the perfusion area of an epicardial coronary artery [34]. The ones that do not have these characteristics are considered "non-ischemic" (Fig. 3.5). For example, the cardiac amyloidosis generally presents a diffuse enhancement more concentrated in the subendocardial area, while idiopathic dilated cardiomyopathy and myocarditis often show a mid-wall pattern; however, none of those patterns are pathognomonic. In the CAD investigation scenario, the presence of an ischemic

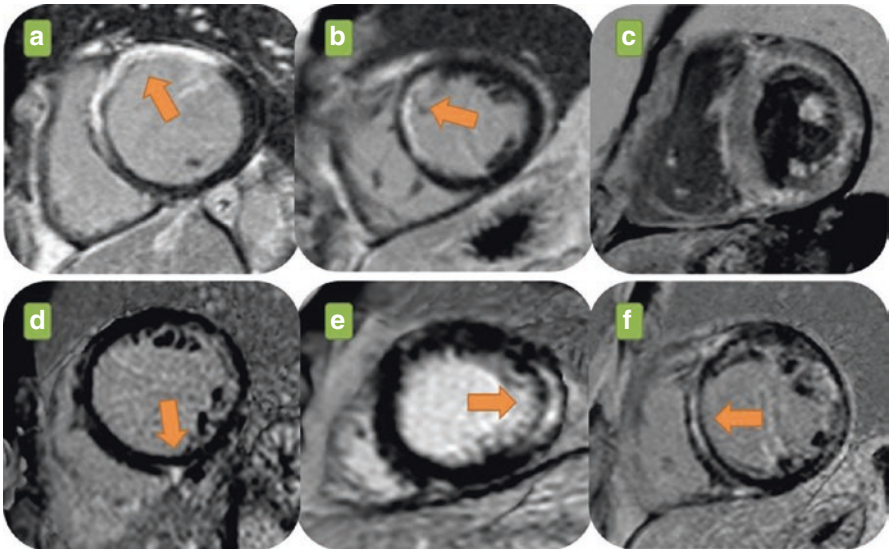


Fig. 3.5 Example of some hyperenhancement patterns in late gadolinium enhancement sequence by cardiac magnetic resonance. The orange arrows point the main areas of scar. Ischemic: (**a**) transmural; (**b**) subendocardial. Non-isquemic: (**c**) diffuse; (**d–f**) midwall. The ischemic pattern always involves the subendocardium and it is consistent with the perfusion area of an epicardial coronary artery (in these examples the left anterior descending). The diffuse pattern is consistent with infiltrative disease such as cardiac amyloidosis. The midwall patterns are less specific and can be found in idiopathic dilated cardiomyopathy, myocarditis, sarcoidosis, Chagas' heart disease and Anderson-Fabry disease

LGE pattern associated with a perfusion defect can improve the accuracy of CMR to identify significant coronary obstructions [31]. Beyond the diagnosis, the presence and the amount of scar can be related to treatment response and prognosis. The classical study from Kim et al. demonstrated poor improvement in LV function after revascularization when the transmurality of the myocardial scar assessed by LGE were more than 50 % [35]. In another study, the amount of viable tissue in patients with HF was an independent predictor of change in LV ejection fraction, mean wall motion score, and LV end-diastolic volume index in patients treated with beta-blockers [36]. The presence of mid-wall fibrosis in non-ischemic dilated cardiomyopathy was also an independent predictor of all-cause death and hospitalization for a cardiovascular event in another subset [37]. Poor response to CRT and inducibility of ventricular tachycardia at electrophysiologic study are also related to the presence of scar [38, 39].

Another important sequence for tissue characterization in the HF scenario is the assessment of the relaxation parameter T2*. The presence of iron overload in the myocardium produces an abnormal loss of signal in T2*-weighted sequences proportional to its amount and this effect can be used to estimate the iron content in the tissue [29]. T2* times lower than 20 ms indicate significant iron overload and are related to ventricular arrhythmias and HF [24, 40]. Moreover, the treatment with iron chelator deferoxamine—which decrease the amount of iron in the myocardium—is related to a significant increasing in T2* times [40].

In the future, cardiac MRI will probably provide even more information. The use of T1 mapping techniques for the calculation native T1 times (pre- and post-gadolinium) and the extracellular volume for the assessment of interstitial fibrosis has the potential to improve not only the diagnosis, but also the treatment of HF [41, 42]. Tissue spectroscopy and imaging with sodium are other good perspectives as well [26, 43].

Cardiac Computed Tomography

The Cardiac Computed Tomography (CCT) is a valuable technique for the investigation of possible CAD. Using multidetector scanners, a high resolution coronary angiography can be performed with good accuracy [44, 45]. Detailed anatomical reconstruction evaluation also offers a great advantage, with precise measurements of the chambers' diameters and volumes. Despite the possibility of functional analysis using retrospective techniques of acquisition, the use of this imaging technique for this purpose is not advised when other modalities such as 2D–Echo and CMR are available. The major limitations are the use of iodine contrasts and radiation, but those problems have been minimized with the Multi-Detector scanners. In the future, the possibility of tissue characterization and myocardial perfusion evaluation offer the biggest potentials.

Cardiac Nuclear Medicine

Nuclear medicine comprises any technique that evolves the use of radioactive tracers to generate its images. The positron emission tomography (PET) [alone or in association with computed tomography], the single-photon emission computed tomography (SPECT), and the radionucleotide ventriculography (RVG) are the ones that have applications in cardiology.

The RVG was first introduced in the early 1970s and has an excellent agreement with the invasive techniques to measure LVEF [46]. Even now RVG and the CMR are considered the most accurate and reproducible modalities to assess the ventricular function. It is performed labeling the blood pool with a radioactive tracer (technetium 99 m–Tc99m) and measuring radioactivity over the anterior chest with a gamma camera. The number of counts recorded at any time is proportional to the amount of the blood radioactivity, which is linearly related to the blood volumes over the cardiac cycle. One of the great advantages of this modality is not to rely on any geometric assumptions, so it is accurate regardless the shape of the ventricle (right or left). Due to the use of ionizing radiation, however, RVG should be performed only in selected cases—when echocardiography and cardiac MRI are not possible or have low quality.

Different from what happens with the RVG, the main use of SPECT and PET are the ischemia and viability assessment. Left ventricular function can be performed as well (Gated SPECT and PET-CT), but this should not be main reason for the exam acquisition. Both modalities rely on the use of radioactive flow tracers to generate the images, generally associated with pharmacologic or exercise cardiovascular stress. In the context of the heart failure assessment, they should be performed when there is a suspected CAD. Despite the fact of PET-CT has more spatial resolution and better sensibility and specificity than gated SPECT (91 % and 82 % respectively, against 88 % and 77 %), this technique still lacks prospective studies for prognostic evaluation. On the other hand, the gated SPECT has been used as a non-invasive tool to investigate ischemia for a long time with a good literature background of diagnostic and prognostic evaluations. Lower cost and large availability are other advantages of gated SPECT.

Conclusion

Imaging exams are important in the heart failure patient evaluation, not only for the proper diagnosis but also for correct treatment and follow-up. From the simple and limited chest x-ray to the complex and complete CMR, the different techniques can provide different amount of information. Today we have available many modalities, so it is important to choose the one that will provide the desired answers with the least harm to the patient and with lower cost.

References

1. Jessup M, Abraham WT, Casey DE, Feldman AM, Francis GS, Ganiats TG, et al. 2009 focused update: ACCF/AHA guidelines for the diagnosis and management of heart failure in adults: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines: developed in collaboration with the International Society for Heart and Lung Transplantation. Circulation. 2009;119(14):1977–2016. Epub 2009/03/28.
2. McMurray JJ, Adamopoulos S, Anker SD, Auricchio A, Bohm M, Dickstein K, et al. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: the task force for the diagnosis and treatment of acute and chronic heart failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. Eur Heart J. 2012;33(14):1787–847. Epub 2012/05/23.
3. Badgett RG, Mulrow CD, Otto PM, Ramirez G. How well can the chest radiograph diagnose left ventricular dysfunction? J Gen Intern Med. 1996;11(10):625–34. Epub 1996/10/01.
4. Knudsen CW, Omland T, Clopton P, Westheim A, Abraham WT, Storrow AB, et al. Diagnostic value of B-Type natriuretic peptide and chest radiographic findings in patients with acute dyspnea. Am J Med. 2004;116(6):363–8. Epub 2004/03/10.
5. Hunt SA, Abraham WT, Chin MH, Feldman AM, Francis GS, Ganiats TG, et al. ACC/AHA 2005 guideline update for the diagnosis and management of chronic heart failure in the adult: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (writing committee to update the 2001 guidelines for the evaluation and management of heart failure): developed in collaboration with the American College of Chest Physicians and the International Society for Heart and Lung Transplantation: endorsed by the heart rhythm society. Circulation. 2005;112(12):e154–235. Epub 2005/09/15.
6. Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA, et al. Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. J Am Soc Echocardiogr. 2005;18(12):1440–63. Epub 2005/12/27.
7. Smart N, Haluska B, Leano R, Case C, Mottram PM, Marwick TH. Determinants of functional capacity in patients with chronic heart failure: role of filling pressure and systolic and diastolic function. Am Heart J. 2005;149(1):152–8. Epub 2005/01/22.
8. Vasan RS, Larson MG, Benjamin EJ, Evans JC, Reiss CK, Levy D. Congestive heart failure in subjects with normal versus reduced left ventricular ejection fraction: prevalence and mortality in a population-based cohort. J Am Coll Cardiol. 1999;33(7):1948–55. Epub 1999/06/11.
9. Grayburn PA, Appleton CP, DeMaria AN, Greenberg B, Lowes B, Oh J, et al. Echocardiographic predictors of morbidity and mortality in patients with advanced heart failure: the Beta-blocker Evaluation of Survival Trial (BEST). J Am Coll Cardiol. 2005;45(7):1064–71. Epub 2005/04/06.
10. Armstrong AC, Gidding S, Gjesdal O, Wu C, Bluemke DA, Lima JA. LV mass assessed by echocardiography and CMR, cardiovascular outcomes, and medical practice. JACC Cardiovasc Imaging. 2012;5(8):837–48. Epub 2012/08/18.
11. Quinones MA, Greenberg BH, Kopelen HA, Koilpillai C, Limacher MC, Shindler DM, et al. Echocardiographic predictors of clinical outcome in patients with left ventricular dysfunction enrolled in the SOLVD registry and trials: significance of left ventricular hypertrophy. Studies of Left Ventricular Dysfunction. J Am Coll Cardiol. 2000;35(5):1237–44. Epub 2000/04/12.
12. Ristow B, Ali S, Whooley MA, Schiller NB. Usefulness of left atrial volume index to predict heart failure hospitalization and mortality in ambulatory patients with coronary heart disease and comparison to left ventricular ejection fraction (from the Heart and Soul Study). Am J Cardiol. 2008;102(1):70–6. Epub 2008/06/24.
13. Franklin KM, Aurigemma GP. Prognosis in diastolic heart failure. Prog Cardiovasc Dis. 2005;47(5):333–9. Epub 2005/07/09.

14. Kirkpatrick JN, Vannan MA, Narula J, Lang RM. Echocardiography in heart failure: applications, utility, and new horizons. J Am Coll Cardiol. 2007;50(5):381–96. Epub 2007/07/31.
15. Redfield MM, Jacobsen SJ, Burnett Jr JC, Mahoney DW, Bailey KR, Rodeheffer RJ. Burden of systolic and diastolic ventricular dysfunction in the community: appreciating the scope of the heart failure epidemic. JAMA. 2003;289(2):194–202.
16. Tsang TS, Barnes ME, Gersh BJ, Bailey KR, Seward JB. Risks for atrial fibrillation and congestive heart failure in patients >/=65 years of age with abnormal left ventricular diastolic relaxation. Am J Cardiol. 2004;93(1):54–8. Epub 2003/12/31.
17. Bax JJ, 3rd Gorcsan J. Echocardiography and noninvasive imaging in cardiac resynchronization therapy: results of the PROSPECT (Predictors of response to cardiac resynchronization therapy) study in perspective. J Am Coll Cardiol. 2009;53(21):1933–43. Epub 2009/05/23.
18. Bleeker GB, Bax JJ, Fung JW, van der Wall EE, Zhang Q, Schalij MJ, et al. Clinical versus echocardiographic parameters to assess response to cardiac resynchronization therapy. Am J Cardiol. 2006;97(2):260–3. Epub 2006/01/31.
19. Corsi C, Lang RM, Veronesi F, Weinert L, Caiani EG, MacEneaney P, et al. Volumetric quantification of global and regional left ventricular function from real-time three-dimensional echocardiographic images. Circulation. 2005;112(8):1161–70. Epub 2005/08/17.
20. Mor-Avi V, Sugeng L, Weinert L, MacEneaney P, Caiani EG, Koch R, et al. Fast measurement of left ventricular mass with real-time three-dimensional echocardiography: comparison with magnetic resonance imaging. Circulation. 2004;110(13):1814–8. Epub 2004/09/24.
21. Gorcsan 3rd J, Tanaka H. Echocardiographic assessment of myocardial strain. J Am Coll Cardiol. 2011;58(14):1401–13. Epub 2011/09/24.
22. Carr JC, Simonetti O, Bundy J, Li D, Pereles S, Finn JP. Cine MR angiography of the heart with segmented true fast imaging with steady-state precession. Radiology. 2001;219(3):828–34. Epub 2001/05/29.
23. Lee VS, Resnick D, Bundy JM, Simonetti OP, Lee P, Weinreb JC. Cardiac function: MR evaluation in one breath hold with real-time true fast imaging with steady-state precession. Radiology. 2002;222(3):835–42. Epub 2002/02/28.
24. Raman SV, Simonetti OP. The CMR examination in heart failure. Heart Fail Clin. 2009;5(3):283–300. v. Epub 2009/07/01.
25. Shehata ML, Cheng S, Osman NF, Bluemke DA, Lima JA. Myocardial tissue tagging with cardiovascular magnetic resonance. J Cardiovasc Magn Reson. 2009;11:55. Epub 2009/12/23.
26. Hudsmith LE, Petersen SE, Francis JM, Robson MD, Neubauer S. Normal human left and right ventricular and left atrial dimensions using steady state free precession magnetic resonance imaging. J Cardiovasc Magn Reson. 2005;7(5):775–82.
27. Abdel-Aty H, Simonetti O, Friedrich MG. T2-weighted cardiovascular magnetic resonance imaging. J Magn Reson Imaging. 2007;26(3):452–9. Epub 2007/08/31.
28. Kellman P, Hernando D, Arai AE. Myocardial fat imaging. Curr Cardiovasc Imaging Rep. 2010;3(2):83–91. Epub 2010/04/20.
29. Carpenter JP, He T, Kirk P, Roughton M, Anderson LJ, de Noronha SV, et al. On T2* magnetic resonance and cardiac iron. Circulation. 2011;123(14):1519–28. Epub 2011/03/30.
30. Schwitter J, Arai AE. Assessment of cardiac ischaemia and viability: role of cardiovascular magnetic resonance. Eur Heart J. 2011;32(7):799–809. Epub 2011/03/15.
31. Greenwood JP, Maredia N, Younger JF, Brown JM, Nixon J, Everett CC, et al. Cardiovascular magnetic resonance and single-photon emission computed tomography for diagnosis of coronary heart disease (CE-MARC): a prospective trial. Lancet. 2012;379(9814):453–60. Epub 2011/12/27.
32. Simonetti OP, Kim RJ, Fieno DS, Hillenbrand HB, Wu E, Bundy JM, et al. An improved MR imaging technique for the visualization of myocardial infarction. Radiology. 2001;218(1):215–23. Epub 2001/01/12.
33. Gerber BL, Lima JA, Garot J, Bluemke DA. Magnetic resonance imaging of myocardial infarct. Top Magn Reson Imaging. 2000;11(6):372–82. Epub 2001/01/12.
34. Mahrholdt H, Wagner A, Judd RM, Sechtem U, Kim RJ. Delayed enhancement cardiovascular magnetic resonance assessment of non-ischaemic cardiomyopathies. Eur Heart J. 2005;26(15):1461–74. Epub 2005/04/16.

35. Kim RJ, Wu E, Rafael A, Chen EL, Parker MA, Simonetti O, et al. The use of contrast-enhanced magnetic resonance imaging to identify reversible myocardial dysfunction. N Engl J Med. 2000;343(20):1445–53. Epub 2000/11/18.
36. Bello D, Shah DJ, Farah GM, Di Luzio S, Parker M, Johnson MR, et al. Gadolinium cardiovascular magnetic resonance predicts reversible myocardial dysfunction and remodeling in patients with heart failure undergoing beta-blocker therapy. Circulation. 2003;108(16):1945–53. Epub 2003/10/15.
37. Assomull RG, Prasad SK, Lyne J, Smith G, Burman ED, Khan M, et al. Cardiovascular magnetic resonance, fibrosis, and prognosis in dilated cardiomyopathy. J Am Coll Cardiol. 2006;48(10):1977–85. Epub 2006/11/23.
38. Bleeker GB, Kaandorp TA, Lamb HJ, Boersma E, Steendijk P, de Roos A, et al. Effect of posterolateral scar tissue on clinical and echocardiographic improvement after cardiac resynchronization therapy. Circulation. 2006;113(7):969–76. Epub 2006/02/16.
39. Schmidt A, Azevedo CF, Cheng A, Gupta SN, Bluemke DA, Foo TK, et al. Infarct tissue heterogeneity by magnetic resonance imaging identifies enhanced cardiac arrhythmia susceptibility in patients with left ventricular dysfunction. Circulation. 2007;115(15):2006–14. Epub 2007/03/29.
40. Tanner MA, Galanello R, Dessi C, Smith GC, Westwood MA, Agus A, et al. A randomized, placebo-controlled, double-blind trial of the effect of combined therapy with deferoxamine and deferiprone on myocardial iron in thalassemia major using cardiovascular magnetic resonance. Circulation. 2007;115(14):1876–84. Epub 2007/03/21.
41. Ugander M, Oki AJ, Hsu LY, Kellman P, Greiser A, Aletras AH, et al. Extracellular volume imaging by magnetic resonance imaging provides insights into overt and sub-clinical myocardial pathology. Eur Heart J. 2012;33:1268–78. Epub 2012/01/27.
42. Bull S, White SK, Piechnik SK, Flett AS, Ferreira VM, Loudon M, et al. Human non-contrast T1 values and correlation with histology in diffuse fibrosis. Heart (British Cardiac Society). 2013;99:932–7. Epub 2013/01/26.
43. Rochitte CE, Kim RJ, Hillenbrand HB, Chen EL, Lima JA. Microvascular integrity and the time course of myocardial sodium accumulation after acute infarction. Circ Res. 2000;87(8):648–55. Epub 2000/10/13.
44. Miller JM, Rochitte CE, Dewey M, Arbab-Zadeh A, Niinuma H, Gottlieb I, et al. Diagnostic performance of coronary angiography by 64-row CT. N Engl J Med. 2008;359(22):2324–36. Epub 2008/11/29.
45. Meijboom WB, Meijs MF, Schuijf JD, Cramer MJ, Mollet NR, van Mieghem CA, et al. Diagnostic accuracy of 64-slice computed tomography coronary angiography: a prospective, multicenter, multivendor study. J Am Coll Cardiol. 2008;52(25):2135–44. Epub 2008/12/20.
46. Burow RD, Strauss HW, Singleton R, Pond M, Rehn T, Bailey IK, et al. Analysis of left ventricular function from multiple gated acquisition cardiac blood pool imaging. Comparison to contrast angiography. Circulation. 1977;56(6):1024–8. Epub 1977/12/01.

Chapter 4
Acute and Chronic Right Ventricular Failure

Gabriel Sayer and Marc J. Semigran

Abbreviations

2D	Two-Dimensional
ARVC	Arrhythmogenic Right Ventricular Cardiomyopathy
CMRI	Cardiac Magnetic Resonance Imaging
CVP	Central Venous Pressure
ERA	Endothelin Receptor Antagonist
HF	Heart Failure
iNO	Inhaled Nitric Oxide
LV	Left Ventricle
LVAD	Left Ventricular Assist Device
PA	Pulmonary Artery
PAH	Pulmonary Arterial Hypertension
PCWP	Pulmonary Capillary Wedge Pressure
PDE-5I	Phosphodiesterase-5 Inhibitor
PE	Pulmonary Embolism
PH	Pulmonary Hypertension
PVR	Pulmonary Vascular Resistance
RAP	Right Atrial Pressure
RHC	Right Heart Catheterization
RIMP	Right Ventricular Index of Myocardial Performance

G. Sayer, MD
Advanced Heart Failure, Section of Cardiology, University of Chicago Medicine,
5841 South Maryland Avenue, MC 2016, Chicago, IL 60637, USA
e-mail: gsayer@medicine.bsd.uchicago.edu

M.J. Semigran, MD (✉)
Cardiology Division, Massachusetts General Hospital,
55 Fruit Street, Boston, MA 02114, USA
e-mail: msemigran@partners.org

H. Eisen (ed.), *Heart Failure*, DOI 10.1007/978-1-4471-4219-5_4

RV	Right Ventricle
RVAD	Right Ventricular Assist Device
RVEF	Right Ventricular Ejection Fraction
RVFAC	Right Ventricular Fractional Area Change
RVI	Right Ventricular Infarction
TAPSE	Tricuspid Annular Plane Systolic Excursion
TPG	Transpulmonary Gradient

Introduction

Recent research has shed new light on the importance of the right ventricle (RV) in normal cardiac physiology and its prominent role in the pathophysiology of heart failure (HF). The RV was previously overshadowed by the left ventricle (LV), whose simpler anatomy conforms better to geometric models and is more accessible to non-invasive imaging. Furthermore, early experiments falsely suggested that the RV did not contribute significantly to the generation of cardiac output [1]. However, a series of investigations over the past 25 years have provided greater insight into the RV's distinct anatomy, its performance under normal physiological conditions, and its adaptations to specific disease states. Advanced imaging, including cardiac magnetic resonance imaging (CMRI), has provided critical assistance in the study of the RV, allowing for non-invasive characterization of the RV's response to stressors, as well as a tool for measuring the success of therapies. As a result, a detailed understanding now exists of the role of the RV in ischemic heart disease, congenital heart disease, pulmonary arterial hypertension (PAH) and chronic left-sided HF. Most importantly, studies have shown that RV failure is a crucial prognostic factor in all of these disease states. In particular, the importance of RV function in left-sided HF may outweigh the importance of LV function in terms of both morbidity and mortality.

Anatomy and Physiology of the Right Ventricle

The RV can be divided into three anatomical units: the inlet from the right atrium (including the tricuspid, the apex, and the outflow tract (infundibulum). The apex contains prominent trabeculations, in contrast to the smooth, muscular infundibulum. Viewed in cross-section, the RV resembles a crescent that lies over the anterior aspect of the LV. The free wall is thin and the overall mass of the RV is a fraction of the LV mass, despite a larger volume. The deep muscle fibers of the RV have a longitudinal orientation, resulting in a primarily vertical direction of contractile forces. The superficial muscle fibers of the RV are oriented in a more concentric direction and are intertwined with the superficial muscle fibers of the LV. This anatomical

interaction between the muscular fibers of the two chambers is also present in the interventricular septum, which is typically displaced into the RV throughout the cardiac cycle. Direct muscular continuity between the LV and RV plays a significant role in ventricular interdependence, which will be discussed in further detail below.

RV contraction proceeds sequentially, initiating in the inlet, continuing through the apex and concluding in the infundibulum. The longitudinal fibers draw the apex towards the tricuspid valve, while the free wall also moves inward toward the septum. Traction on the free wall is applied by LV contraction at attachment points in the superficial muscle layer. The RV is coupled with the high compliance of the pulmonary vasculature, leading to a pressure-volume relationship that is distinct from the relationship seen in the LV. Whereas the LV continues to generate pressure until the closure of the aortic valve, RV pressure falls prior to the closure of the pulmonic valve. Ejection continues however due to the low resistance within the pulmonary circuit (Fig. 4.1) [2]. The RV takes advantage of this physiology by producing an identical cardiac output to the LV with markedly reduced work and myocardial oxygen demand. However, one consequence of this interaction is the RV's heightened sensitivity to afterload, which can be deleterious in acute pressure overload states.

Ventricular interdependence occurs in both systole and diastole. Systolic interdependence is mediated by the shared musculature between the LV and the RV, which means that the contractile state of one ventricle can influence the performance of the

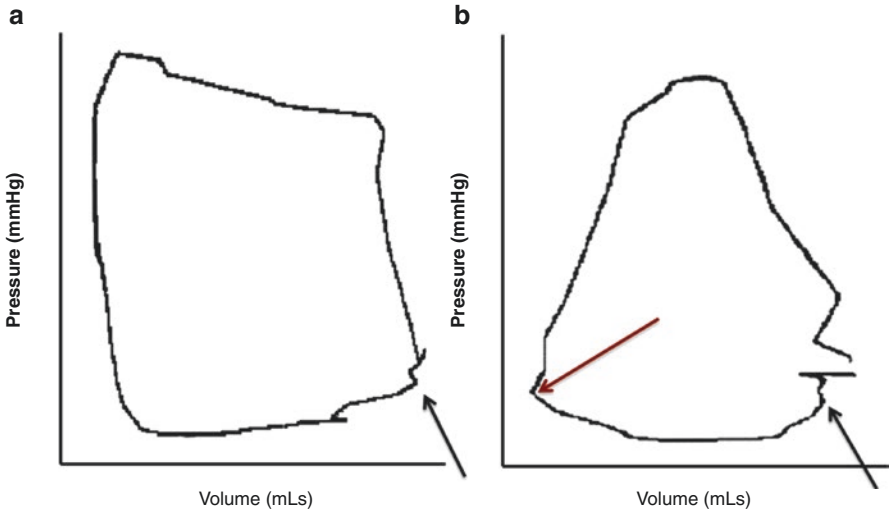


Fig. 4.1 A comparison of typical pressure-volume loops for a single cardiac cycle of the left ventricle (**a**) and right ventricle (**b**). In the left ventricle, pressure continues to increase slightly throughout the entire duration of ventricular ejection. In the right ventricle, intracardiac pressure falls prior to closure of the pulmonic valve (*red arrow*), resulting in less myocardial work. End-diastole is indicated by the black arrows (Adapted with permission from Redington [2], with permission from Elsevier)

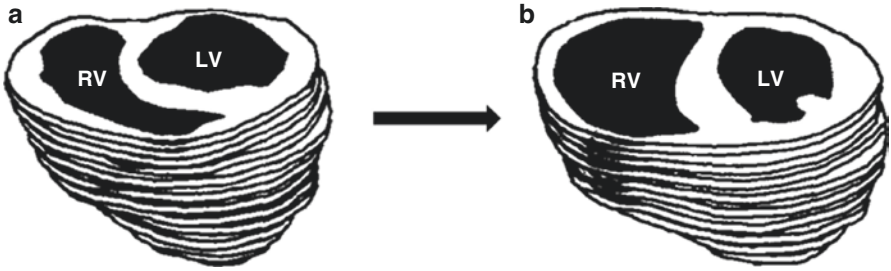


Fig. 4.2 Ventricular interdependence. During normal loading conditions (*left side of diagram*), the intraventricular septum bulges into the right ventricle (*RV*). In the context of right ventricular volume overload, the septum becomes flattened, with an increase in RV volume and a decrease in left ventricular (*LV*) volume (Reprinted with permission from Greyson [3], © 2008, with permission from Lippincott Williams & Wilkins/Wolters Kluwer/Society of Critical Care Medicine)

other ventricle. Diastolic interdependence is a result of the common pericardial sac. The pericardium is unable to stretch acutely in response to ventricular dilatation, and is limited in its ability to accommodate chronic ventricular dilatation. Therefore, a volume load in either chamber will cause displacement of the septum into the other chamber, resulting in a decreased diastolic volume and an impairment of ventricular output (Fig. 4.2) [3]. As the RV is the more compliant chamber, this diastolic interaction most commonly occurs in volume overload states of the RV, such as an atrial septal defect.

Right Ventricular Adaptations to Disease States

RV pathophysiology can be broadly categorized by the mechanism of the insult and its rapidity of onset. Acute events, such as a pulmonary embolism, lead to maladaptive compensatory responses, and quickly progress to RV failure. Chronic disease processes, such as congenital heart defects, often present a gradual stress on the RV, allowing it to develop adaptive mechanisms to preserve cardiac output for a prolonged period of time prior to decompensation. Conditions characterized by volume overload are generally well tolerated by the RV due to its compliant nature. On the other hand, the RV has difficulty adapting to pressure overload due to its afterload-sensitivity (Fig. 4.3) [4]. Interestingly, the timing of onset of pressure overload is a crucial determinant of the RV response. In Eisenmenger syndrome, the RV is able to remain compensated much longer than in adult patients with acquired pulmonary hypertension (PH). This finding has been attributed to the preservation of the fetal phenotype, which is accustomed to systemic levels of vascular resistance [5]. Intrinsic myocardial diseases, such as various forms of nonischemic cardiomyopathies, may impair RV contractility, but rarely affect the RV in isolation. However, RV involvement in a cardiomyopathy can play a significant role in morbidity and mortality, particularly in the setting of pulmonary hypertension (PH). A list of diseases that cause RV dysfunction and RV failure can be found in Table 4.1.

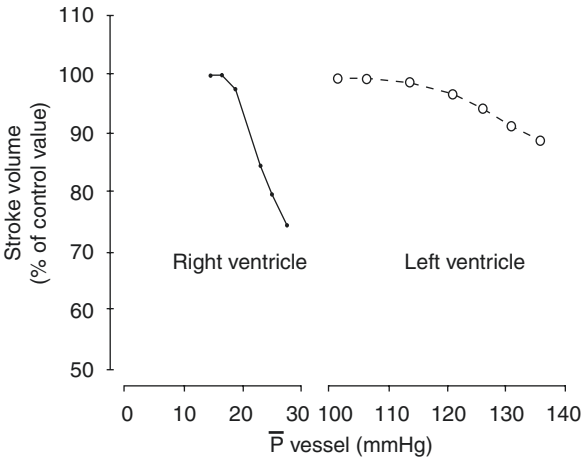


Fig. 4.3 Response of canine right ventricular and left ventricular stroke volume to acute changes in afterload. The steep slope in the right ventricle indicates enhanced sensitivity to afterload (Reprinted with permission from Abel and Waldhausen [4], © 1967, with permission from Elsevier)

Table 4.1 Causes of right ventricular failure

Acute causes	*Intrinsic myocardial disease*
Pulmonary Embolism	Cardiomyopathy
Right Ventricular Infarction	Idiopathic
Sepsis	Viral
Acute lung injury	Familial
ARDS	Ischemic
TRALI	Infiltrative
Acute Chest Syndrome	Restrictive
Post-cardiotomy	Arrhythmogenic RV dysplasia
Pulmonary hypertensive crisis	
Cardiac tamponade	*Pericardial disease*
	Constrictive pericarditis
Chronic volume overload	*Chronic pressure overload*
Tricuspid valve regurgitation	Pulmonary arterial hypertension
Infective endocarditis	Pulmonary venous hypertension
Rheumatic disease	Left heart failure
Carcinoid	Pulmonary veno-occlusive disease
Traumatic	Hypoxia-associated PH
Pulmonic valve regurgitation	Chronic thromboembolic PH
Congenital heart disease	Congenital heart disease
Atrial septal defect	Tetralogy of Fallot
Ebstein's anomaly	Pulmonic stenosis
Coronary artery fistula	L-transposition of the great arteries
Anomalous pulmonary venous return	Pulmonary artery stenosis
	Eisenmenger's syndrome

ARDS acute respiratory distress syndrome, *PH* pulmonary hypertension, *RV* right ventricle, *TRALI* transfusion associated lung injury

Acute Pressure Overload

Following a submassive or massive pulmonary embolism (PE), there is a rapid rise in pulmonary vascular resistance (PVR) due to both obstructed blood flow and the release of vasoconstrictors [6]. Vasoconstriction may be further exacerbated by hypoxemia. The rapid rise in afterload increases RV wall tension, which quickly leads to RV dilatation and RV systolic dysfunction. As the RV pressure rises acutely, the interventricular septum shifts into the LV, reducing LV preload and further compromising cardiac output. Finally, coronary perfusion is impaired by both the compression of the right coronary artery by elevated RV wall stress and the reduction in cardiac output. In the setting of the increased myocardial oxygen demand in the failing RV, the reduction in coronary blood flow leads to a significant supply-demand imbalance. The final consequence of this sequence of events is worsening cardiac output, systemic hypotension and cardiac arrest.

Ischemia

Right ventricular infarction (RVI) occurs after occlusion of the right coronary artery in a sufficiently proximal portion to prevent perfusion of the RV branches. The immediate result of an RVI is RV free wall dyskinesis due to ischemia, although this alone may not be sufficient to produce clinical RV failure. Secondary effects include stiffening of the myocardium and dilation of the RV. Similar to the consequences of an acute PE, the acute pressure changes within the RV, in this case provoked by diastolic dysfunction, cause septal shifting and impaired LV-RV interaction. In addition septal ischemia further compromises LV performance, and diminishes the LV's ability to compensate for RV dysfunction [7].

Chronic Pressure Overload

PH is the end-product of many cardiovascular and pulmonary diseases and is the most common cause of a chronic pressure overload on the RV. As the pulmonary artery (PA) pressure gradually increases over time, the RV adapts to the increase in afterload through multiple compensatory mechanisms. Myocyte hypertrophy and the expansion of the extracellular matrix result in increased chamber thickness. At the same time, the RV remodels into a more spherical shape with a smaller radius [8]. Through the application of LaPlace's law, which states that wall stress is proportional to chamber radius and inversely proportional to chamber thickness, it is evident that the primary result of these initial adaptations is to reduce wall stress, countering the effect of the rise in afterload. In addition, central venous pressure (CVP) is allowed to rise, taking advantage of the Frank-Starling mechanism to maintain a normal stroke volume.

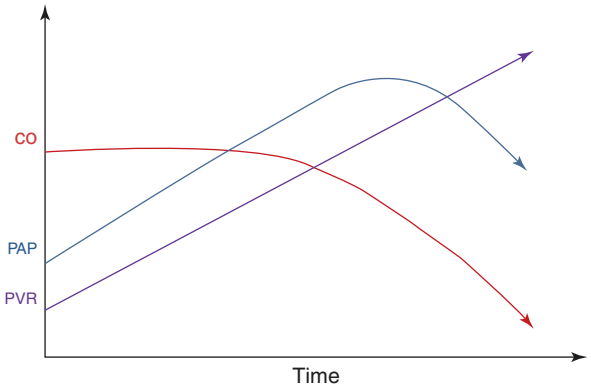


Fig. 4.4 The natural history of persistent pulmonary hypertension. As pulmonary artery pressure (*PAP*) and pulmonary vascular resistance (*PVR*) climb, cardiac output (*CO*) is initially maintained, but eventually begins to fall. When CO falls sufficiently to cause advanced RV failure, PAP fells as well due to insufficient pressure generation by the weak RV. PVR continues to rise despite falling PAP due to the concomitant fall in CO. *MPAP* mean pulmonary artery pressure, *PCWP* pulmonary capillary wedge pressure (Reprinted, with permission, from Haddad et al. [9], © 2008, with permission from Lippincott Williams & Wilkins/American Heart Association/Wolters Kluwer)

Several mechanisms have counterproductive effects, including reversion to a fetal gene pattern and upregulation of neurohormonal systems [8]. The result is a decrement in contractility, followed by progressive ventricular dilatation. As with acute RV pressure overload, dilatation increases myocardial oxygen demand while simultaneously reducing coronary perfusion and oxygen delivery. This supply-demand mismatch further compromises RV performance and ultimately leads to RV failure if the PH remains untreated. Both cardiac output and PA pressure fall when RV contractile reserve is no longer sufficient to maintain an adequate stroke volume (Fig. 4.4) [9].

Chronic Volume Overload

The thin, distensible wall of the RV permits it to accommodate large changes in preload without incurring significant changes in pressure. States of chronic volume overload, such as an atrial septal defect, can persist for decades prior to the development of RV dysfunction. Two consequences of persistent RV dilatation are distortion of the tricuspid annulus and septal shift. The dilated tricuspid annulus permits tricuspid regurgitation, which can further exacerbate the volume load on the RV. Septal shift occurs when the pericardium is unable to distend any further to accommodate the dilation of the RV. As noted above, septal shift can subsequently impair LV filling and adversely affect LV performance. Finally, prolonged volume overload may cause PA pressures to rise due to increased flow through the pulmonary circuit. The development of PH is often the trigger for

decompensation of the chronic volume overloaded state, as the dilated RV lacks the compensatory mechanisms to augment its contractility in the setting of increased afterload [10].

Intrinsic Myocardial Disease

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is a cardiomyopathy characterized by fibro-fatty replacement of myocardium, with a predilection for RV involvement. It may present with focal RV dysfunction at the sites of involvement, and may ultimately progress to RV dilatation and global RV dysfunction. The typical clinical presentation is ventricular arrhythmias, with symptoms of RV failure affecting less than 10 % of ARVC patients [11]. In most patients, RV dysfunction can be present for decades without significant symptomatology. A similar observation has been made in animal experiments, in which an isolated reduction in RV contractility does not impair cardiac output in the setting of a normal PVR. In these animals, central filling pressures rise to permit sufficient flow through the pulmonary circuit. However, when PVR is raised, there is rapid cardiac decompensation, suggesting that the progression of RV dysfunction to RV failure may require the presence of an additional stressor, such as PH [12]. The Fontan operation, in which a passive conduit is created between systemic venous return and the pulmonary arteries, takes advantage of this physiology to maintain adequate flow to the LV despite the absence of RV contractility.

Diagnosis and Assessment of Right Ventricular Dysfunction and Failure

A thorough history and physical examination can provide important clues to the presence of RV failure, including the presence of a right-sided third heart sound, elevated jugular venous pressure, ascites and peripheral edema. A prominent pulmonic component of the second heart sound (P2) indicates the presence of PH. Patients may report early satiety, abdominal fullness and fatigue. Hepatic function and renal function are often compromised, and should be followed regularly in a patient with RV failure. Imaging studies play a crucial role in the initial assessment and serial monitoring of RV function. Echocardiography is the most frequently used imaging modality for RV assessment due to its ease of use, low cost and accessibility. However, CMRI has become the gold standard for evaluation of the RV because of its ability to overcome some of the anatomic limitations of two-dimensional (2D) echocardiography. While both echocardiography and CMRI can provide some assessment of RV hemodynamics, invasive measurement of intracardiac pressures by right heart catheterization is often required to diagnose the etiology of RV failure and determine the appropriate therapeutic approach.

Non-invasive Imaging Studies

RV size and function can be assessed with radionuclide ventriculography, using either first-pass or gated equilibrium techniques. While accurate measurements of volume and RV ejection fraction (RVEF) can be derived, this modality does not provide additional anatomic information, and exposes patients to radioisotopes. With the widespread availability of echocardiography, radionuclide ventriculography is rarely indicated as the primary method for RV functional assessment in the current era.

2D echocardiography has excellent spatial and temporal resolution, enabling precise evaluation of RV anatomy and valvular function. RV dimensions can be obtained through multiple views, providing an estimate of RV size. However, due to the RV's anatomic configuration, the calculation of accurate RV volumes with 2D echocardiography is not possible. Qualitatively comparing RV size to LV size in the apical view can provide a reasonable assessment of RV dilatation. Additional anatomic information that can be easily obtained is the appearance of the tricuspid and pulmonary valves, and the presence of valvular stenosis or regurgitation. Doppler evaluation of the tricuspid regurgitant jet allows the estimation of the systolic pulmonary artery pressure through the use of the modified Bernoulli equation. Important information is also provided by the appearance of the interventricular septum in the short-axis views. Pressure overload states cause flattening of the septum, particularly during systole, which volume overload states cause flattening during diastole (Fig. 4.5). With increasing pressure or volume overload, the septum is further shifted into the LV, leading to the hemodynamic effects of ventricular interdependence discussed previously.

RV function is challenging to determine with 2D echocardiography due to the lack of accurate ventricular volumes and the sensitivity of the RVEF to loading conditions. Visual assessment is the most commonly used technique but may be limited due to the complex shape of the RV. Multiple techniques are available for quantitative measurement of RV function. RV fractional area change (RVFAC) measures the change in area of the RV between diastole and systole from the apical 4-chamber view. The tricuspid annular plane systolic excursion (TAPSE) measures the vertical motion of the tricuspid valve annulus, with a value of less than 1.6 cm indicating RV dysfunction. RVFAC and TAPSE are both load-independent, and may provide varying information under different hemodynamic conditions. The RV index of myocardial performance (RIMP), also known as the Tei index, is less influenced by loading conditions, and may be a more accurate measure of underlying RV contractility [13]. This index is measured with Doppler of flow through the RV outflow tract, and is calculated as the sum of RV isovolumic contraction time and RV isovolumic relaxation time divided by ventricular ejection time.

Recent advances in CMRI have established it as the best modality for obtaining accurate information about RV size and function. CMRI is not affected by the anatomic limitations that prevent 2D echocardiography from obtaining a complete picture of the RV. CMRI has excellent spatial and temporal resolution, permitting

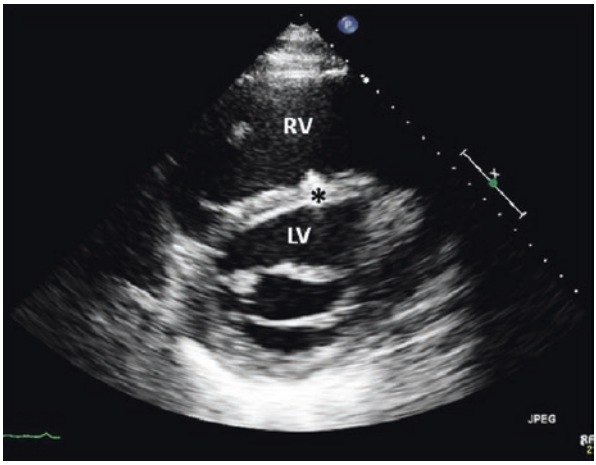


Fig. 4.5 A 2-dimensional echocardiogram image showing dilation of the right ventricle (*RV*) and flattening of the intraventricular septum (*) due to right ventricular pressure and volume overload. *LV* left ventricle

accurate assessment of RV volumes throughout the cardiac cycle. Additionally, CMRI provides information on ventricular hypertrophy, the presence of infiltrative diseases and the presence of fibrosis. For complex congenital heart disease, CMRI offers substantial advantages over 2D echocardiography for assessment of RV anatomy and function prior to and following surgical interventions. Barriers to more widespread application of CMRI in evaluation of the RV include the time required for testing, the cost of CMRI technology, and the need for technical expertise. Most importantly, CMRI is not compatible with most implantable cardiac devices, such as pacemakers, although the ongoing development of devices compatible with the magnetic field will allow for a broader application of CMRI in the assessment of RV failure [14].

Invasive Hemodynamic Assessment

Right heart catheterization (RHC) is a critical component of RV assessment, particularly in patients with PH. Measurement of the right atrial pressure (RAP), PA pressure and pulmonary capillary wedge pressure (PCWP) can distinguish the etiology of RV failure and help determine the therapeutic approach (Table 4.2). The most important information provided by RHC is about PH, which has been classified into groups by the World Health Organization:

- Group I incorporates PAH, which may be idiopathic, familial or associated with specific entities such as congenital heart disease, collagen vascular disease, HIV infection or toxins
- Group II includes PH that is found in conjunction with left heart disease and is the most common form of PH
- Group III includes PH associated with lung disease or hypoxemia

Table 4.2 Hemodynamic profiles of different mechanisms of right ventricular failure

Cause of RV failure	RAP	PAP	PCWP	TPG	PVR	Clinical examples
Volume overload without PH	↑	↓	↓	↓	↓	ASD Isolated TV disease
Precapillary PH	↑	↑	↓	↓	↓	Idiopathic PAH CTEPH Hypoxia-associated PH Congenital Heart Disease
Postcapillary PH						
Passive	↑	↑	↑	↓	↓	Left-sided Heart Failure MV Disease
Mixed	↑	↑	↑	↑	↑	
Reactive (after vasodilator challenge)	↑	↑	↓	↓	↓	
Nonreactive (after vasodilator challenge)	↑	↑	↓	↑	↑	

ASD atrial septal defect, *CTEPH* chronic thromboembolic pulmonary hypertension, *MV* mitral valve, *PAH* pulmonary arterial hypertension, *PAP* pulmonary artery pressure, *PCWP* pulmonary capillary wedge pressure, *PH* pulmonary hypertension, *PVR* pulmonary vascular resistance, *RAP* right atrial pressure, *TPG* transpulmonary gradient, *TV* tricuspid valve

- Group IV is PH due to chronic thromboembolic disease
- Group V is a miscellaneous category

A RHC can assist in the diagnosis of PAH, by identifying PH in the presence of normal left-sided filling pressures. While left heart disease is often manifested on imaging studies by a reduced LV ejection fraction or mitral valve disease, RHC can identify elevated PCWP in the absence of valvular disease or LV dysfunction (heart failure with preserved ejection fraction). Distinguishing the underlying etiology of PH will direct the choice of therapy, as therapies that have proven benefit in some forms of PH have been shown to be harmful in PH related to left heart disease [15]. Beyond anatomy, RHC provides information about the severity of RV failure. For example, the RAP is typically about 50 % of the PCWP [16]. As RV failure progresses, the RAP will approach or exceed the PCWP. Another sign of worsening RV failure is a decrease in the PA pressure despite a rising RAP due to insufficient power generation by the RV.

Another key variable obtained during right heart catheterization is the transpulmonary gradient (TPG), which is the difference between the PCWP and the mean PA pressure. This takes on importance in the assessment of PH due to left heart failure (i.e. patients with a PCWP >15 mmHg). When the PCWP is elevated, but the TPG is less than 10–12 mmHg, PH is termed “passive” or “post-capillary”, indicating that the elevation in PA pressures can be solely attributed to the elevated left-sided filling pressures. When the TPG is greater than 15 mmHg, the PH is termed “mixed” indicating that there is both a pre-capillary and post-capillary component of the PH. This may be secondary to vasoconstriction and pulmonary arterial remodeling as a response to chronically increased pulmonary venous pres-

sures. Mixed PH can be further stratified into "reactive" and "nonreactive" forms through administration of a vasodilator, such as sodium nitroprusside or milrinone, to reduce the PCWP. In non-reactive PH, the TPG will remain elevated despite a lower PCWP, whereas patients with reactive PH will have concurrent decreases in the PCWP and TPG. The presence of reactive PH may indicate a more favorable prognosis, particularly when considering a patient for advanced therapies such as cardiac transplantation [17]. Whether patients with either reactive PH or nonreactive PH will benefit from selective pulmonary vasodilators is a subject of ongoing investigation.

When World Health Organization Group I PAH is present, the administration of selective pulmonary vasodilators, such as nitric oxide or epoprostenol, provides both prognostic and therapeutic information. Patients in whom the mean PA pressure drops by more than 10 mmHg to a value less than 40 mmHg without a reduction in cardiac output have an excellent prognosis, and typically respond well to calcium-channel blockers [18]. Non-responders have a worse prognosis, but still get a therapeutic benefit from selective pulmonary vasodilators.

Finally, RHC enables the calculation of the PVR, which provides a good estimate of RV afterload. PVR is both a prognostic factor, as well as a therapeutic target, that takes on considerable importance in the assessment of a patient's appropriateness for cardiac transplantation. A PVR >5 Woods Units is considered a relative contraindication to transplantation unless it can be lowered with medical therapy or mechanical circulatory support [19]. Frequency-domain analysis is an investigational method that accounts for the pressure wave reflected backwards into the main PA during late systole, and may provide a more accurate assessment of RV afterload [20].

Prognosis of Right Ventricular Failure

RV dysfunction plays a defining role in the pathogenesis of multiple diseases, ranging from left-sided HF to congenital heart disease to PH. In each of these entities, RV failure is the culmination of chronic pathophysiological disturbances, and often marks the transition to an advanced disease state. Numerous investigations have connected markers of RV dysfunction to adverse outcomes (Table 4.3). In chronic HF with LV dysfunction, RVEF, as measured by radionuclide ventriculography, invasive hemodynamics or CMRI, has been correlated with exercise capacity [21, 22], ventilatory efficiency [23], and survival [24–29]. This association has been demonstrated in both ischemic and nonischemic cardiomyopathies [24, 25, 29]. Importantly, there appears to be an additive effect of PH and RV dysfunction, leading to worse outcomes than the presence of either PH or RV dysfunction alone (Fig. 4.6) [30]. Other imaging parameters that have been associated with outcomes in chronic HF include CMRI-derived RV volumes [31], TAPSE [32–34] and RIMP [35]. Similar findings have been demonstrated in RV dysfunction due to PAH [36–40] and congenital heart disease [41, 42].

Table 4.3 Selected studies of the association of right ventricular dysfunction with adverse outcomes [21–23, 27, 29–32, 35, 36, 38–42]

	Population	Findings
Studies using radionuclide ventriculography		
Baker et al. [22]	25 pts. with symptomatic LV failure	RVEF associated with peak VO_2 LVEF not associated with peak VO_2
Lewis et al. [23]	30 pts. with symptomatic LV failure	Exercise RVEF and PVR associated with V_E/V_{CO2} slope
Di Salvo et al. [21]	67 pts. referred for OHT evaluation	RVEF >35 % predictor of survival
Studies using RHC/thermodilution		
Gavazzi et al. [27]	142 pts. referred for OHT evaluation	RVEF lower in pts. who died or had OHT
Ghio et al. [30]	377 pts. with LVEF <35 % and NYHA Class III-IV	RVEF and PAP predictors of survival.
Studies using Echocardiography		
Damy et al. [32]	1547 pts. referred for HF	Low TAPSE predictor of mortality
Harjai et al. [35]	60 pts. with LVEF<30 %	RIMP >1.14 predictive of death
Forfia et al. [36]	63 pts. with idiopathic PAH	TAPSE <18 mm associated with mortality
Ghio et al. [38]	72 inpatients with idiopathic PAH	RV diameter >36.5 mm associated with mortality
Yeo et al. [39]	53 pts. with idiopathic PAH	RIMP independent predictor of death
Moceri et al. [41]	181 pts. with Eisenmenger syndrome	TAPSE, RIMP and elevated CVP strongest predictors of mortality
Studies using CMRI		
Larose et al. [29]	147 pts. post-MI	RVEF <40 % independent predictor of mortality
Bourantas et al. [31]	380 pts. with LVEF <45 %	RVESV predicts mortality; LVESV does not predict mortality
van Wolferen et al. [40]	64 pts. with idiopathic PAH	RV dilation, low RV stroke volume and decreased LV filling predict mortality
Knauth et al. [42]	88 pts. followed up at mean of 20.7 years after TOF repair	Severe RV dilation predictor of death, VT, advanced NYHA class

CMRI cardiac magnetic resonance imaging, *HF* heart failure, *LV* left ventricle, *LVEF* left ventricular ejection fraction, *LVESV* left ventricular end systolic volume, *MI* myocardial infarction, *NYHA* New York Heart Association, *OHT* orthotopic heart transplantation, *PAH* pulmonary arterial hypertension, *PAP* pulmonary artery pressure, *PVR* pulmonary vascular resistance, *RIMP* right ventricular index of myocardial performance, *RV* right ventricle, *RVEF* right ventricular ejection fraction, *RVESV* right ventricular end systolic volume, *TAPSE* tricuspid annular plane systolic excursion, *TOF* tetralogy of Fallot, V_E/V_{CO2} ratio of minute ventilation to production of carbon dioxide, *VT* ventricular tachycardia

Management of Right Ventricular Failure

The initial approach to RV failure relies on identifying and correcting the underlying etiology. As opposed to the LV, in which dysfunction is often irreversible, the RV is highly pliable, and typically regains function after the causative factors

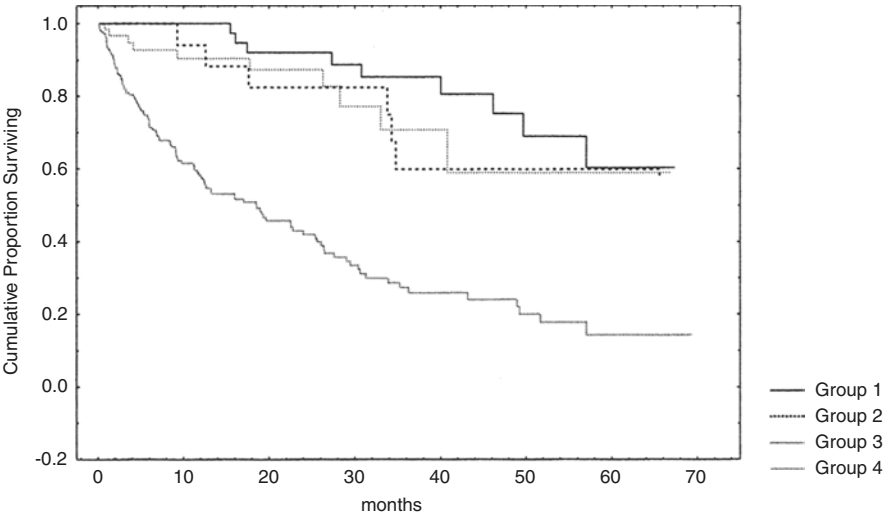


Fig. 4.6 Survival curves for heart failure patients grouped by presence or absence of pulmonary hypertension (PH) and presence or absence of an abnormal right ventricular ejection fraction (RVEF). Group 1 patients have normal RVEF and no PH. Group 2 patients have a low RVEF without PH. Group 3 patients have a normal RVEF with PH. Group 4 patients have both an abnormal RVEF and PH. The presence of both factors leads to significantly worse outcomes than any of the other three scenarios (Reprinted, with permission, from Ghio et al. [30], © 2001, with permission from Elsevier)

of RV dysfunction are addressed. This is especially important in acute RV failure, where reversing the underlying disease state may drastically alter a patient's outcome. For example, coronary revascularization for an RVI reduces RV dysfunction, hemodynamic compromise and increased mortality [43]. Likewise, for an acute PE, rapid relief of the thrombotic burden through medical or surgical intervention produces a substantial survival benefit [44]. Causes of chronic RV failure are not as easily corrected, although RV function improves over time with therapy that is appropriately targeted at the underlying pathophysiology. Ultimately, managing both acute and chronic RV failure requires an understanding of the roles played by preload, afterload and contractility. A management algorithm is shown in Fig. 4.7.

Preload

Optimizing RV performance requires adequate preload to generate a sufficient stroke volume without causing a degree of RV distention that impairs LV performance through ventricular interdependence. The ideal preload required may differ between patients and will rely on both the degree of RV contractility and the severity of RV afterload. In patients with acute RV failure, central venous

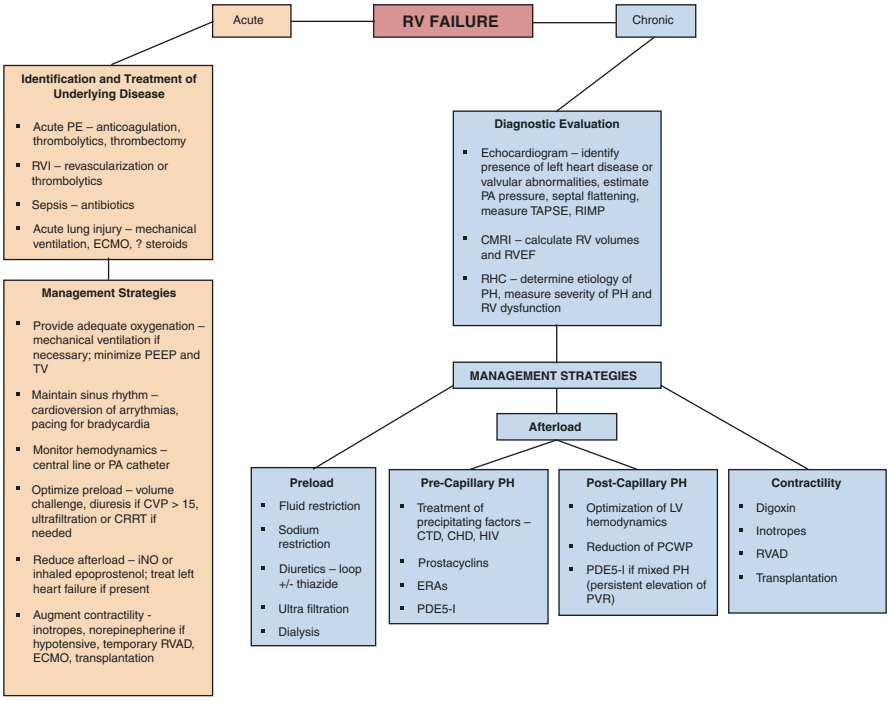


Fig. 4.7 Management algorithm for acute and chronic RV failure. Abbreviations: *CHD* congenital heart disease, *CMRI* cardiac magnetic resonance imaging, *CRRT* continuous renal replacement therapy, *CTD* connective tissue disease, *CVP* central venous pressure, *ECMO* extracorporeal membrane oxygenation, *ERA* endothelin receptor antagonist, *HIV* human immunodeficiency virus, *iNO* inhaled nitric oxide, *PA* pulmonary artery, *PDE5-I* phosphodiesterase-5 inhibitor, *PE* pulmonary embolism, *PEEP* positive end-expiratory pressure, *PH* pulmonary hypertension, *RHC* right heart catheterization, *RIMP* right ventricular index of myocardial performance, *RV* right ventricular, *RVAD* right ventricular assist device, *RVI* right ventricular infarction, *TAPSE* tricuspid annular plane systolic excursion, *TV* tidal volume

monitoring can guide decision-making about the volume status. Patients with RVI are often described as "volume-sensitive", and may require higher preloads to maintain cardiac output. However, too much volume may have deleterious consequences because RV dilation will increase wall stretch, worsen ischemia and cause septal shifting. Although mechanical ventilation is sometimes necessary in the management of patients with acute RV failure, its use should be minimized due to the adverse effects of positive end-expiratory pressure on preload.

In chronic RV failure, the focus is typically on volume removal, which is primarily achieved with loop diuretics. Selecting an agent with better oral bioavailability, such as torsemide, may be preferred in the setting of RV failure due to the possibility of intestinal edema and poor absorption. Thiazide diuretics can be added as needed to enhance diuresis. As with LV dysfunction, sodium and fluid restriction

are essential to maintaining euvolemia. In extreme circumstances, ultrafiltration or hemodialysis may be required in diuretic-resistant patients, although these strategies have not been well studied in this population.

Afterload

Afterload reduction is a critical component of the management of most causes of RV failure. Addressing afterload is of particular urgency in acute RV failure due to the inability of the RV to compensate for acute changes in afterload. Persistently low oxygen saturations should be addressed with supplemental oxygen to alleviate hypoxia-induced vasoconstriction. If mechanical ventilation is required, tidal volumes should be minimized to prevent further augmentation of PA pressures.

Pulmonary vasodilators relax pulmonary vascular smooth muscle, lowering PA pressures and PVR. Inhaled nitric oxide (iNO) has the advantages of pulmonary selectivity, avoiding the hypotension associated with systemic vasodilators. It is also only active in ventilated areas of the lung, reducing the potential for V/Q mismatching. iNO is most commonly used in acute RV failure due to difficulty in administration to non-ventilated patients. Short-term hemodynamic improvements have been demonstrated with the use of iNO in the treatment of RVI [45] and in a study of intensive care patients with mixed causes of RV failure [46], but outcomes data are limited. Transitioning from iNO to oral vasodilators may prevent rapid rebound of PA pressures on discontinuation. Inhaled prostacyclins may be used as an alternative to iNO, although they have been less extensively studied.

In chronic RV failure, therapy depends on the underlying mechanism of the elevated PA pressures. In PAH, there are three classes of vasodilators that have shown clinical benefit: prostacyclins, endothelin receptor antagonists (ERAs) and phosphodiesterase-5 inhibitors (PDE-5Is). As mentioned previously, a small subset of PAH patients will respond to calcium-channel blockers, and may not require any further treatment. Outside of this subset, most PAH patients will be started on oral therapy with an ERA or PDE-5I. As the disease progresses, these patients may need to be transitioned to intravenous prostacyclin therapy. Patients who present with severe symptoms, such as syncope, often require intravenous prostacyclin therapy from the outset.

When RV failure is due to post-capillary PH (i.e. LV dysfunction or valvular disease), the initial therapeutic target is the PCWP, which should be lowered into the normal range if possible. If the PH is reactive, lowering the PCWP should also reduce PA pressures and PVR. However, if PVR remains elevated, consideration should be given to pulmonary vasodilator therapy. Sildenafil citrate, a PDE-5I, has shown benefits on hemodynamics and functional status in patients with left-sided heart failure [47–49]. A large trial to assess outcomes of patients with PH related to LV dysfunction is underway. Neither ERAs nor prostacyclins should be used for post-capillary PH due to adverse outcomes in clinical trials [15, 50].

Contractility

In acute RV failure, inotropes are often required to support the RV until the etiology can be treated. Milrinone may be the preferred agent due to its vasodilatory properties in the pulmonary vasculature, but its use is limited in patients with significant hypotension. Dobutamine and dopamine are more likely to cause tachycardia, which may exacerbate ischemia in the setting of an RVI. In some cases of RVI, mechanical support with an intraaortic balloon pump or a temporary right ventricular assist device (RVAD) has been used, although neither of these approaches has been well studied. Temporary RVADs have also been used to treat RV failure that occurs following cardiovascular surgery or cardiac transplantation.

For chronic RV failure, choices for augmenting contractility are limited. Digoxin is often used as an inotrope in the management of RV failure, based on its short-term hemodynamic benefits in patients with PAH [51]. The use of intravenous inotropes for chronic left heart failure has been associated with worse outcomes. Intravenous inotropes may be used for management of exacerbations of chronic RV failure, but the chronic administration of these agents has been associated with worse outcomes. When biventricular heart failure is refractory, a RVAD may be placed in conjunction with a left ventricular assist device (LVAD) as a means of bridging a patient to transplantation. The devices that are approved for RV support are extracorporeal (i.e. non-implantable) and are not meant for long-term support, although the development of more durable RVADs is ongoing. In some cases, these devices can be explanted once stable LVAD support has been established. Cardiac transplantation is a definitive treatment for patients with advanced RV failure that is associated with LV failure, but this therapy is limited in use due to a shortage of donor organs. Cardiac transplantation should not be attempted in patients with high PVR (>6 Woods Units) due to high risk for RV failure and graft loss postoperatively.

Summary

The onset of RV failure carries a poor prognosis in multiple diseases and is often a marker of a progression to an advanced disease state. RV failure is the end result of a series of pathophysiological adaptations that are distinct from the pathogenesis of LV failure. A detailed understanding of the RV's response to specific disease states informs the clinical management of those diseases. Imaging plays a critical role in the assessment of RV dysfunction, and can provide information about the severity of RV failure. Hemodynamic assessment with cardiac catheterization complements the findings from imaging, directing the appropriate therapeutic approach. The treatment of RV failure due is highly dependent on the underlying etiology. Acute causes respond best to removal of the offending pathophysiology. Chronic RV failure requires a targeted approach, as has been applied in the setting of PAH. Research continues into the optimal treatment strategy for PH that is secondary to left heart failure.

References

1. Starr I, Jeffers WA, Meade RH. The absence of conspicuous increments of venous pressure after severe damage to the right ventricle of the dog, with a discussion of the relation between clinical congestive failure and heart disease. Am Heart J. 1943;26(3):291–301.
2. Redington AN. Right ventricular function. Cardiol Clin. 2002;20(3):341–9.
3. Greyson CR. Pathophysiology of right ventricular failure. Crit Care Med. 2008;36(1 Suppl):S57–65.
4. Abel FL, Waldhausen JA. Effects of alterations in pulmonary vascular resistance on right ventricular function. J Thorac Cardiovasc Surg. 1967;54:886.
5. Hopkins WE, Waggoner AD. Severe pulmonary hypertension without right ventricular failure: the unique hearts of patients with Eisenmenger syndrome. Am J Cardiol. 2002;89(1):34–8.
6. Lualdi JC, Goldhaber SZ. Right ventricular dysfunction after acute pulmonary embolism: pathophysiologic factors, detection, and therapeutic implications. Am Heart J. 1995;130(6):1276–82.
7. Goldstein JA, Tweddell JS, Barzilai B, Yagi Y, Jaffe AS, Cox JL. Importance of left ventricular function and systolic ventricular interaction to right ventricular performance during acute right heart ischemia. J Am Coll Cardiol. 1992;19(3):704–11.
8. Bogaard HJ, Abe K, Vonk Noordegraaf A, Voelkel NF. The right ventricle under pressure: cellular and molecular mechanisms of right-heart failure in pulmonary hypertension. Chest. 2009;135(3):794–804.
9. Haddad F, Doyle R, Murphy DJ, Hunt SA. Right ventricular function in cardiovascular disease, Part II: pathophysiology, clinical importance, and management of right ventricular failure. Circulation. 2008;117(13):1717–31.
10. Szabo G, Soos P, Bahrle S, Radovits T, Weigang E, Kekesi V, et al. Adaptation of the right ventricle to an increased afterload in the chronically volume overloaded heart. Ann Thorac Surg. 2006;82(3):989–95.
11. Hulot JS, Jouven X, Empana JP, Frank R, Fontaine G. Natural history and risk stratification of arrhythmogenic right ventricular dysplasia/cardiomyopathy. Circulation. 2004;110(14):1879–84.
12. Brooks H, Kirk ES, Vokonas PS, Urschel CW, Sonnenblick EH. Performance of the right ventricle under stress: relation to right coronary flow. J Clin Invest. 1971;50(10):2176–83.
13. Tei C, Dujardin KS, Hodge DO, Bailey KR, McGoon MD, Tajik AJ, et al. Doppler echocardiographic index for assessment of global right ventricular function. J Am Soc Echocardiogr. 1996;9(6):838–47.
14. Wilkoff BL, Bello D, Taborsky M, Vymazal J, Kanal E, Heuer H, et al. Magnetic resonance imaging in patients with a pacemaker system designed for the magnetic resonance environment. Heart Rhythm. 2011;8(1):65–73.
15. Califf RM, Adams KF, McKenna WJ, Gheorghiade M, Uretsky BF, McNulty SE, et al. A randomized controlled trial of epoprostenol therapy for severe congestive heart failure: The Flolan International Randomized Survival Trial (FIRST). Am Heart J. 1997;134(1):44–54.
16. Drazner MH, Hamilton MA, Fonarow G, Creaser J, Flavell C, Stevenson LW. Relationship between right and left-sided filling pressures in 1000 patients with advanced heart failure. J Heart Lung Transplant. 1999;18(11):1126–32.
17. Costard-Jackle A, Fowler MB. Influence of preoperative pulmonary artery pressure on mortality after heart transplantation: testing of potential reversibility of pulmonary hypertension with nitroprusside is useful in defining a high risk group. J Am Coll Cardiol. 1992;19(1):48–54.
18. Sitbon O, Humbert M, Jagot JL, Taravella O, Fartoukh M, Parent F, et al. Inhaled nitric oxide as a screening agent for safely identifying responders to oral calcium-channel blockers in primary pulmonary hypertension. Eur Respir J. 1998;12(2):265–70.
19. Mehra MR, Kobashigawa J, Starling R, Russell S, Uber PA, Parameshwar J, et al. Listing criteria for heart transplantation: International Society for Heart and Lung Transplantation guidelines for the care of cardiac transplant candidates--2006. J Heart Lung Transplant. 2006;25(9):1024–42.

20. Champion HC, Michelakis ED, Hassoun PM. Comprehensive invasive and noninvasive approach to the right ventricle-pulmonary circulation unit: state of the art and clinical and research implications. Circulation. 2009;120(11):992–1007.
21. Di Salvo TG, Mathier M, Semigran MJ, Dec GW. Preserved right ventricular ejection fraction predicts exercise capacity and survival in advanced heart failure. J Am Coll Cardiol. 1995;25(5):1143–53.
22. Baker BJ, Wilen MM, Boyd CM, Dinh H, Franciosa JA. Relation of right ventricular ejection fraction to exercise capacity in chronic left ventricular failure. Am J Cardiol. 1984;54(6):596–9.
23. Lewis GD, Shah RV, Pappagianopolas PP, Systrom DM, Semigran MJ. Determinants of ventilatory efficiency in heart failure: the role of right ventricular performance and pulmonary vascular tone. Circ Heart Fail. 2008;1(4):227–33.
24. Juilliere Y, Barbier G, Feldmann L, Grentzinger A, Danchin N, Cherrier F. Additional predictive value of both left and right ventricular ejection fractions on long-term survival in idiopathic dilated cardiomyopathy. Eur Heart J. 1997;18(2):276–80.
25. Polak JF, Holman BL, Wynne J, Colucci WS. Right ventricular ejection fraction: an indicator of increased mortality in patients with congestive heart failure associated with coronary artery disease. J Am Coll Cardiol. 1983;2(2):217–24.
26. de Groote P, Millaire A, Foucher-Hossein C, Nugue O, Marchandise X, Ducloux G, et al. Right ventricular ejection fraction is an independent predictor of survival in patients with moderate heart failure. J Am Coll Cardiol. 1998;32(4):948–54.
27. Gavazzi A, Berzuini C, Campana C, Inserra C, Ponzetta M, Sebastiani R, et al. Value of right ventricular ejection fraction in predicting short-term prognosis of patients with severe chronic heart failure. J Heart Lung Transplant. 1997;16(7):774–85.
28. Miszalski-Jamka T, Klimeczek P, Tomala M, Krupinski M, Zawadowski G, Noelting J, et al. Extent of RV dysfunction and myocardial infarction assessed by CMR are independent outcome predictors early after STEMI treated with primary angioplasty. JACC Cardiovasc Imaging. 2010;3(12):1237–46.
29. Larose E, Ganz P, Reynolds HG, Dorbala S, Di Carli MF, Brown KA, et al. Right ventricular dysfunction assessed by cardiovascular magnetic resonance imaging predicts poor prognosis late after myocardial infarction. J Am Coll Cardiol. 2007;49(8):855–62.
30. Ghio S, Gavazzi A, Campana C, Inserra C, Klersy C, Sebastiani R, et al. Independent and additive prognostic value of right ventricular systolic function and pulmonary artery pressure in patients with chronic heart failure. J Am Coll Cardiol. 2001;37(1):183–8.
31. Bourantas CV, Loh HP, Bragadeesh T, Rigby AS, Lukaschuk EI, Garg S, et al. Relationship between right ventricular volumes measured by cardiac magnetic resonance imaging and prognosis in patients with chronic heart failure. Eur J Heart Fail. 2011;13(1):52–60.
32. Damy T, Kallvikbacka-Bennett A, Goode K, Khaleva O, Lewinter C, Hobkirk J, et al. Prevalence of, associations with, and prognostic value of tricuspid annular plane systolic excursion (TAPSE) among out-patients referred for the evaluation of heart failure. J Card Fail. 2012;18(3):216–25.
33. Dini FL, Fontanive P, Panicucci E, Andreini D, Chella P, De Tommasi SM. Prognostic significance of tricuspid annular motion and plasma NT-proBNP in patients with heart failure and moderate-to-severe functional mitral regurgitation. Eur J Heart Fail. 2008;10(6):573–80.
34. Kjaergaard J, Akkan D, Iversen KK, Kober L, Torp-Pedersen C, Hassager C. Right ventricular dysfunction as an independent predictor of short- and long-term mortality in patients with heart failure. Eur J Heart Fail. 2007;9(6–7):610–6.
35. Harjai KJ, Scott L, Vivekananthan K, Nunez E, Edupuganti R. The Tei index: a new prognostic index for patients with symptomatic heart failure. J Am Soc Echocardiogr. 2002;15(9):864–8.
36. Forfia PR, Fisher MR, Mathai SC, Housten-Harris T, Hemnes AR, Borlaug BA, et al. Tricuspid annular displacement predicts survival in pulmonary hypertension. Am J Respir Crit Care Med. 2006;174(9):1034–41.
37. Mathai SC, Sibley CT, Forfia PR, Mudd JO, Fisher MR, Tedford RJ, et al. Tricuspid annular plane systolic excursion is a robust outcome measure in systemic sclerosis-associated pulmonary arterial hypertension. J Rheumatol. 2011;38(11):2410–8.

38. Ghio S, Pazzano AS, Klersy C, Scelsi L, Raineri C, Camporotondo R, et al. Clinical and prognostic relevance of echocardiographic evaluation of right ventricular geometry in patients with idiopathic pulmonary arterial hypertension. Am J Cardiol. 2011;107(4):628–32.
39. Yeo TC, Dujardin KS, Tei C, Mahoney DW, McGoon MD, Seward JB. Value of a Doppler-derived index combining systolic and diastolic time intervals in predicting outcome in primary pulmonary hypertension. Am J Cardiol. 1998;81(9):1157–61.
40. van Wolferen SA, Marcus JT, Boonstra A, Marques KM, Bronzwaer JG, Spreeuwenberg MD, et al. Prognostic value of right ventricular mass, volume, and function in idiopathic pulmonary arterial hypertension. Eur Heart J. 2007;28(10):1250–7.
41. Moceri P, Dimopoulos K, Liodakis E, Germanakis I, Kempny A, Diller GP, et al. Echocardiographic predictors of outcome in eisenmenger syndrome. Circulation. 2012;126(12):1461–8.
42. Knauth AL, Gauvreau K, Powell AJ, Landzberg MJ, Walsh EP, Lock JE, et al. Ventricular size and function assessed by cardiac MRI predict major adverse clinical outcomes late after tetralogy of Fallot repair. Heart. 2008;94(2):211–6.
43. Bowers TR, O'Neill WW, Grines C, Pica MC, Safian RD, Goldstein JA. Effect of reperfusion on biventricular function and survival after right ventricular infarction. N Engl J Med. 1998;338(14):933–40.
44. Kucher N, Goldhaber SZ. Management of massive pulmonary embolism. Circulation. 2005;112(2):e28–32.
45. Inglessis I, Shin JT, Lepore JJ, Palacios IF, Zapol WM, Bloch KD, et al. Hemodynamic effects of inhaled nitric oxide in right ventricular myocardial infarction and cardiogenic shock. J Am Coll Cardiol. 2004;44(4):793–8.
46. Bhorade S, Christenson J, O'Connor M, Lavoie A, Pohlman A, Hall JB. Response to inhaled nitric oxide in patients with acute right heart syndrome. Am J Respir Crit Care Med. 1999;159(2):571–9.
47. Lewis GD, Lachmann J, Camuso J, Lepore JJ, Shin J, Martinovic ME, et al. Sildenafil improves exercise hemodynamics and oxygen uptake in patients with systolic heart failure. Circulation. 2007;115(1):59–66.
48. Lewis GD, Shah R, Shahzad K, Camuso JM, Pappagianopoulos PP, Hung J, et al. Sildenafil improves exercise capacity and quality of life in patients with systolic heart failure and secondary pulmonary hypertension. Circulation. 2007;116(14):1555–62.
49. Guazzi M, Vicenzi M, Arena R, Guazzi MD. Pulmonary hypertension in heart failure with preserved ejection fraction: a target of phosphodiesterase-5 inhibition in a 1-year study. Circulation. 2011;124(2):164–74.
50. Kaluski E, Cotter G, Leitman M, Milo-Cotter O, Krakover R, Kobrin I, et al. Clinical and hemodynamic effects of bosentan dose optimization in symptomatic heart failure patients with severe systolic dysfunction, associated with secondary pulmonary hypertension--a multicenter randomized study. Cardiology. 2008;109(4):273–80.
51. Rich S, Seidlitz M, Dodin E, Osimani D, Judd D, Genthner D, et al. The short-term effects of digoxin in patients with right ventricular dysfunction from pulmonary hypertension. Chest. 1998;114(3):787–92.

Chapter 5
Inhibition of the Renin-Angiotensin-Aldosterone System

Erika D. Feller

Introduction

In mild to severe heart failure, activation of the renin-angiotensin-aldosterone system is the primary abnormality. Increasing plasma levels of renin, angiotensin and aldosterone have direct effects on myocardium but also sodium and water handling, vascular contractility and reverse remodeling. Medical therapy to inhibit the renin-angiotensin-aldosterone system is the cornerstone of treatment for cardiomyopathy and heart failure.

This chapter will examine this neurohormonal pathway and discuss the deleterious effects when these pathways are activated. Current medical therapy, aimed to block activation points along the pathway, will be reviewed.

The Renin-Angiotensin-Aldosterone System

The renin-angiotensin-aldosterone system (RAAS) describes a cellular, enzymatic pathway involving primarily the heart, kidney, adrenal gland and vasculature that has various functions. Perhaps, most importantly, the RAAS regulates body-fluid volume. It does so by activating a series of reactions that then affect the absorption or secretion of sodium from the kidney. Congestive heart failure describes the state when intravascular fluid becomes extravascular secondary to a poor and/or decreased cardiac output [1] . During this disturbance in fluid balance, RAAS is activated, exacerbating the problem. Thus, inhibition of RAAS is a major target for therapeutic intervention.

E.D. Feller, MD
Assistant Professor, Medical Director Heart Transplant and Ventricular Assist Devices, University of Maryland Division of Cardiology, 110 South Paca Street, Baltimore, MD 21201, USA
e-mail: efeller@medicine.umaryland.edu

H. Eisen (ed.), *Heart Failure*, DOI 10.1007/978-1-4471-4219-5_5

The RAAS is first activated when renin blood levels increase. Increased renin levels are due to multiple factors. In particular, decreased blood flow to kidneys from decreased cardiac output, as well as hypotension, can increase renin secretion. A decrease in plasma sodium levels as a result of dilution from water retention in heart failure can have a similar result. Renin is secreted by the kidney's juxtaglomerular cells into the lumen of the afferent arterioles. Angiotensinogen is released from the liver, interacts with renin to form inactive angiotensin I. Angiotensin converting enzyme (ACE) degrades angiotensin I further to form angiotensin II [2] .

Most angiotensin II effects are mediated by the two receptors; angiotensin 1 receptor (AT1) and angiotensin 2 receptor (AT2). The AT1 mediates vasoconstriction and is widely expressed. The AT2 mediates vasodilation. This process happens primarily in the lungs on the endothelial surface of blood vessels. Angiotensin II is the main effector chemical of the RAAS.

Renin-dependent elevations in angiotensin II are associated with increases in circulating aldosterone. Aldosterone is a neurohormone and is secreted by the adrenal glands in response to angiotensin II, catecholamines, endothelins and potassium. Aldosterone works to maintain salt, water and potassium hemostasis, by binding to mineralocorticoid receptors in the kidney. Elevated levels of aldosterone add to the volume expansion seen in acute and chronic heart failure. Aldosterone has also been implicated in contributing to myocardial fibrosis [3]. Abundant myocardial fibrosis leads to cardiomyopathy and decreased myocardial systolic and diastolic function

The major hormone of the RAAS is angiotensin II. When angiotensin II, a strong vasoconstrictor is reduced, bradykinin, a strong vasodilator is increased. In addition to its vasodilatory properties, bradykinin can release tissue plasminogen activator (tPA). tPA has anti-ischemic properties.

The RAAS system is a complex interaction between multiple organ systems to regulate body-fluid volume in hemostasis as well as disease states, namely congestive heart failure. In the initial stages of developing left ventricular systolic dysfunction, if cardiac output declines or if peripheral arterial pressure decreases RAAS is activated in order to maintain and/or increase cardiac filling pressures, cardiac output and systemic blood pressure. Figure 5.1 shows the Renin-Angiotensin-Aldosterone System [4] .

Activation of the Renin-Angiotensin-Aldosterone System

The RAAS is activated in heart failure. The exact mechanisms by which activation occur are yet to be fully elucidated. Most likely, though, the combination of decreased perfusion to the kidney, decreased cardiac output, and low arterial pressure activate RAAS.

As a compensatory mechanism to decreased cardiac output, renin is released from the kidneys and is responsible for converting angiotensinogen to angiotensin

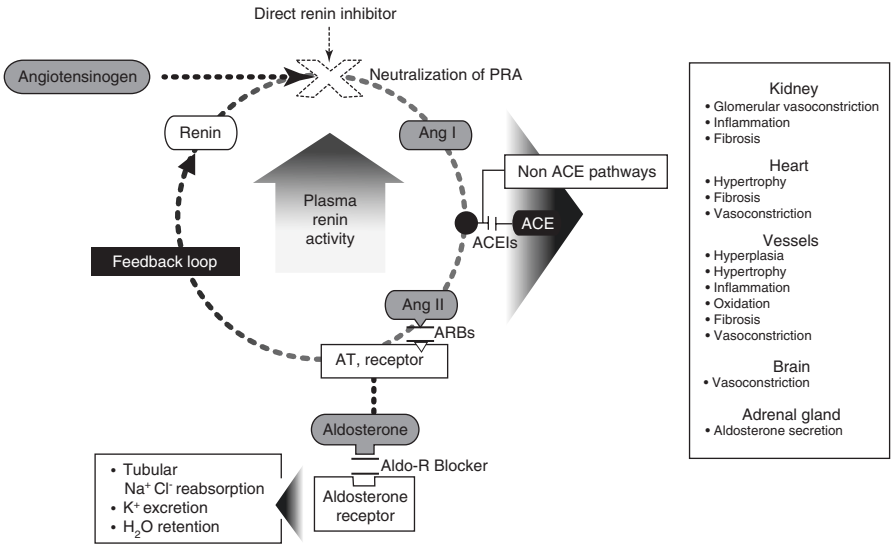


Fig. 5.1 The Renin-Angiotensin-Aldosterone System. The major components of RAAS are shown in the above figure. As depicted, an increase in plasma renin levels initiates the cascade. Multiple organ systems are involved (Reproduced with permission of Informa Healthcare, Haroonur [4], © 2008, Informa Healthcare. Reproduced with permission of Informa Healthcare)

I. Angiotensin I is then converted to angiotensin II by angiotensin-converting enzyme (ace). Angiotensin II stimulates the receptors AT1 and AT2.

Heart failure is defined as the pathological state in which the heart is unable to pump blood to adequately supply tissues to affect metabolism, or can do that but only with an increase in filling pressures. In the presence of an acute or subacute insult to the myocardium, which effects contractility, the heart depends on adaptive strategies to maintain pumping ability and cardiac output. Among the most important mechanism is activation of neurohormonal systems, including the sympathetic nervous system and the RAAS. The activation of RAAS can occur rapidly, over minutes to hours, to maintain cardiac function. The RAAS does this acutely by retaining salt and water to augment preload or cardiac filling. Additionally, RAAS activation can cause vasoconstriction, to help perfuse organs and tissues. Although, these mechanisms are adaptive in the short term, they are maladaptive in the long term.

As a result of activation of the RAAS, sympathetic nervous system and release of norepinephrine, myocardial hypertrophy and remodeling develop over weeks, months and years. With chronic activation of these pathways, these mechanisms become maladaptive. Although able to sustain cardiac function for some time, high filling pressures over time will ultimately cause worsening cardiac performance effecting organ perfusion and circulation. Many of the symptoms of heart failure, lower extremity swelling, dyspnea, orthopnea, paroxysmal nocturnal dys-

pnea, abdominal bloating are a consequence of the retention of fluid causing high filling pressures.

When the RAAS is activated in low cardiac output states, it is closely associated with the adrenergic system to maintain arterial pressure. Stimulation of beta1 adrenoceptors in the juxtaglomerular apparatus of the kidneys is a principle activator of renin release in acute heart failure. Fig. 5.2 shows the activation of the Renin-Angiotensin-Aldosterone System [5] .

Aldosterone is predominantly produced by the adrenal glands and, to a lesser degree, the endothelial and vascular smooth muscle cells in the heart and blood vessels. Aldosterone is regulated by the RAAS as well as potassium levels. Angiotensin II is the principal stimulator of aldosterone in the adrenal cortex [6]. Plasma levels of aldosterone can increase dramatically in patients with heart failure. This increase is attributed mainly to increased synthesis of aldosterone in response to activation of RAAS.

Aldosterone has been implicated in several harmful effects contributing to heart failure. Aldosterone vasoconstricts and also potentiates catecholamines. It upregulates inflammatory mediators such as macrophages, cytokines and chemokines.

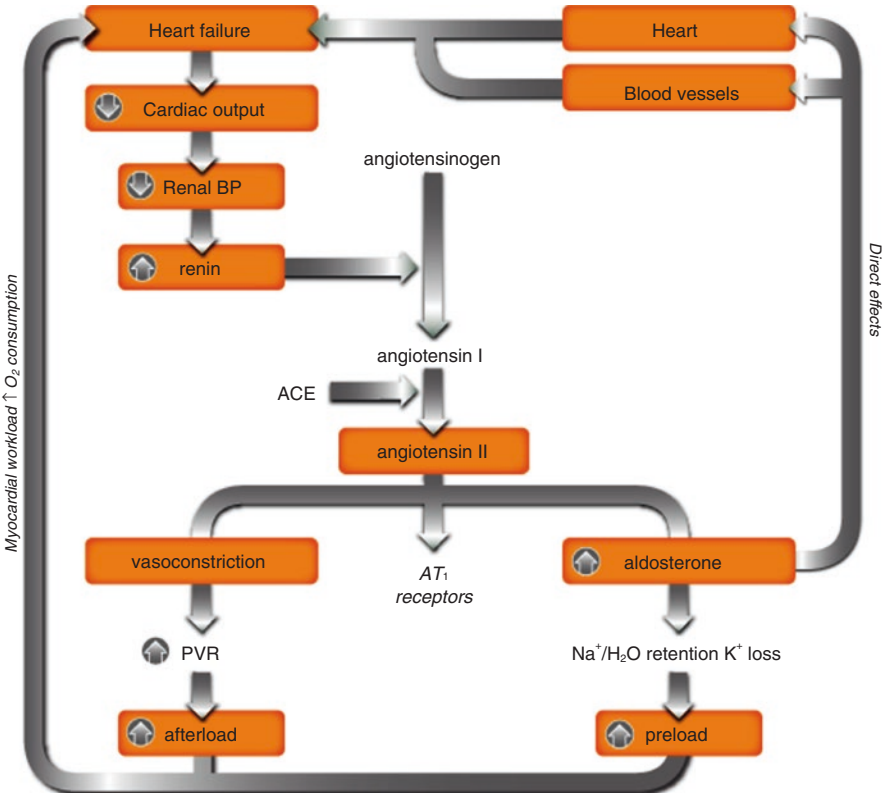


Fig. 5.2 Activation of the Renin-Angiotensin-Aldosterone System. Scheme picturing the primary hemodynamic mechanisms by which the RAAS is activated (Reproduced from Jackson et al. [5], © 2000, with permission from BMJ Publishing Group Ltd)

Aldosterone also plays a role in myocyte necrosis and scarring. Chronically elevated aldosterone levels contribute to myocardial fibrosis and deleterious remodeling. More recent studies have shown that aldosterone promotes platelet aggregation and activation [7, 8]. For these reasons, decreasing aldosterone levels with aldosterone inhibitors remain a therapeutic target and goal of modern heart failure therapy.

Treatment with ace-inhibitors results in an acute reduction in aldosterone levels. In chronic ace-inhibition, the reduction in aldosterone levels is weaker and more variable. This finding is referred to as aldosterone "escape" [9].

Effects of RAAS Activation

The actions of RAAS are beneficial in some circumstances. In heart failure, though, RAAS is chronically activated and results in deleterious effects. Chronic activation and up regulation of RAAS causes increased circulating angiotensin I, angiotensin II and aldosterone. Acute activation of RAAS maintains vascular tone or vasoconstriction. As a result, renal function is also maintained in the short term. In addition, cardiac output is preserved and left ventricular filling pressures are reduced.

Chronic activation of RAAS results in maladaptive remodeling of the myocardium. This includes fibrosis formation and myocyte hypertrophy.

Angiotensin II has several effects that contribute to the syndrome of heart failure and the progressive nature of left ventricular dysfunction. In particular, angiotensin II promotes hypertension, atherosclerosis and hypertrophic changes in the walls of arteries as well as the left ventricle [10].

Table 5.1 Major actions of RAAS components

Chemical	Actions
Aldosterone	Cardiac fibrosis, sodium and water retention, magnesium and potassium loss, vasoconstriction, sympathetic activation, parasympathetic inhibition, impairs arterial compliance, platelet activation and aggregation, activates macrophages, stimulates growth of fibroblasts and synthesis of collagen
Angiotensin converting enzyme	Proliferative and proinflammatory signaling
Angiotensinogen	Releases Angiotensin II, substrate for renin
Angiotensin I	Largely inactive precursor to angiotensin II, weak vasoconstrictor
Angiotensin II	Arterial vasoconstriction, pro-inflammatory, salt and water retention by the kidneys, stimulation of thirst, release of anti-diuretic hormone, augments norepinephrine release, remodels heart and blood vessels, induce cardiac myocyte hypertrophy, stimulates aldosterone, vasopressin, catecholamines and endothelin
Renin	Activates RAAS by cleaving angiotensinogen
Bradykinin	Vasodilator, anti-proliferative, cough, angioedema

Aldosterone promotes the retention of sodium and the loss of magnesium and potassium. Aldosterone also promotes sympathetic activation, parasympathetic inhibition myocardial and vascular fibrosis. Table 5.1.

Inhibition of Raas

Earlier segments of this chapter described activation of RAAS and the detrimental effects that activation of RAAS has on the ailing and/or failing heart. The rationale for combination therapy is to inhibit the production of angiotensin II, the major hormone involved in RAAS, at every step. Angiotensin II has several harmful effects. The reduction of angiotensin II by inhibiting RAAS activation is responsible for the many positive effects of ace-inhibition, angiotensin receptor blockade and aldosterone inhibition.

The current standard therapy for heart failure and cardiomyopathy is designed to interrupt the RAAS and the sympathetic nervous system (SNS) by using a combination of medications. Multiple trials have demonstrated the beneficial effects of using medications that target different hormones. Pharmacologic approaches to blocking the effects of angiotensin II, have been aimed at decreasing its production by inhibiting angiotensin converting enzyme or by direct inhibition at the level of the angiotensin receptor 1.

Ace-Inhibition

An angiotensin-converting-enzyme inhibitor (ace-inhibitor) is considered the first line therapy in treating patients with heart failure and left ventricular dysfunction. Ace-inhibitors have shown improved survival in patients with mild to severe chronic heart failure.

Ace-inhibitors block the conversion of angiotensin I to angiotensin II and prevent the degradation of bradykinin. The efficacy of ace-inhibition is due not only to blocking the harmful effects of angiotensin II, but also due to the promotion of bradykinin, a vasodilator. It is the bradykinin that causes some of the side effects of ace inhibitors (angioedema and cough). Ace-inhibitors also block the negative feedback in renin release by decreasing renin release and the rate of angiotensin I formation. Studies have shown multiple (pleiotropic) effects of ace-inhibition.

Ace-inhibitors have been shown to decrease left ventricular hypertrophy and smooth muscle proliferation. They decrease coronary vasoconstriction and have antimacrophage effects. Ace-inhibitors also have been shown to stabilize arterial plaque. In addition, ace-inhibitors also prevent ventricular remodeling. This has been shown clinically in patients with hypertension, symptomatic heart failure, elderly patients with heart failure and patients status-post myocardial infarction [11, 12].

Angiotensin Receptor Blockade

Angiotensin Receptor Blockers or ARBs have their effect further down the RAAS cascade. Unlike ace-inhibitors, ARBs have little effect on bradykinin, therefore no cough or angioedema. ARBs block angiotensin II at the receptor site.

While initiation of ace-inhibitors lead to a rapid decline in circulating angiotensin II, chronic use of ace-inhibitors can lead to an increase in angiotensin II, from initial decline. This increase in angiotensin II or "ACE escape" is thought to be due to conversion of angiotensin I to angiotensin II by means other than ACE. ARBs would avoid this phenomenon, based on their mechanism of action. In theory, ARBs would have a more complete blockade of angiotensin II [13].

ARBs have shown benefit in patients that are intolerant to ace-inhibitors or as an alternative to ace-inhibitors. The addition of ARBs to ace-inhibitors has shown benefit in decreasing hospital admissions, their benefit may be attenuated by increased risk of hyperkalemia. In patients intolerant to ace-inhibitors, valsartan, losartan and candesartan have shown benefits in mortality reduction [14–16].

Aldosterone Inhibition

Since the RALES trial was published in 1999, aldosterone inhibitors have been used for patients with heart failure. In the RALES trial, patients were assigned to receive aldosterone inhibitor (spironolactone) 25 mg daily or placebo. To enter the trial, patients had to have ejection fraction < 35 % and NYHA III–IV heart failure symptoms. The trial was stopped early due to significant benefits in the spironolactone arm. There was a 30 % reduction in deaths in the spironolactone group. This was due largely to a decreased risk of progressive heart failure and a decrease in sudden cardiac death [17].

Aldosterone inhibitors block the effect of aldosterone by binding to mineralocorticoid receptors. The two major aldosterone inhibitors are spironolactone and eplerenone. Spironolactone is a non-selective mineralocorticoid receptor antagonist. It also up-regulates progesterone receptors and down-regulates androgen receptors. Some of the side effects of spironolactone-gynecomastia, changes in libido and menses-are due to this effect. Spironolactone also causes hyperkalemia, which needs to be monitored closely.

Eplerenone is a selective mineralocorticoid receptor antagonist. It has fewer side effects than Spironolactone. Importantly, it can cause hyperkalemia as well, and must be also monitored closely.

Aldosterone can stimulate angiotensin II production, leading to fibrosis. The myocardium has mineralocorticoid receptors. The amount of aldosterone produced is proportional to the degree of heart failure.

Blockade of aldosterone can also help prevent hypokalemia caused by diuretics. This strategy may help prevent arrhythmogenic deaths attributed to hypokalemia.

Aliskiren is the first direct renin inhibitor that has been trialed in a hypertensive population. It has not been fully studies in heart failure, so its properties and effects in heart failure patients is unknown.

Data Supporting Inhibition of Raas

Ace inhibitors have been shown to reduce the risk of death and hospitalization. They have also been shown to alleviate symptoms of heart failure and improve quality of life. Clinical status, as measured by New York Heart Association class (NYHA), also improves when treated with ace inhibitors.

Ace inhibitors and ARBs have been extensively studied in clinical trials in patients with congestive heart failure. The first major trial showing benefit of ace inhibitors was the CONSENSUS trial, which compared enalapril with placebo in patients with NYHA IV heart failure. The enalapril group had a 40 % reduction in mortality ($p = 0.002$) and their symptoms significantly improved as measured by NYHA classification [18]. Soon after CONSENSUS, the SOLVD Treatment trial studied enalapril vs. placebo in a less ill patient population (NYHA II-IV). In SOLVD Treatment, the enalapril-treated group had a significant decrease in mortality and enjoyed fewer hospitalizations related to heart failure. In summary, this translated into a 16 % relative risk reduction in death and a 26 % reduction in hospitalization [19]. In SOLVD prevention trial, enalapril was studied in asymptomatic patients with ejection fraction < 35 %. Although in the enalapril group, there was not shown a significant reduction in mortality, there was a significant reduction in the combined end-point of death or worsening heart failure [20].

The V-Heft II trial compared enalapril to the combination of hydralazine and isosorbide dinitrate in patients with mild-moderate heart failure and ejection fraction of < 45 %. Enalapril reduced mortality by 34 % after 1 year and 28 % at 2 years compared to the hydralazine isosorbide group [21].

More recently, trials have been designed to specifically answer the lingering question as to how to best utilize ARBs; either added to ace-inhibitors or as an alternative. In the ELITE study, patients over the age of 65 with chronic heart failure were randomized to Losartan or Captopril. The primary endpoint was worsening renal function. Although the primary endpoint showed no statistical significance, there was a decrease in mortality among the Losartan treated patients [14]. Because of this finding, ELITE II was initiated which was powered to detect a mortality benefit between ace-inhibitors and ARBs. Patients were randomized to Losartan or Captopril. They were age greater than 60 and were NYHA II-IV. There was found to be no difference in all cause mortality (primary endpoint) or cardiac arrest (secondary endpoint) between the two groups [22].

The Val-HeFT trial was undertaken to assess the utility of the ARB Valsartan in heart failure patients already receiving an ace-inhibitor and/or beta-blocker. Val-HeFT had two end points, all cause mortality and a combined end point of mortality and morbidity. There was found to be no significant difference between the two groups in terms of all cause mortality (primary endpoint). In the Losartan group, there was a risk reduction in mortality and morbidity (secondary endpoint). This was felt to be largely due to the decrease in hospital admissions for heart failure in the Valsartan group [15].

In the CHARM-Alternative trial, patients were randomized to the ARB Candesartan or placebo. Criteria for entry into the trial were NYHA II–IV, EF of 40 % or less and intolerant to ace-inhibitors. The primary outcome was all cause mortality or hospital admission for heart failure. There was a 23 % risk reduction of cardiovascular death or heart failure admission in those taking Candesartan. [16] This finding confirmed the VAL-HeFT subgroup analysis that ARBs had a mortality benefit in those patients intolerant to ace-inhibitors. In the CHARM-Added trial, a similar patient demographic group was studied. Patients were already taking an ace-inhibitor and were randomized to Candesartan or placebo. Cardiovascular mortality and hospitalization for heart failure were reduced in the Candesartan group [23]. This trial, as well as VAL-Heft, suggests that an ARB, when added to ace-inhibitors and beta-blockers, confer benefit. In the CHARM-Preserved study, patients with preserved ejection fractions were studied. They were randomized to Candesartan or placebo. There was no significance between the groups in terms of mortality or heart failure hospitalizations.

The RALES trial (Randomized Aldactone Evaluation Study) enrolled patients with symptomatic heart failure and ejection fractions < 35 %. Patients were randomized to get spironolactone or placebo. Patients enrolled were receiving ace-inhibitors, diuretics and many times, digoxin. The primary end-point was death from all causes. The trial was stopped early after an interim analysis showed that spironolactone was significantly efficacious compared to placebo. The 30 % decrease in the risk of death in the spironolactone group was primarily attributed to a lower risk of death from progressive heart failure and sudden death from cardiac causes [17]. Additionally, the spironolactone group enjoyed a significant improvement in symptoms based on the New York Heart Association scale and had fewer hospital admissions for decompensated heart failure.

The RALES trial was undertaken after data emerged revealing that ace-inhibitors transiently, and not fully, suppress aldosterone.

The Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS) was designed to test the hypothesis that eplerenone, a selective aldosterone blocker would reduce overall mortality and cardiovascular mortality or hospitalization for cardiovascular events among patients with acute myocardial infarction complicated by diminished ejection fraction and heart failure. Patients with acute myocardial infarction, left ventricular dysfunction and heart failure were randomized to eplerenone or placebo. The primary end points were death from any cause and death from cardiovascular causes or hospitalization for heart failure, acute myocardial infarction, stroke or ventricular arrhythmia. The rate of

death, cardiovascular deaths and hospitalizations and sudden death were all reduced by eplerenone [24].

Congestive heart failure is a complex syndrome. When an insult to the heart results in a change in hemodynamics and a perturbation in homeostasis, the RAAS is activated to ensure that vital organs maintain adequate perfusion. In so doing, mechanisms that improve perfusion in the short term, cause congestive symptoms and abnormal cardiac preload and afterload in the acute and chronic periods. These changes, if not checked, may result in chronic progressive damage and worsening heart failure and cardiomyopathy. The therapies that control the increase activity of the RAAS, ace-inhibitors, ARBs and aldosterone inhibitors, have been studied in multiple large scale trials, and have been shown to decrease mortality, morbidity and RAAS activation. It has yet to be shown, if other targets of the RAAS will yield similar results.

Angiotensin Receptor-Neprilysin Inhibition

In late 2014, The Paradigm-HF study was published. This double-blind trial of NYHA class II-IV heart failure patients with ejection fraction <40 % were randomized to either an ace-inhibitor (enalapril) or a novel agent, neprilysin-inhibitor (sacubitril)-angiotensin receptor inhibitor (valsartan) combination.

Neprilysin is an enzyme that degrades natriuretic peptides, bradykinin and adrenomedullin [25]. Degradation of these neurohormones can result in vasoconstriction, sodium retention and myocardial remodeling; all maladaptive actions. Inhibition of neprilysin can increase the levels of these peptides countering these maladaptive actions.

The combination of inhibition of RAAS and inhibition of neprilysin had effects that were superior to inhibition of either alone, in smaller trials. In the Paradigm-HF trial, approximately 4200 patient received enalapril 10 mg twice daily and 4200 patients received combination valsartan and sacubitril, the neprilysin inhibitor. Patients in each cohort had similar baseline characteristics. The primary outcome was a composite of death from cardiovascular causes or hospitalization for heart failure. The trial was designed to detect a difference in rates of death from cardiovascular causes. The primary end point was reached in 914 patients in the valsartan/sacubitril group and 1117 patients in the enalapril group ($p < 0.001$). There were 558 cardiovascular deaths in the valsartan/sacubitril cohort and 693 cardiovascular deaths in the enalapril group ($p < 0.001$) [25]. As compared with enalapril, valsartan/sacubitril also reduced the risk of hospitalizations for heart failure, and decreased the symptoms and physical limitations associated with heart failure. The angiotensin receptor-neprilysin inhibitor significantly reduced the rates of death from any cause and from cardiovascular causes and the rates of hospitalizations for worsening heart failure as compared to enalapril [25].

The Paradigm-HF trial introduced the first new successful agent in the treatment of chronic, symptomatic heart failure in the last decade. The combination angotensin

Table 5.2 RAAS inhibition

Agent	Level of evidence	Strength of recommendation	Use
Angiotensin converting enzyme ace-i	High quality research in support	Strong	Heart failure with reduced ejection fraction and prior or current symptoms
Angiotensin receptor blocker arb	High quality research in support	Strong	Intolerant to ace-i Heart failure with reduced ejection fraction and prior or current symptoms
Angiotensin receptor/ neprilysin inhibitor arb	Moderate quality research in support	Strong	Tolerating adequate doses of ace-i or arb with continued class II-III symptoms Replace to further reduce morbidity and mortality
Aldosterone receptor antagonist	High quality research in support	Strong	Add to ace-i or arb Prior or current symptoms

ACC/AHA/AHFS summary recommendations for treatment of heart failure with reduced ejection fraction

II receptor antagonist and neprilysin-inhibitor, known as Entresto, work in synergy to inhibit RAAS and increase the beneficial effects of neuropetide activity.

Due to the strength of the Paradigm-HF data for sacubitril-valsartan, the American College of Cardiology the American Heart Association and Heart Failure Society recommended Entresto as class 1 for patients with chronic congestive heart failure, reduced ejection fraction and NYHA class II-III symptoms to replace an ace-I or ARB, in their 2016 practice guidelines [26]. (Table 5.2).

References

1. Schrier RW. Pathogenesis of sodium and water retention in high-output and low-output cardiac failure, nephrotic syndrome cirrhosis, and pregnancy. N Engl J Med. 1988;319:1065–72 1127-34.
2. Edwin K. Jackson. Goodman and gilman's the pharmacological basis of therapeutics, 10th edn. McGraw Hill, New York; 2001, p. 809–21.
3. Hensen J, Abraham WT, Durr J, Shrier RW. Aldosterone in congestive heart failure: analysis of determinants and role in sodium retention. Am J Nephrol. 1991;11:441–6.
4. Rashid H. Direct renin inhibition: an evaluation of the safety and tolerability of aliskiren. Curr Med Res Opin. 2008;24:2627–37.
5. Jackson G, Gibbs CR, Davies MK, Lip GYH. Pathophysiology. Brit Med J. 2000;320:1676.
6. Dluhy RG, Williams GH. Aldosterone-villain or bystander? N Engl J Med. 2004;351:8–10.
7. Weber KT. Aldosterone in congestive heart failure. N Engl J Med. 2001;345:1689–97.
8. Mizuno Y, Yoshimura M, Yasue H, Sakamoto T, Ogawa H, Kugiyama K, et al. Aldosterone production is activated in failing ventricle in humans. Circulation. 2001;103:72–7.
9. Pitt B, Reichek N, Willenbrock R, Zannad F, Phillips RA, Roniker B, et al. Effects of eplerenone, enalapril, and eplerenone/enalapril in patients with essential hypertension and left ventricular hypertrophy: The 4E-left ventricular hypertrophy study. Circulation. 2003;108:1831–8.

10. McEwan PE, Gray GA, Sherry L, Webb DJ, Kenyon CJ. Differential effects of angiotensin II on cardiac cell proliferation and intramyocardial perivascular fibrosis in vivo. Circulation. 1998;98:2765–73.
11. Captopril Multicenter Trial (Captopril Multicenter Research Group). A placebo controlled trial: captopril in refractory chronic congestive heart failure. J Am Coll Cardiol. 1983;2:755–63.
12. Pilote L, Abrahamowicz M, Rodriguez E, Eisenberg MJ, Rahme E. Mortality rates in elderly patients who take different angiotensin-converting enzyme inhibitors after acute myocardial infarction: a class effect? Ann Intern Med. 2004;141:102–12.
13. Jorde UP, Ennezat PV, Lisker J, Suryadevara V, Infeld J, Cukon S, et al. Maximally recommended doses of angiotensin-converting enzyme (ACE) inhibitors do not completely prevent ACE-mediated formation of angiotensin II in chronic heart failure. Circulation. 2000;101:844–6.
14. Pitt B, Segal R, Martinez FA, Meurers G, Cowley AJ, Thomas I, et al. Randomized trial of losartan versus captopril in patients over 65 with heart failure (Evaluation of Losartan in the Elderly Study, ELITE). Lancet. 1997;349:747–52.
15. Cohn JN, Tognoni G, for the Valsartan Heart Failure Trial Investigators. A randomized trial of the angiotensin receptor blocker valsartan in chronic heart failure. N Engl J Med. 2001;341:1675.
16. Granger CB, McMurray JJ, Yusuf S, Held P, Michelson EL, Olofsson B, Ostergren J, et al. CHARM Investigators and Committees.. Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function intolerant to angiotensin-converting-enzyme inhibitors: the CHARM-Alternative trial. Lancet. 2003;362:772–6.
17. Pitt B, Zannad F, Remme WJ, Cody R, Castaigne A, Perez A, et al. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized aldactone evaluation study investigators. N Engl J Med. 1999;341:709–17.
18. The Consensus Trial Study Group. Effects of enalapril on mortality in severe congestive heart failure. Results of the Cooperative North Scandinavian Enalapril Survival Study (Consensus). N Engl J Med. 1987;316:1429–35.
19. The SOLVD Investigators. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. N Engl J Med. 1991;325:293–302.
20. The SOLVD Investigators. Effect of enalapril on mortality and the development of heart failure in asymptomatic patients with reduced left ventricular ejection fractions. N Engl J Med. 1992;327:685–91.
21. Carson P, Ziesche S, Johnson G, Cohn JN. Racial differences in response to therapy for heart failure: analysis of the vasodilator-heart failure trials. J Card Fail. 1999;5:178–87.
22. Pitt B, Poole-Wilson PA, Segal R, Martinez FA, Dickstein K, Camm AJ, et al. Effect of losartan compared with captopril on mortality in patients with symptomatic heart failure: randomized trial—the Losartan Heart Failure Survival Study, ELITE II. Lancet. 2000;355:1582–7.
23. McMurray JJ, Ostergren J, Swedberg K, Granger CB, Held P, Michelson EL, et al. CHARM Investigators and Committees.Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic dysfunction taking angiotensin-converting-enzyme inhibitors: the CHARM-Added trial. Lancet. 2003;362:767–71.
24. Pitt B, Remme W, Zannad F, Neaton J, Martinez F, Roniker B, et al. Eperenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. N Engl J Med. 2003;348:1309–21.
25. McMurray JJ, Packer M, Desai A, et al. Angiotensin-Neprilysin Inhibition versus Enalapril in Heart Failure. N Engl J Med. 2014;371:993–1004.
26. Yancy, Clyde et al 2016 ACC/AHA?HFSA focused update on new pharmacological therapy for hearty failure: an update on new pharmacological therapy for heart failure: an update of the 2013 ACCF/AHA/guideline for the management of heart failure. Circulation. 2016; 134.

Chapter 6
Inhibition of the Sympathetic Nervous System

Evan P. Kransdorf and D. Eric Steidley

Introduction

Activation of the sympathetic nervous system (SNS) is a fundamental component of the pathophysiology of heart failure, especially heart failure with reduced ejection fraction (HFREF). Prolonged SNS activation contributes to several of the clinical sequelae of HFREF, such as loss of contractile reserve, ventricular remodeling, and sudden cardiac death. Over the last 30 years, extensive clinical research has shown that inhibition of the SNS in patients with heart failure improves outcomes including mortality, hospitalization for heart failure, progression of symptoms, and sudden cardiac death. The cornerstone therapy for inhibiting the SNS is administration of drugs that antagonize the β-adrenergic receptor (β-blockers). A robust body of evidence shows that β-blockers reduce symptoms and improve outcomes in all patients with HFREF. Non-pharmacologic therapies, such as cardiac resynchronization therapy (CRT) and exercise training, have been found to improve outcomes in patients with heart failure. Many beneficial effects arise from inhibition of the SNS. Here, we review the literature that supports the use of these pharmacologic and non-pharmacologic therapies and offer practical advice regarding their application in clinical care.

E.P. Kransdorf, MD, PhD
Cedars-Sinai Heart Institute, 8536 Wilshire Blvd #302, Los Angeles, CA 90211, USA
e-mail: evan.kransdorf@cshs.org

D.E. Steidley, MD (✉)
Mayo Clinic Arizona, Department of Cardiovascular Diseases,
5777 East Mayo Blvd., Phoenix, AZ 85259, USA
e-mail: steidley.d@mayo.edu

H. Eisen (ed.), *Heart Failure*, DOI 10.1007/978-1-4471-4219-5_6

Rationale for the Inhibition of the SNS in Heart Failure

The sympathetic nervous system (SNS) was accurately described as the regulator of "fight or flight" responses by Cannon in the early twentieth century [1]. Strong sympathetic stimuli cause several cardiac and peripheral vascular actions, including increased heart rate and contractility, as well as venous and arterial vasoconstriction [2]. The net effect of these changes is an increase in cardiac output, systemic blood pressure (BP) and blood volume, which support the organism's response to an acute threat. Over the last 100 years, research into the pathophysiology of several common cardiovascular diseases, such as heart failure and hypertension, has uncovered that the SNS is not only the mediator of the "fight or flight" responses, but is one of the mechanisms responsible for continuous maintenance of cardiovascular homeostasis [2].

The SNS maintains cardiovascular homeostasis via a complex system of nerve relays that contain two neurons and extend from the central nervous system to the target organs [3]. The preganglionic neuron has its cell body in the spinal cord, and projects its axon to a collection of neurons, or ganglion, that is distant from the target organ. In the heart, the sympathetic ganglion is known as the stellate ganglion and is located between the subclavian artery and the first rib [4]. The axons of the postganglionic neurons project to ventricular myocardium [5], where they release the neurotransmitter norepinephrine (NE). NE binds to specific β_1- and β_2-adrenergic receptors (AR) on the cardiac myocytes, through which G-protein coupled cell signaling leads to phosphorylation of multiple intracellular proteins, such as L-type calcium channels and the ryanodine receptor [6, 7]. These phosphorylated proteins mediate an increase in heart rate and contractility by increasing intracellular calcium levels.

In the most fundamental sense, heart failure is characterized by a decrease in myocardial performance [8]. In HFREF, contractile reserve at any degree of filling is suboptimal [9]. This hemodynamic abnormality increases the frequency of sympathetic nerve firing (activation) via the physiologic cardiovascular reflexes of the SNS that maintain homeostasis of systemic BP (the baroreflex), blood volume (cardiopulmonary reflex), and oxygenation (the chemoreceptor reflex) [10].

Activation of the SNS leads to increased myocardial NE levels [11], which despite favorable acute effects, act through direct and indirect mechanisms to cause cardiac pathology. Bristow and colleagues were the first to show that hearts from patients with advanced cardiomyopathy had a 50 % lower density of β_1-AR as compared to controls [12]. Fowler and colleagues showed that the degree of β_1-AR downregulation was proportional to the severity of heart failure and left ventricular systolic dysfunction [13]. High NE levels cause myocyte apoptosis by a direct effect [14], which worsens myocardial performance via adverse cardiac remodeling [15]. Activation of the SNS also causes alterations in the distribution of sympathetic neurons in the left ventricle [16]. Taken together, these data connect the activation of SNS with the clinical sequelae of heart failure: loss of contractile reserve, ventricular remodeling, and ventricular arrhythmia. Figure 6.1 summarizes the role of the SNS in the pathophysiology of HFREF.

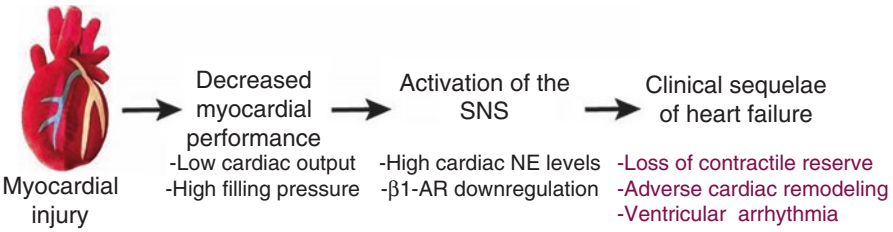


Fig. 6.1 Summary of the role of the sympathetic nervous system (SNS) in the pathophysiology of heart failure with reduced ejection fraction. An initial myocardial injury, such as myocardial infarction, leads to impaired cardiac performance. The cardiovascular reflexes sense the decreased cardiac performance and respond by increasing the sympathetic nerve-firing rate to compensate. Increased sympathetic nerve activity leads to high norepinephrine release and β_1-adrenergic receptor downregulation. The high norepinephrine levels lead to myocyte apoptosis and sympathetic nerve redistribution. Taken together, the activation of the SNS leads to the clinical sequelae of heart failure.

Sir James Black is credited with the development of propranolol, the first clinically useful β-adrenergic receptor antagonist (β-blocker) [17, 18]. His goal had been to find a new drug for the treatment of angina. He reasoned that a drug that could block α- and β-AR would decrease myocardial oxygen demand and relieve symptoms. For his pioneering work in pharmacology, he received the 1988 Nobel Prize for Physiology or Medicine.

Although there are 16 β-blockers currently approved by the U.S. Food and Drug Administration (FDA) [19] only carvedilol, bisoprolol, and metoprolol succinate have been approved for the treatment of HFREF based on evidence of their beneficial effects on outcomes. Both bisoprolol and metoprolol are cardioselective; they preferentially antagonize the β_1-AR that mediate the adverse effects of SNS activation [20]. Carvedilol is nonselective and antagonizes β_1-, β_2-, and α_1-AR [21], but exhibits long-lasting effects on β_1-AR signaling [22]. The pharmacology of these agents is highlighted in Table 6.1.

The Evidence Basis for β-Blocker Therapy in Heart Failure with Reduced Ejection Fraction

Propranolol entered clinical use for angina and myocardial infarction in the 1960s [23]. At that time, the existing therapies for chronic heart failure were digitalis, diuretics, and bed rest [24]. Early work into the pathophysiology of heart failure suggested that the heart was functionally deinnervated in heart failure [25] and that the elevated heart rate seen in patients with advanced cardiomyopathy was required to maintain cardiac output [26]. Therefore, it is not surprising that there was a long delay before the first clinical use of β-blockers for HFREF.

Then in the early 1970s, Waagstein and colleagues made the observation that treatment with propranolol improved pulmonary edema in patients with acute heart

Table 6.1 Pharmacological properties of β-blockers approved for use in HFREF [21]

Drug	Receptor activity			Plasma half-life (hours)	Starting dose (mg)	Target dose (mg)
	α	β_1	β_2			
Carvedilol	+	++	+	7–10	3.125 mg twice daily[a]	25 mg twice daily[b]
Bisoprolol	–	++	–	9–12	1.25 mg daily	10 mg daily
Metoprolol succinate	–	+	–	3–7	25 mg daily[a]	200 mg daily

[a]The starting dose can be halved for patients with severe heart failure, relative hypotension or bradycardia

[b]The maximum target dose is patients with mild to moderate heart failure weighing more than 85 kg is 50 mg twice daily

failure due to ischemia [27]. The mechanism of this benefit was thought to be reduction of tachycardia and decreased myocardial oxygen utilization [28]. Waagstein reasoned that patients with cardiomyopathy and resting tachycardia might derive a similar benefit from treatment with β-blockers. They treated seven patients with dilated cardiomyopathy for 2–12 months and found that β-blocker treatment decreased heart failure symptoms, improved exercise tolerance, and increased ejection time; they even noted an increased ejection fraction (EF) in three patients [27]. The next demonstration of the clinical utility of β-blocker therapy was by Swedberg and colleagues [29]. They initiated 24 patients with dilated cardiomyopathy already being treated with diuretics and digoxin on metoprolol, practolol, or alprenolol, and slowly increased the dose over 1–4 weeks. Treatment duration was at least six months. Survival was markedly improved in the group treated with β-blocker therapy in addition to diuretics and digoxin, as compared to historical controls treated with diuretics and digoxin alone (survival at 2 years 66 % versus 19 %).

β-blocker therapy for HFREF was initially met with skepticism [30], perhaps due to the small sample size and lack of control use in these early studies. This skepticism was further sustained by two small clinical trials that failed to show clinical benefit of β-blocker treatment in a total of 25 patients with dilated cardiomyopathy [31, 32].

The first randomized, placebo-controlled, multicenter clinical trial of β-blocker therapy in HFREF was the Metoprolol in Dilated Cardiomyopathy (MDC) trial [33]. In this trial, 383 patients with symptomatic dilated cardiomyopathy with a left ventricular EF less than 40 %, already on background treatment with an angiotensin converting enzyme inhibitor (ACEI), were treated with metoprolol tartrate or placebo, and followed for 12–18 months. Metoprolol tartrate was initiated at 10 mg twice daily and the dose titrated up to a target of 100–150 mg daily (mean dose 108 mg daily). Metoprolol treatment was associated with a 34 % reduction in the combined endpoint of death or need for heart transplantation, but this trend was not statistically significant. Treatment with metoprolol also lead to improvements in both exercise capacity and New York Heart Association (NYHA) class.

The Cardiac Insufficiency Bisoprolol Study (CIBIS) was initiated to determine the effect of β-blocker therapy on mortality in patients with dilated as well as

ischemic cardiomyopathy, and to assess the tolerability of β-blocker therapy [34]. In the study, 641 patients with advanced symptomatic heart failure (NYHA classes III and IV) with an EF less than 40 % were treated with bisoprolol or placebo and followed for a mean of 1.9 years. Bisoprolol treatment was associated with a 20 % reduction in all-cause mortality, but once again this was not statistically significant (confidence interval 0.56–1.15). However, there was a statistically significant decrease in hospitalization for heart failure and improvement in NYHA class with bisoprolol treatment. Two possible explanations for the failure of both the MDC and CIBIS trials to show a statistically significant effect of β-blocker therapy on mortality are either insufficient power in both trials, and/or the relatively low drug doses used in the studies (mean metoprolol dose in MDC of 108 mg, mean bisoprolol dose in CIBIS of 3.8 mg).

By 1994, β-blocker therapy had been shown to improve quality of life and decrease hospitalization for heart failure, but had not proven to affect mortality. Several large-scale clinical trials were initiated to determine if β-blocker therapy would indeed improve survival: (1) US Carvedilol Trials Program, (2) Cardiac Insufficiency Bisoprolol Study II (CIBIS-II), and (3) Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure (MERIT-HF). The US Carvedilol Trials Program was actually four clinical trials that were performed as part of phase III evaluation of carvedilol and were analyzed together [20]. In that trials program, 1094 patients with symptomatic heart failure were treated with carvedilol or placebo [35]. The program was ended early due to the significantly lower number of deaths in patients receiving carvedilol. The annual mortality rate was 3.2 % in the carvedilol group as compared to 7.8 % in the placebo group (relative risk reduction of 65 %). In May 1997, carvedilol became the first β-blocker to be approved by the FDA for the treatment of HFREF.

The US Carvedilol Trials Program was followed by publication of the CIBIS-II trial and the MERIT-HF trial. In CIBIS-II, treatment with bisoprolol as compared to placebo conveyed a strong mortality benefit in patients with advanced heart failure (83 % of patients were NYHA class III and 17 % were NYHA class IV) and an EF of less than 35 % [36]. In MERIT-HF, 3991 patients with symptomatic heart failure (mostly NYHA classes II and III) and an EF of less than 40 % were randomized to metoprolol succinate or placebo [37]. It showed statistically significant improvement in multiple outcomes: a 34 % reduction in mortality, a 49 % reduction in death from heart failure, and a 41 % reduction in sudden cardiac death with metoprolol treatment. Table 6.2 is a summary of the five β-blocker trials that have shown statistically significant decreases in mortality.

Despite the results of CIBIS-II, there was not widespread adoption of β-blocker therapy for patients with advanced heart failure [38]. In addition, there was concern whether certain racial minorities and women, who had both been underrepresented in previous trials, would also derive benefit from β-blocker therapy. To address these issues, the Beta-Blocker Evaluation of Survival Trial (BEST) was performed. In BEST, 2708 patients with advanced symptomatic heart failure (NYHA classes III and IV) and an EF less than 35 % were treated with bucindolol or placebo and followed for a mean of 24 months [39]. The BEST study population was 30 %

Table 6.2 Major clinical trials of β-blockers in HFREF that show a statistically significant decrease in mortality and morbidity

Trial	Year	Agent	Patient group	Endpoints			
				All-cause mortality	Death from HF	Sudden cardiac death	Admission for HF
US Carvedilol Study Group	1996	Carvedilol vs. placebo	NYHA II-IV, EF ≤ 35	⇓ 65 %	⇓ NS	⇓ NS	⇓ 27 %
CIBIS II	1999	Bisoprolol vs. placebo	NYHA III-IV EF < 35	⇓ 34 %	⇓ NS	⇓ 44 %	⇓ 20 %
MERIT-HF	1999	Metoprolol succinate vs. placebo	NYHA II-IV EF < 40	⇓ 34 %	⇓ 49 %	⇓ 41 %	⇓ 18 %
COPERNICUS	2001	Carvedilol vs. placebo	NYHA III-IV EF < 25	⇓ 35 %	NR	NR	⇓ 24 %[a]
COMET	2003	Carvedilol vs. metoprolol tartrate	NYHA II-IV, EF ≤ 35	⇓ 17 %	NR	NR	⇓ NS

NYHA New York heart association class, *EF* Ejection fraction, *HF* heart failure, *NR* not reported, *NS* not statistically significant

[a]Combined endpoint of death or hospitalization

minorities and 23 % women. The trial was ended early due to the absence of a significant difference in mortality between the treatment and placebo groups (hazard ratio of 0.9). It is worth noting that there were statistically significant decreases in the secondary outcomes of death from cardiovascular causes and hospitalization for heart failure.

Subgroup analysis of the BEST study showed that patients with non-black race received a mortality benefit from bucindolol, whereas black patients had no benefit. Given this, possible explanations for the failure of the trial to show a mortality benefit included that bucindolol had different pharmacologic properties as compared to the other β-blocking drugs, or that the population under study had pharmacogenetic differences that led to non-response. A subsequent study by Bristow and colleagues has suggested that the lack of efficacy in African-American patients may be due to a specific deletion within the α_{2c}-AR gene [40]. Additional work has confirmed that β-blockers do improve outcomes in African-American patients with heart failure, although to a lesser extent than in white patients [41].

Given that the BEST trial showed no survival benefit of bucindolol in patients with advanced cardiomyopathy, there was continuing concern that β-blocker therapy

would worsen heart failure in patients with advanced cardiomyopathy. This led in part to the design and execution of the Carvedilol Prospective Randomized Cumulative Survival Study Group trial (COPERNICUS) [35]. In this trial, 2289 patients with advanced symptomatic heart failure (NYHA classes III and IV) and an EF less than 25 % were treated with carvedilol or placebo and followed for a mean duration of 10.4 months. The trial was stopped early due to a statistically significant 35 % decrease in the risk of death in the treatment group. Importantly, therapy with carvedilol was well tolerated in this population, with a higher withdrawal rate at 1 year in the placebo group (18.5 % vs. 14.8 %).

Packer and colleagues published a meta-analysis in 2001 that showed that treatment with carvedilol led to a greater increase in EF as compared to metoprolol [42]. To assess whether this difference in EF led to a difference in outcome, the Carvedilol Or Metoprolol European Trial (COMET) was performed. In this trial, 3029 patients with symptomatic heart failure and an admission for heart failure within the last 2 years were randomized to carvedilol or metoprolol tartrate [43]. The mean doses achieved were 41.6 mg daily for carvedilol and 85 mg daily for metoprolol. After a mean of 58 months, patients treated with carvedilol had a 17 % lower risk of death, but there was no difference in the risk of hospital admission between the two groups. The results of the COMET trial are controversial because metoprolol tartrate is not FDA-approved for heart failure and the dose achieved in the metoprolol arm was relatively low [44]. Post-hoc analysis of the data from the Multicenter Automatic Defibrillator Implantation Trial With Cardiac Resynchronization Therapy (MADIT-CRT) showed that carvedilol was superior to metoprolol [45]. Over a follow up of 3.4 years in 1515 patients with mild heart failure (NYHA class I and II, EF $\leq$ 30 %), carvedilol treatment was associated with a 28 % lower risk of death or hospitalization for heart failure as compared to metoprolol.

These five clinical trials form the evidence-basis for the utilization of β-blockers in HFREF (summarized in Table 6.2). Use of β-blockers has been shown to decrease mortality, hospitalization and death from heart failure, and sudden cardiac death; therefore all patients with a left ventricular EF of 40 % and below should be treated with a β-blocker in the absence of a significant contraindication [46]. Because MERIT-HF used metoprolol succinate, BEST showed no benefit with bucindolol, and carvedilol was found to be superior to metoprolol tartrate in COMET, guidelines from the American College of Cardiology [47] and the Heart Failure Society of America [46] recommend that only carvedilol, bisoprolol, or metoprolol succinate be used to treat patients with HFREF.

In practice, clinicians caring for patients with newly diagnosed HFREF need to decide whether to initiate medical therapy for heart failure with an ACEI or a β-blocker. This dilemma is especially pertinent for patients whose initial BP is not sufficient to allow treatment with evidence-based doses of both agents. It is important to note that in the five β-blocker trials showing a decrease in mortality, nearly all patients (>90 %) in each trial were already being treated with an ACEI or angiotensin receptor blocker (ARB). Given this, current guidelines recommend initiation of an ACEI or ARB prior to the initiation of a β-blocker [46]. However, there is a small body of data that suggests that upfront initiation of a β-blocker is safe and

effective. Sliwa and colleagues performed a single-center randomized trial of carvedilol or perindopril (an ACEI) as initial therapy for 78 patients with idiopathic dilated cardiomyopathy [48]. Treatment with the first agent was continued for 6 months and then the second agent added. Endpoints were reviewed after 1 year. They found that patients in the carvedilol-first group experienced a greater improvement in NYHA class, EF, B-type natriuretic peptide levels, with a higher carvedilol dose achieved. These positive findings led to the CIBIS-III trial, in which 1010 patients with symptomatic heart failure and an EF less than 35 % were randomized to monotherapy with bisoprolol or enalapril for 6 months [49]. After this time, the complimentary drug was initiated and maintained through the end of the trial. Treatment with bisoprolol-first was noninferior to enalapril-first in the intention-to-treat sample with regards to the primary endpoint of mortality or hospitalization for HF. There was no statistical difference in the frequency of adverse events between the groups. Further analysis of CIBIS-III has shown that 60 % of the adverse events occurred during the monotherapy period [50], suggesting that both guideline-based therapies should be implemented and uptitrated without delay.

Additional Clinical Benefits of SNS Inhibition with β-Blocker Therapy

In addition to a mortality benefit, β-blocker therapy has been shown to have other significant clinical benefits in patients with HFREF. Treatment with carvedilol and metoprolol succinate have been shown to lead to reverse remodeling of the left ventricle, characterized by an increase in the EF and a decrease in the end-systolic and end-diastolic volumes [51]. β-blocker therapy improves heart failure symptoms, with a net effect of lowering NYHA class by one grade and improving exercise time [52]. Only one meta-analysis of ten trials showed no significant improvement in quality of life with β-blocker therapy [53].

Peak oxygen consumption (VO_2) and natriuretic peptides are commonly used markers of heart failure severity that are affected by treatment with β-blockers. In 1991 Mancini and colleagues followed a group of ambulatory heart failure patients with a $VO_2 > 14$ mL/kg/min who had similar one- and two-year survival rates with or without heart transplantation [54]. Subsequently, this VO_2 value has served as a useful threshold to inform the timing of heart transplantation. This study was completed before the widespread use of β-blockers in HFREF. While β-blocker treatment does not change peak VO_2, long-term mortality is improved with a hazard ratio of 0.6 [55]. Because of this improved mortality while on treatment, Peterson and colleagues showed that advanced cardiomyopathy patients receiving β-blockers do not benefit from heart transplantation until $VO_2 < 12$ mL/kg/min [56].

B-type natriuretic peptide (BNP) and N-terminal proBNP (NT-BNP) are used as both diagnostic and prognostic markers for heart failure [57]. Stanek and colleagues were among the first to examine the effect of β-blocker treatment on BNP and NT-BNP levels [58]. They found that treatment with atenolol for 6 months reduced

NT-BNP but not BNP levels. In a substudy of the COPERNICUS trial, treatment with carvedilol did not decrease the median level of NT-BNP as compared to placebo, but did strongly decrease NT-BNP when analyzed as a change from baseline level for each patient (25 % decrease with carvedilol as compared to 5 % decrease with placebo at 6 months) [59]. Treatment with a β-blocker does not affect the utility of these prognostic markers, as BNP and NT-BNP levels remain strongly predictive of mortality [58, 60].

Considerations and Cautions with β-Blocker Therapy

Patients with chronic heart failure are a heterogeneous group with a wide spectrum of cardiovascular diseases and underlying comorbidities. Despite this heterogeneity, multiple subgroups of patients with HFREF are able to be safety treated with β-blocker therapy and there are few absolute contraindications to their use.

There are important considerations and cautions for the use of β-blockers in the treatment of HFREF. Table 6.3 contains a list of the comorbidities and conditions in which β-blocker therapy for HFREF is generally tolerated or in which therapy should be used with caution or avoided.

Concerns that treating HFREF with β-blockers would worsen heart failure symptoms and precipitate decompensation shortly after drug initiation have been prevalent [61]. Hemodynamic data confirm that left ventricular systolic pressure and cardiac index acutely decrease [62]. β-blocker administration may decrease sodium excretion and thereby increase volume overload [63]. Consistent with this, both BNP and NT-BNP levels are increased compared to baseline when measured 6 weeks after β-blocker initiation, and then decline by 3 months [59, 64]. These data underscore the point that β-blocker initiation may cause a transient worsening of clinical status.

By following three principles during initiation of β-blocker therapy, clinicians can help ensure tolerability and patient acceptance. First, β-blockers should not be initiated in patients in acute hemodynamic instability. Second, β-blockers should not be initiated in patients with worsening symptoms and signs of volume overload. In all of the large clinical trials discussed above, patients were clinically euvolemic at the time of drug initiation. Third, β-blockers should be initiated at a low dose, and then titrated upwards at regular intervals over several weeks. Before each dose increase, the clinician should ensure the patient has maintained clinical stability in terms of symptoms, volume status, heart rate, and BP. The frequency of dose increase in clinical trials has varied between 1 week (as in CIBIS-II and BEST) and 2 weeks (as in MERIT-HF, COPERNICUS, and COMET), with current guidelines recommending dose increases at 2 week intervals [46]. In our practice, we individualize both the starting dose and the speed of uptitration according to multiple clinical characteristics of the patient, including NYHA class, EF, BP, heart rate, and diuretic requirements. Specialized programs for uptitration of β-blocker dose by nurse clinicians may be helpful, as they have been shown to achieve higher rates of target β-blocker dose utilization as compared to standard of care [65].

Table 6.3 Comorbidities and conditions in which β-blocker therapy for HFREF is tolerated or in which therapy should be used with caution or avoided

Generally tolerated	Use with caution	Avoid use
Comorbidities		
Diabetes mellitus	Diabetes mellitus with recurrent hypoglycemic events	
Mild to moderate COPD	Severe COPD with frequent exacerbations	COPD with active bronchoconstriction
Stable RAD, treated with a cardioselective β-blocker	RAD with frequent exacerbations	RAD with active bronchoconstriction
Peripheral arterial disease without claudication	Peripheral arterial disease with claudication	Peripheral arterial disease with critical limb ischemia
Hemodynamic conditions		
Asymptomatic hypotension with SBP > 90 mmHg	Asymptomatic hypotension with SBP 80–90 mmHg	Symptomatic hypotension (e.g. orthostatic symptoms)
Stable advanced heart failure (left ventricular EF ≤ 25 %)	Decompensated heart failure; resting sinus tachycardia > 100 BPM	Acute hemodynamic instability or use of I.V. beta-agonist (e.g. dobutamine)
Heart rhythm conditions		
Sinus rhythm with heart rate 60–100 BPM	Sniusbradycardia with HR < 60 BPM	Sinus bradycardia with HR < 55 BPM
First-degree AV block; sinus bradycardia during sleep	Type I second-degree AV block (Wenckebach)	Type II second-degree AV block; third-degree AV block

COPD chronic obstructive pulmonary disease, *RAD* reactive airway disease, *SBP* systolic blood pressure, *EF* ejection fraction, *BPM* beats per minute, *HR* heart rate, *AV* atrioventricular

The above three principles have been followed by all of the above-mentioned clinical trials of β-blockers and have contributed to the remarkable tolerability of therapy in these studies. Analysis of data from the MERIT-HF trial showed that as early as 90 days after initiation of metoprolol succinate there was a decrease in the risk of mortality or hospitalization, no change in symptoms, and a decrease in the daily dose of furosemide [66]. Even in patients at very high risk of decompensation, there was no increase in death or hospitalization at 8 weeks in the COPERNICUS trial [67].

Overall tolerability of β-blocker therapy in clinical trials has been excellent, with more patients discontinuing therapy in the placebo group than in the active treatment group [68]. Side effects of bradycardia, dizziness, and hypotension do occur more frequently with β-blocker treatment as compared to placebo, but have been shown to be infrequent causes of discontinuation of therapy. Table 6.4 lists the incidence of these side effects as determined in a meta-analysis by Ko and colleagues [68]. It is important to note that β-blockers will decrease the sinus rate and prolong conduction through the atrioventricular node, and so use is contraindicated in patients with bradycardia (HR < 55 BPM) or second- and third-degree AVB [69].

Table 6.4 Frequency of side effects more commonly seen with β-blocker treatment than placebo by meta-analysis [68]

Side effect	Frequency during treatment with β-blocker	Frequency during treatment with placebo	Risk ratio
Hypotension	7.6 %	6.1 %	1.41
Dizziness	21.5 %	16.6 %	1.37
Bradycardia	5.7 %	1.8 %	3.62

The role of pacemaker placement to facilitate β-blocker therapy, in the absence of indications for an implantable cardiac defibrillator or cardiac resynchronization therapy (CRT) is unclear. The Dual Chamber and VVI Implantable Defibrillator II Trial (DAVID-II) showed that atrial pacing at a rate of 70 BPM was safe, although it provided no clinical benefit over backup ventricular pacing at 40 BPM, in patients with HFREF (mean EF 26 %) and an implanted defibrillator [70]. Notably, the percentage of patients receiving target dose β-blocker therapy was similar between the two groups, suggesting that pacemaker mode did not significantly affect β-blocker dose titration.

Physicians should follow the systemic BP closely during titration of medical therapy for HFREF. Indeed, BP is linked to outcome in heart failure with lower BP associated with more advanced cardiomyopathy and consequently higher mortality [71]. Patients with hypotension (BP < 100 mmHg) were excluded from all the major β-blocker trials except COPERNICUS and COMET. Analysis of outcomes data by baseline BP in the COPERNICUS trial showed that patients with the lowest BP, ranging from 85–95 mmHg, had an equal benefit of β-blocker therapy [72]. However, these patients did experience a higher frequency of side effects and were more likely to stop treatment. In practice, β-blocker therapy can be initiated cautiously in asymptomatic patients (i.e., without orthostatic symptoms) and chronic BP 85–95 mmHg. These patients require careful monitoring to ensure stability of their clinical status during treatment.

Diabetes mellitus (DM) is present in about 25 % of patients with HFREF [73]. Patients with DM and HFREF are at an increased risk of mortality and derive a survival benefit from treatment with β-blockers [74]. However, because β-blockers can blunt the autonomic response that alerts patients to the presence of hypoglycemia, there are long-standing concerns that β-blocker use may be dangerous in patients with DM. In contrast to these concerns, Shorr and colleagues found a decreased risk of serious hypoglycemia with cardioselective β-blocker use (relative risk 0.73) and a small, non-significant increased risk with nonselective β-blocker use (relative risk 1.26) in 13,559 patients being treated with antihypertensive medications [75].

Peripheral arterial disease with claudication was initially a contraindication to β-blocker therapy because of case reports describing a worsening of symptoms with therapy [76]. A subsequent meta-analysis of six small trials has shown no significant effect of β-blocker therapy on time to claudication or walking distance [77].

Thus, β-blocker therapy can be used cautiously in patients with advanced peripheral arterial disease.

Pulmonary disease has been another comorbidity affecting the utilization of β-blocker therapy. The lung contains β_2-AR that mediates bronchial smooth muscle cell relaxation and are the pharmacologic target of agonist drugs used in both reactive airway disease (RAD) and chronic obstructive pulmonary disease (COPD) [78]. Early on, the nonselective β-blocker propranolol was shown to precipitate bronchospasm in asthmatic patients [79]. Salpeter and colleagues showed that in patients with RAD, treatment with a cardioselective β-blocker led to a 7.5 % decrease in forced expiratory volume in 1 second (FEV1) after the first dose without causing respiratory symptoms. Continued treatment was not associated with a further decline in FEV1 and was well tolerated in the short-range trials analyzed in this meta-analysis [80]. By comparison, the nonselective β-blocker carvedilol was tolerated in only six of 12 patients with asthma [81]. The use of cardioselective β-blockers in patients with stable RAD is acceptable but treatment of patients with severe disease should be avoided. The use of selective β-blockers should be considered.

Patients with COPD are able to tolerate β-blocker therapy more readily than those with RAD, and newer data suggests that COPD patients without heart failure may have decreased mortality with β-blocker treatment [82]. Salpeter and colleagues have examined the use of cardioselective β-blockers in patients with COPD and found that they are well tolerated [83]. Two studies have evaluated the use of nonselective β-blockers in patients with COPD and HFREF. Jabbour and colleagues performed a trial with 35 patients with COPD and HFREF and found that FEV1 was lower with carvedilol as compared to metoprolol or bisoprolol, but all three agents were well-tolerated [84]. Furthermore, an analysis of data from the Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients With Heart Failure (OPTIMIZE-HF) showed that there was no difference in survival between patients treated with selective versus nonselective β-blockers in HFREF patients with COPD [85].

β-Blocker Therapy in Hospitalized Heart Failure Patients

Hospitalization for acute decompensated heart failure is common with over one million hospitalizations occurring in 2009 [86]. In 1999, due to studies indicating that antagonism of the adrenergic system could lead to volume overload [87] as well as an absence of data showing benefit of β-blocker use in patients with NYHA class IV symptoms, the Advisory Council To Improve Outcomes Nationwide in Heart Failure (ACTION HF) guidelines recommended that patients with decompensation requiring hospitalization or the use of intravenous agents have their β-blocker dose reduced or discontinued [61]. Furthermore, *de novo* initiation or re-initiation of therapy was recommended to be performed

exclusively in the outpatient setting after discharge [88]. However, over the last 10 years, several clinical studies have shown that outcomes are improved by continuing β-blocker therapy during hospitalization and initiating therapy before hospital discharge. In the Initiation Management Predischarge: Process for Assessment of Carvedilol Therapy in Heart Failure (IMPACT-HF) trial, 363 patients were randomized to initiation of carvedilol before discharge or at least 2 weeks after discharge [89]. The number of patients treated with any β-blocker at 60 days after discharge was significantly higher in the before discharge group (91 % vs. 73 %), without a significant difference in outcome between the groups. Fonarow and colleagues extended these findings in an analysis of patients with HFREF hospitalized in the OPTIMIZE-HF registry [90]. They found that patients continued on β-blocker therapy at hospital admission or started *de novo* had a lower risk of mortality at 60–90 days after discharge, even after adjusting for clinical variables predictive of post-discharge mortality. Thus, continuation of β-blocker therapy in patients with HFREF that are hospitalized for an acute decompensation is recommended, unless other contraindications to continued therapy, such as bradycardia or shock, are present [46]. Data from OPTIMIZE-HF showed that patients who are initiated on β-blocker therapy while hospitalized for heart failure are three times more likely to be treated with a β-blocker at 60–90 day follow-up [91]. Thus, we conclude that therapy should be initiated before discharge for most patients with HFREF.

Patients hospitalized with acute decompensated heart failure who are placed on inotropic therapy for hemodynamic support represent a special category of patients with advanced cardiomyopathy [92]. The inotropes approved for use in the United States are the β_1-agonist, dobutamine and the phosphodiesterase III inhibitor, milrinone. Inotropic therapy has long been used to improve hemodynamics in NYHA class IV patients with depressed cardiac output. However, given the improvement in clinical outcomes seen in patients with NYHA class IV heart failure in COPERNICUS, it might be beneficial to treat patients with advanced disease with both an inotrope and a β-blocker [93]. Mehtra and colleagues were the first to carefully study this issue by measuring the hemodynamic response to dobutamine and enoximone (an oral phosphodiesterase III inhibitor) before and after treatment with a β-blocker in 34 patients with HFREF [94]. They found that the hemodynamic effects of dobutamine infusion were blunted by treatment with metoprolol and carvedilol, but the effects of enoximone were not blunted by treatment with either agent. This trial showed that β-blockers should not be used in conjunction with dobutamine, but can be used with phosphodiesterase III inhibitors. A review of four studies examining combination treatment with milrinone and β-blockers showed that co-treatment is well-tolerated and has a neutral or beneficial effect on mortality [95]. Combination treatment has also been investigated as a method to help improve cardiac function sufficiently to allow inotrope weaning [96]. We have concluded that β-blockers should not be used with dobutamine because of their blunting effect on the hemodynamic response, but appear to be safe to be used with milrinone, and may improve outcomes.

Optimization of β-Blocker Therapy

There are patient-related and system-based barriers for the optimal utilization of β-blocker therapy in patients with HFREF. Given that β-blockers decrease heart rate and BP, a small number of patients may not tolerate even low-dose therapy or be able to reach target doses of therapy. In the OPTIMIZE-HF registry, 9.4 % of patients with HFREF were not discharged on a β-blocker due to a documented contraindication (Fig. 6.2) [91]. Patient characteristics associated with the inability to tolerate the initiation of carvedilol in the outpatient setting include higher NYHA class, older age, lower diastolic blood pressure, and higher blood urea nitrogen concentration [97]. In a cohort of 340 patients with HFREF, 10 % of patients discontinued therapy over a 2 year period. The most common reason for discontinuation was a failure to restart a β-blocker after hospitalization [98].

Based on the dosing strategy utilized in the major clinical trials, β-blockers should be generally initiated at a low dose and uptitrated until dose-limiting side effects occur or until the target dose is reached. Analysis of the clinical trial data supports this "target dose" strategy, with dose-related improvements in outcomes seen in the MOCHA [99], CIBS-II [100], and COMET trials [101]. This benefit has not been uniformly shown however, as patients in MERIT-HF receiving low-dose metoprolol (≤ 100 mg daily) or high-dose metoprolol (> 100 mg daily) had a similar benefit of therapy [102]. In practice, only a minority of patients treated with β-blockers reach target doses. In the Carvedilol Heart Failure Registry (COHERE), 55 % of patients were receiving less than the target dose of carvedilol [103].

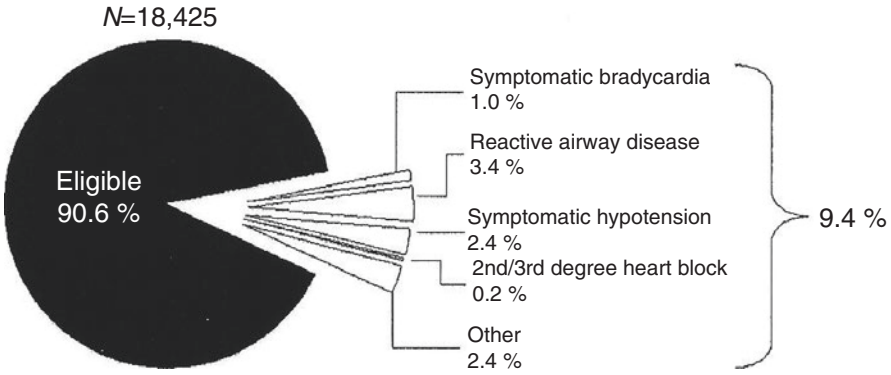


Fig. 6.2 Documented contraindications for β-blocker non-use at the time of hospital discharge in the OPTIMIZE-HF registry. In OPTIMIZE-HF, 9.4 % of 18,425 patients had a documented contraindication for β-blocker treatment, which are listed in the figure. (Figure reproduced with modification from Fonarow et al. [91], © 2007, with permission from Elsevier)

Another potential strategy is to uptitrate the β-blocker dose based on the heart rate, as analyses of the CIBIS-II and COMET trials showed that the benefit of therapy was related to the magnitude of heart rate reduction [101, 104]. McAllister and colleagues performed a meta-analysis of 17 β-blocker clinical trials and found that the magnitude of survival benefit was related to the heart rate reduction, with a relative risk reduction for death of 18 % for each decrease in heart rate by five beats/minute [105]. In this meta-analysis there was no relationship between the β-blocker dose achieved and the survival benefit. At this time the optimal dosing strategy is unclear, but guidelines recommend titration to target the doses used in the clinical trials of β-blockers [47].

β-Blocker Therapy in Heart Failure with Preserved Ejection Fraction

Heart failure with preserved ejection fraction (HFPEF) is a distinct heart failure syndrome as compared to HFREF [106]. At the cellular level, ATP-dependent relaxation is impaired in patients with HFPEF, which leads to decreased chamber compliance and elevated filling pressures. The available data suggest that the level of SNS activation is less in HFPEF as compared to HFREF [107, 108]. However, based on a small body of data, β-blocker therapy may be beneficial in patients with HFPEF.

In the Study of the Effects of Nebivolol Intervention on Outcomes and Rehospitalization in Seniors with Heart Failure (SENIORS) trial, 2135 patients age 70 or older with an admission for heart failure within the last year or an EF ≤ 35 % were randomized to treatment with nebivolol or placebo [109]. The enrolled population was a mix of patients with HFREF (65 % with EF ≤ 35 %) and mildly reduced EF (35 % with EF > 35 %). After a mean of 20 months, patients treated with nebivolol had a 14 % lower risk of death or hospitalization for heart failure, verifying that elderly patients with heart failure benefit from β-blocker therapy. When analyzed by baseline EF, there was a similar trend towards benefit in patients with HFREF and those with a mildly reduced EF [110]. El-Refai and colleagues performed a retrospective analysis of the effects of β-blocker therapy in a mixed cohort (both HFPEF and HFREF) of patients with a hospitalization for heart failure treated with β-blocker therapy [111]. Treatment with a β-blocker decreased the combined endpoint of death or hospitalization for heart failure both in patients with HFPEF and HFREF (hazard ratio 0.68 and 0.53, respectively), after multivariate adjustment for baseline predictors of outcome. In contrast to these results, patients with HFPEF who were initiated on β-blocker therapy during a hospitalization for heart failure did not have improved survival or decreased rehospitalization for heart failure at 1 year in the OPTIMIZE-HF registry [112]. Thus, additional clinical trials are needed to address these conflicting findings of β-blocker therapy in patients with HFPEF.

Monitoring the Response to β-Blocker Therapy

Metaiodobenzylguanidine (MIBG) imaging and heart rate variability are methods to determine the level of SNS activation. In patients with heart failure, SNS activation leads to high levels of NE in the synapse, which overwhelm the presynaptic transporter responsible for moving NE back into the cell [113]. Iodine-123 labeled MIBG is an analog of NE, and so the decreased reuptake of NE from the synapse leads to low MIBG uptake and high washout [114]. Clinical imaging is performed using single-photon emission computed tomography (SPECT) [115] or positron emission tomography (PET) [116]. See Fig. 6.3 for an example of MIBG imaging in heart failure [115].

Decreased myocardial uptake of iodine-123 labeled MIBG was first shown to be associated with adverse outcomes in heart failure patients in 1992 [117], but the first prospective validation of MIBG imaging was the AdreView Myocardial Imaging for Risk Evaluation in Heart Failure (ADMIRE-HF) study published in 2010 [118].

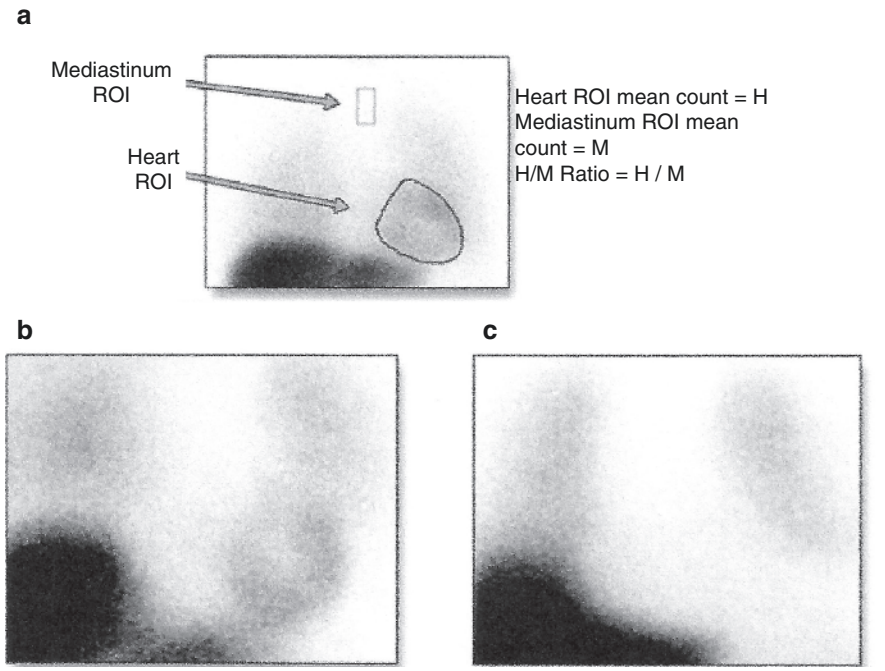


Fig. 6.3 Quantification of sympathetic nervous system activation with metaiodobenzylguanidine (MIBG) imaging. (**a**) Method for calculation of the heart-to-mediastinum ratio on MIBG imaging of the chest. Regions of interest (ROI) are drawn over the heart and mediastinum. (**b**) Normal SNS activation level and MIBG activity in a patient with a heart-to-mediastinum ratio of 1.8. (**c**) Abnormal SNS activation level and low MIBG activity in a patient with a heart-to-mediastinum ratio of 1.1 (Figure reproduced with modification from Carrió et al. [115] © 2010, with permission from Elsevier)

In this study, 961 subjects underwent MIBG imaging and were followed for a median of 17 months. A low heart-to-mediastinum ratio of MIBG uptake was found to predict a composite outcome of cardiac events, as well as the individual outcomes of heart failure progression, arrhythmic events, and cardiac death. Currently, the role of MIBG imaging in risk stratification as compared to established methods such as cardiopulmonary exercise testing is unclear. Treatment with carvedilol has been shown to improve MIBG uptake, which further serves as proof of principle that monitoring SNS activation may help patient level prediction of outcomes and help clinicians individualize neurohormonal therapies for heart failure [119, 120].

The sympathetic and parasympathetic nervous systems innervate the sinoatrial node and lead to fluctuations in heart rate via activation of their corresponding receptors [121]. Measurements of these normally occurring variations in the R-R interval due to autonomic tone are collectively termed heart rate variability (HRV) [122]. HRV can be measured by several different parameters, the most popular of which is the standard deviation of all R-R intervals in a 24 hour period (SDNN) [123].

The activation of the sympathetic nervous system that occurs in heart failure leads to a reduction in HRV [124]. This reduction in HRV is not uniform in patients with advanced cardiomyopathy [125], with several different HRV parameters having been shown to predict outcome in patients with advanced heart failure. Bilchik and colleagues showed that SDNN < 65.3 milliseconds was associated with a 3.7-fold higher risk of mortality and a 2.4-fold higher risk of sudden cardiac death [126]. Figure 6.4 presents an example of abnormal HRV in heart failure. Therapy with carvedilol has been shown to improve HRV in patients with HFREF [127, 128]. Therefore, both abnormal MIBG imaging and HRV correlate with adverse

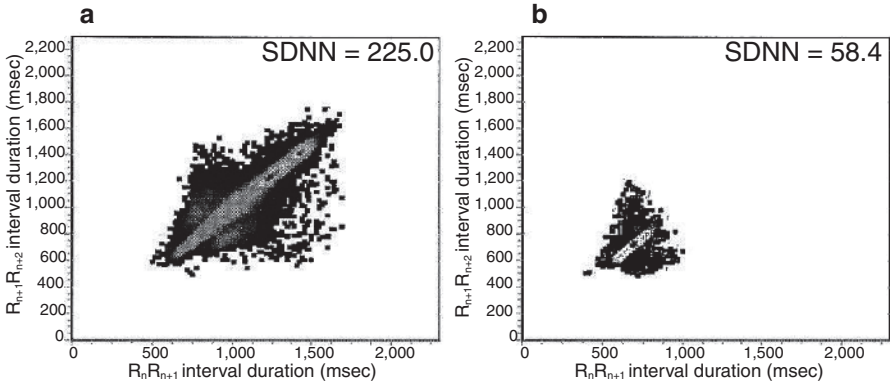


Fig. 6.4 Poincaré plots of heart rate variability from a patient with no cardiac disease and a patient with advanced cardiomyopathy. In the Poincaré plot, each R-R interval (R_nR_{n+1}) is plotted on the *x*-axis against the succeeding R-R interval ($R_{n+1}R_{n+2}$) on the *y*-axis. (**a)** Poincaré plot in a 77 year-old man without heart disease. SDNN was normal at 225.0. (**b)** Poincaré plot in a 61 year-old woman with advanced cardiomyopathy (EF 15 %). SDNN was abnormal at 58.4, consistent with low heart rate variability. The patient underwent heart transplantation 3 months after this study

clinical outcomes in patients with HFREF, and as such are non-invasive methods for monitoring the level of activation of the SNS. These methods are not routinely used in clinical practice, but they hold promise [129]. Improvements in SNS activation as assessed by these methods may be reasonable surrogate endpoints to clinical outcomes in trials investigating the effects of heart failure therapies.

Non-pharmacologic Therapies for SNS Inhibition

Several clinically important non-pharmacologic therapies have been shown to reduce SNS activity in heart failure. Several of these therapies, such as CRT, continuous positive airway pressure (CPAP) for obstructive sleep apnea and exercise training, have entered into the standard management of HFREF. Alternative therapies, such as Tai Chi and meditation, have been shown to be beneficial but are underutilized. At the same time, a novel therapeutic device, the baroreceptor stimulator, is undergoing clinical trials. Decreased SNS activity may serve as a critical early signal that a therapeutic advance will show itself to positively impact clinical outcomes.

Cardiac resynchronization therapy (CRT) is as an important therapy in HFREF patients with ventricular dyssynchrony, as marked by prolonged interventricular conduction [130]. CRT is discussed in further detail in Chap. 17, but has been shown to improve heart failure symptoms, lead to reverse remodeling, and decrease both hospitalizations and deaths from heart failure. Three studies have shown that CRT improved HRV as measured by mean atrial cycle length [131], SDNN [132], or standard deviation of the sensed atrial-to-atrial intervals (SDAAN) [133]. Cha and colleagues also showed that CRT leads to an improved heart-to-mediastinum ratio on MIBG imaging [132].

Obstructive sleep apnea (OSA) is common in patients with HFREF, with Sin and colleagues finding a prevalence of 37 % in 450 patients referred for polysomnography [134]. Sleep is associated with a decrease in sympathetic outflow, and a reduction in BP and heart rate [135]. In contrast, patients with OSA have elevated sympathetic activation, both during episodes of apnea during sleep as well as during wakefulness [136]. Importantly, treatment of OSA with nocturnal CPAP has been shown to reduce sympathetic outflow and consequently reduce heart rate and BP [137]. Furthermore, the use of nocturnal CPAP for a month in a group of 12 patients with HFREF (mean EF 25 %) was associated with reverse remodeling, as indicated by an improvement in the left ventricular end-systolic dimension and EF [138]. Patients with HFREF and OSA, that are either not treated with CPAP, or not fully compliant with therapy, have a higher mortality [139]. Given these data, all patients with HFREF should be screened for the presence of OSA and considered for therapy with nocturnal CPAP.

Exercise training has been perscribed in order to imporve the quality of life and outcomes in patients with heart failure [140]. In the Heart Failure: A Controlled Trial Investigating Outcomes of Exercise Training (HF-ACTION) trial, the implementation of a structured exercise program led to a statistically-significant decrease in the

composite endpoint of all-cause mortality or hospitalization [141]. A review of multiple studies by Gademan, et al, demonstrates that exercise training clearly improves heart rate variability in a popluation of heart failure patients [142]. Furthermore, Roveda and colleagues recorded muscle sympathetic nerve activity in 16 patients with HFREF and found that it decreased significantly after exercise training in HFREF patients, even to the levels seen in normal controls [143].

Emotional stress affects the level of activation of the SNS via the hypothalamus [144]. This heart-brain connection is most clinically relevant in stress cardiomyopathy (also known as Takotsubo cardiomyopathy), in which a sudden, severe, mental or physical stress leads to acute myocardial dysfunction [145]. Stress cardiomyopathy is felt to be mediated, at least in part, by high circulating levels of catecholamines [146]. Therefore, it is not surprising that non-pharmacologic therapies aimed at decreasing mental stress have been shown to have benefit in HFREF. Tai Chi is a Chinese martial art that combines physical exercise and mental relaxation [147]. In 2004, Yeh and colleagues randomized 30 patients with HFREF to 12 weeks of Tai Chi training or no training [148]. At the conclusion of the study, patients in the Tai Chi group demonstrated an improved quality of life, improved six minute walk distance, and a trend toward lower BNP levels. Meditation has also been shown to lower norepinephrine levels and increase Minnesota Living with Heart Failure Questionnaire scores [149]. These alternative therapies have potential to improve quality of life and outcomes in patients with HFREF.

Concurrent to the activation of the SNS that occurs in HFREF is withdrawal of vagal activity [150]. To counteract the effects of SNS activation, reestablishment of vagal tone has been investigated as a novel therapeutic strategy in HFREF. Chronic vagal nerve electrical stimulation (VNS) was shown to improve HRV and lead to reverse remodeling in a pacing-induced animal model of HFREF [151]. In the Cardiofit Multicenter trial, the safety and efficacy of the CardioFit VNS device was tested in an uncontrolled trial of 32 patients with HFREF [152]. After 6 months of therapy, 41 % of patients experienced a serious adverse event, not unanticipated for a novel device. However, there were significant improvements in heart failure symptoms, 6-min walk distance, and EF. A larger, multi-center randomized clinical trial was initiated in 2011 to test the CardioFit VNS device [153]. If VNS therapy is shown to improve outcomes, non-invasive markers of SNS activation such as low HRV and low heart-to-mediastinum ratio on MIBG may identify patients that will benefit from this therapy.

Conclusions

Activation of the SNS is among the earliest neurohormonal abnormalities in heart failure [154]. Initially SNS activation is compensatory, but subsequently contributes to disease progression and the clinical sequelae of heart failure. A few pioneering clinical studies in the late 1970s showed that treatment with β-blockers improved clinical status in patients with heart failure, which was a surprise given their acute

negative inotropic properties. Despite early skepticism, multiple multicenter clinical trials, that have enrolled a population of over 11,000 patients, have shown that β-blockers improve multiple clinical outcomes in patients with HFREF, including decreasing mortality, hospitalization for heart failure, and sudden cardiac death [155]. β-blocker therapy has additional benefits such as decreasing heart failure symptoms and improving EF through reverse remodeling. A small number of patients, about 10 %, will not be able to tolerate β-blocker therapy due to comorbidities such as RAD or bradycardia. However, given the overwhelming benefits of therapy, all eligible patients should be initiated on treatment with one of the β-blockers recommended for use in heart failure, and the dose uptitrated at regular intervals until the target dose is reached, a target heart rate is reached, or side-effects occur. Other heart failure therapies that have been found to improve outcomes, such as CRT and exercise therapy, have also been found to work via inhibition of the SNS. Since the several decades after the first trial of β-blockers in patients with heart failure, much has been accomplished. Understanding how SNS is central to the pathophysiology of heart failure, researchers maybe able to develop additional therapeutic interventions.

References

1. Cannon WB. Bodily changes in pain, hunger, fear and rage. New York/Littleton: D. Appleton and Co.; 1929.
2. Malpas SC. Sympathetic nervous system overactivity and its role in the development of cardiovascular disease. Physiol Rev. 2010;90(2):513–57.
3. Jänig W. The integrative action of the autonomic nervous system: neurobiology of homeostasis. Cambridge: Cambridge University Press; 2006.
4. Janes RD, Brandys JC, Hopkins DA, Johnstone DE, Murphy DA, Armour JA. Anatomy of human extrinsic cardiac nerves and ganglia. Am J Cardiol. 1986;57(4):299–309.
5. Randall WC, Szentivanyi M, Pace JB, Wechsler JS, Kaye MP. Patterns of sympathetic nerve projections onto the canine heart. Circ Res. 1968;22(3):315–23.
6. Fuller MD, Emrick MA, Sadilek M, Scheuer T, Catterall WA. Molecular mechanism of calcium channel regulation in the fight-or-flight response. Sci Signal. 2010;3(141):ra70. doi:10.1126/scisignal.2001152.
7. Shan J, Kushnir A, Betzenhauser MJ, Reiken S, Li J, Lehnart SE, et al. Phosphorylation of the ryanodine receptor mediates the cardiac fight or flight response in mice. J Clin Invest. 2010;120(12):4388–98.
8. Katz AM, Konstam MA. Heart failure: pathophysiology, molecular biology, and clinical management. 2 ed. Philadelphia: Lippincott Williams & Wilkins; 2012.
9. Ginsburg R, Bristow MR, Billingham ME, Stinson EB, Schroeder JS, Harrison DC. Study of the normal and failing isolated human heart: decreased response of failing heart to isoproterenol. Am Heart J. 1983;106(3):535–40.
10. Floras JS. Sympathetic nervous system activation in human heart failure. J Am Coll Cardiol. American College of Cardiology Foundation. 2009;54(5):375–85.
11. Swedberg K, Viquerat C, Rouleau JL, Roizen M, Atherton B, Parmley WW, et al. Comparison of myocardial catecholamine balance in chronic congestive heart failure and in angina pectoris without failure. Am J Cardiol. 1984;54(7):783–6.
12. Bristow MR, Ginsburg R, Minobe W, Cubicciotti RS, Sageman WS, Lurie K, et al. Decreased catecholamine sensitivity and beta-adrenergic-receptor density in failing human hearts. N Engl J Med. 1982;307(4):205–11.

13. Fowler MB, Laser JA, Hopkins GL, Minobe W, Bristow MR. Assessment of the beta-adrenergic receptor pathway in the intact failing human heart: progressive receptor down-regulation and subsensitivity to agonist response. Circulation. 1986;74(6):1290–302.
14. Communal C, Singh K, Pimentel DR, Colucci WS. Norepinephrine stimulates apoptosis in adult rat ventricular myocytes by activation of the beta-adrenergic pathway. Circulation. 1998;98(13):1329–34.
15. Narula J, Haider N, Virmani R, DiSalvo TG, Kolodgie FD, Hajjar RJ, et al. Apoptosis in myocytes in end-stage heart failure. N Engl J Med. 1996;335(16):1182–9.
16. Cao JM, Fishbein MC, Han JB, Lai WW, Lai AC, TJ W, et al. Relationship between regional cardiac hyperinnervation and ventricular arrhythmia. Circulation. 2000;101(16):1960–9.
17. Black JW, Crowther AF, Shanks RG, Smith LH, Dornhorst AC. A new adrenergic betareceptor antagonist. Lancet. 1964;1(7342):1080–1.
18. Stapleton MP. Sir James Black and propranolol. The role of the basic sciences in the history of cardiovascular pharmacology. Tex Heart Inst J. 1997;24(4):336–42.
19. Frishman WH, Alwarshetty M. Beta-adrenergic blockers in systemic hypertension: pharmacokinetic considerations related to the current guidelines. Clin Pharmacokinet. 2002;41(7):505–16.
20. Bristow MR. Treatment of chronic heart failure with beta-adrenergic receptor antagonists: a convergence of receptor pharmacology and clinical cardiology. Circ Res. 2011;109(10):1176–94.
21. Brunton L, Chabner B, Knollman B. Goodman and Gilman's the pharmacological basis of therapeutics. 12 ed. Columbus: McGraw-Hill Education; 2010.
22. Kindermann M. Carvedilol but not metoprolol reduces beta-adrenergic responsiveness after complete elimination from plasma in vivo. Circulation. 2004;109(25):3182–90.
23. Snow PJ. Effect of propranolol in myocardial infarction. Lancet. 1965;2(7412):551–3.
24. Burch GE, Walsh JJ, Ferrans VJ, Hibbs R. Prolonged bed rest in the treatment of the dilated heart. Circulation. 1965;32(5):852–6.
25. Chidsey CA, Braunwald E, Morrow AG, Mason DT. Myocardial norepinephrine concentration in man. Effects of reserpine and of congestive heart failure. N Engl J Med. 1963;269:653–8.
26. Gaffney TE, Braunwald E. Importance of the adrenergic nervous system in the support of circulatory function in patients with congestive heart failure. Am J Med. 1963;34:320–4.
27. Waagstein F, Hjalmarson A, Varnauskas E, Wallentin I. Effect of chronic beta-adrenergic receptor blockade in congestive cardiomyopathy. Br Heart J. 1975;37(10):1022–36.
28. Gobel FL, Norstrom LA, Nelson RR, Jorgensen CR, Wang Y. The rate-pressure product as an index of myocardial oxygen consumption during exercise in patients with angina pectoris. Circulation. 1978;57(3):549–56.
29. Swedberg K, Hjalmarson A, Waagstein F, Wallentin I. Prolongation of survival in congestive cardiomyopathy by beta-receptor blockade. Lancet. 1979;1(8131):1374–6.
30. Goodwin JF. The frontiers of cardiomyopathy. Br Heart J. 1982;48(1):1–18.
31. Ikram H, Fitzpatrick D. Double-blind trial of chronic oral beta blockade in congestive cardiomyopathy. Lancet. 1981;2(8245):490–3.
32. Currie PJ, Kelly MJ, McKenzie A, Harper RW, Lim YL, Federman J, et al. Oral beta-adrenergic blockade with metoprolol in chronic severe dilated cardiomyopathy. J Am Coll Cardiol. 1984;3(1):203–9.
33. Waagstein F, Bristow MR, Swedberg K, Camerini F, Fowler MB, Silver MA, et al. Beneficial effects of metoprolol in idiopathic dilated cardiomyopathy. Metoprolol in Dilated Cardiomyopathy (MDC) Trial Study Group. Lancet. 1993;342(8885):1441–6.
34. Investigators C, Committees A. randomized trial of beta-blockade in heart failure. The Cardiac Insufficiency Bisoprolol Study (CIBIS). Circulation. 1994;90(4):1765–73.
35. Packer M, Coats AJ, Fowler MB, Katus HA, Krum H, Mohacsi P, et al. Effect of carvedilol on survival in severe chronic heart failure. N Engl J Med. 2001;344(22):1651–8.
36. The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II): a randomised trial. Lancet. 1999;353(9146):9–13.
37. Group M-HS. Effect of metoprolol CR/XL in chronic heart failure: Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF). Lancet. 1999;353(9169):2001–7.

38. Macdonald PS, Keogh AM, Aboyoun CL, Lund M, Amor R, DJ MC. Tolerability and efficacy of carvedilol in patients with New York Heart Association class IV heart failure. J Am Coll Cardiol. 1999;33(4):924–31.
39. Beta-Blocker Evaluation of Survival Trial Investigators. A trial of the beta-blocker bucindolol in patients with advanced chronic heart failure. N Engl J Med. 2001;344(22):1659–67.
40. Bristow MR, Murphy GA, Krause-Steinrauf H, Anderson JL, Carlquist JF, Thaneemit-Chen S, et al. An alpha-2c-adrenergic receptor polymorphism alters the norepinephrine-lowering effects and therapeutic response of the beta-blocker bucindolol in chronic heart failure. Circ Heart Fail. 2010;3(1):21–8.
41. Lanfear DE, Hrobowski TN, Peterson EL, Wells KE, Swadia TV, Spertus JA, et al. Association of beta-blocker exposure with outcomes in heart failure differs between African American and white patients. Circ Heart Fail. 2012;5(2):202–8.
42. Packer M, Antonopoulos GV, Berlin JA, Chittams J, Konstam MA, Udelson JE. Comparative effects of carvedilol and metoprolol on left ventricular ejection fraction in heart failure: Results of a meta-analysis. Am Heart J. 2001;141(6):899–907.
43. Poole-Wilson PA, Swedberg K, Cleland JGF, Di Lenarda A, Hanrath P, Komajda M, et al. Comparison of carvedilol and metoprolol on clinical outcomes in patients with chronic heart failure in the Carvedilol Or Metoprolol European Trial (COMET): randomised controlled trial. Lancet. 2003;362(9377):7–13.
44. Bristow MR, Feldman AM, Adams Jr KF, Goldstein S. Selective versus nonselective beta-blockade for heart failure therapy: are there lessons to be learned from the COMET trial? J Card Fail. 2003;9(6):444–53.
45. Ruwald MH, Ruwald ACH, Jons C, Alexis J, McNitt S, Zareba W, et al. Effect of metoprolol versus carvedilol on outcomes in MADIT-CRT (Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy). J Am Coll Cardiol. 2013;61(14):1518–26.
46. Heart Failure Society of America, Lindenfeld J, NM A, JP B, SP C, JA E, et al. HFSA 2010 comprehensive heart failure practice guideline. J Card Fail. 2010;16(6):e1–194. doi:10.1016/j.cardfail.2010.04.004.
47. Hunt SA, Abraham WT, Chin MH, Feldman AM, Francis GS, Ganiats TG, et al. Focused update incorporated into the ACC/AHA 2005 guidelines for the diagnosis and management of heart failure in adults. J Am Coll Cardiol. 2009;53(15):e1–e90. doi:10.1016/j.jacc.2008.11.013.
48. Sliwa K, Norton GR, Kone N, Candy G, Kachope J, Woodiwiss AJ, et al. Impact of initiating carvedilol before angiotensin-converting enzyme inhibitor therapy on cardiac function in newly diagnosed heart failure. J Am Coll Cardiol. 2004;44(9):1825–30.
49. Willenheimer R, van Veldhuisen DJ, Silke B, Erdmann E, Follath F, Krum H, et al. Effect on survival and hospitalization of initiating treatment for chronic heart failure with bisoprolol followed by enalapril, as compared with the opposite sequence: results of the Randomized Cardiac Insufficiency Bisoprolol Study (CIBIS) III. Circulation. 2005;112(16):2426–35.
50. Funck-Brentano C, van Veldhuisen DJ, van de Ven LLM, Follath F, Goulder M, Willenheimer R, et al. Influence of order and type of drug (bisoprolol vs. enalapril) on outcome and adverse events in patients with chronic heart failure: a post hoc analysis of the CIBIS-III trial. Eur J Heart Fail. 2011;13(7):765–72.
51. Kramer DG, Trikalinos TA, Kent DM, Antonopoulos GV, Konstam MA, Udelson JE. Quantitative evaluation of drug or device effects on ventricular remodeling as predictors of therapeutic effects on mortality in patients with heart failure and reduced ejection fraction. J Am Coll Cardiol. 2010;56(5):392–406.
52. Abdulla J, Kober L, Christensen E, Torppedersen C. Effect of beta-blocker therapy on functional status in patients with heart failure — A meta-analysis. Eur J Heart Fail. 2006;8(5):522–31.
53. Dobre D, van Jaarsveld CHM, deJongste MJL, Haaijer Ruskamp FM, Ranchor AV. The effect of beta-blocker therapy on quality of life in heart failure patients: a systematic review and meta-analysis. Pharmacoepidemiol Drug Saf. 2007;16(2):152–9.
54. Mancini DM, Eisen H, Kussmaul W, Mull R, Edmunds LH, Wilson JR. Value of peak exercise oxygen consumption for optimal timing of cardiac transplantation in ambulatory patients with heart failure. Circulation. 1991;83(3):778–86.

55. O'Neill JO. Peak oxygen consumption as a predictor of death in patients with heart failure receiving beta-blockers. Circulation. 2005;111(18):2313–8.
56. Peterson LR, Schechtman KB, Ewald GA, Geltman EM, de las Fuentes L, Meyer T, et al. Timing of cardiac transplantation in patients with heart failure receiving beta-adrenergic blockers. J Heart Lung Transplant. 2003;22(10):1141–8.
57. Maisel A, Mueller C, Adamsjr K, Anker S, Aspromonte N, Cleland J, et al. State of the art: using natriuretic peptide levels in clinical practice. Eur J Heart Fail. 2008;10(9): 824–39.
58. Stanek B, Frey B, Hülsmann M, Berger R, Sturm B, Strametz-Juranek J, et al. Prognostic evaluation of neurohumoral plasma levels before and during beta-blocker therapy in advanced left ventricular dysfunction. J Am Coll Cardiol. 2001;38(2):436–42.
59. Hartmann F, Packer M, Coats AJ, Fowler MB, Krum H, Mohacsi P, et al. NT-proBNP in severe chronic heart failure: rationale, design and preliminary results of the COPERNICUS NT-proBNP substudy. Eur J Heart Fail. 2004;6(3):343–50.
60. Hartmann F, Packer M, Coats AJ, Fowler MB, Krum H, Mohacsi P, Rouleau JL, Tendera M, Castaigne A, Anker SD, Amann-Zalan I, Hoersch S, Katus HA. Prognostic impact of plasma N-terminal pro-brain natriuretic peptide in severe chronic congestive heart failure: a substudy of the Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS) Trial. Circulation. 2004;110(13):1780–6.
61. Advisory council to improve outcomes nationwide in heart failure. Consensus recommendations for the management of chronic heart failure. Am J Cardiol. 1999;83(2A):1A–38A.
62. Haber HL, Simek CL, Gimple LW, Bergin JD, Subbiah K, Jayaweera AR, et al. Why do patients with congestive heart failure tolerate the initiation of beta-blocker therapy? Circulation. 1993;88(4):1610–9.
63. Epstein SE, Braunwald E. The effect of beta adrenergic blockade on patterns of urinary sodium excretion. Studies in normal subjects and in patients with heart disease. Ann Intern Med. 1966;65(1):20–7.
64. Davis ME, Richards AM, Nicholls MG, Yandle TG, Frampton CM, Troughton RW. Introduction of metoprolol increases plasma b-type cardiac natriuretic peptides in mild, stable heart failure. Circulation. 2006;113(7):977–85.
65. Driscoll A, Krum H, Wolfe R, Tonkin A, Study Group BENCH. Nurse-led titration of beta-adrenoreceptor blocking agents in chronic heart failure patients in the community. J Card Fail. 2011;17(3):224–30.
66. Gottlieb SS, Fisher ML, Kjekshus J, Deedwania P, Gullestad L, Vitovec, et al. Tolerability of beta-blocker initiation and titration in the Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure (MERIT-HF). Circulation. 2002;105(10):1182–8.
67. Krum H, Roecker EB, Mohacsi P, Rouleau JL, Tendera M, Coats AJS, et al. Effects of initiating carvedilol in patients with severe chronic heart failure: results from the COPERNICUS Study. JAMA. 2003;289(6):712–8.
68. Ko DT, Hebert PR, Coffey CS, Curtis JP, Foody JM, Sedrakyan A, et al. Adverse effects of beta-blocker therapy for patients with heart failure: a quantitative overview of randomized trials. Arch Intern Med. 2004;164(13):1389–94.
69. Proclemer A, Gradnik R, Savonitto S, Feruglio GA. Electrophysiological effects of bisoprolol. Eur Heart J. 1987;8(Suppl M):81–5.
70. Wilkoff BL, Kudenchuk PJ, Buxton AE, Sharma A, Cook JR, Bhandari AK, et al. The DAVID (Dual Chamber and VVI Implantable Defibrillator) II Trial. J Am Coll Cardiol. 2009;53(10):872–80.
71. Cheng RK, Horwich TB, Fonarow GC. Relation of systolic blood pressure to survival in both ischemic and nonischemic systolic heart failure. Am J Cardiol. 2008;102(12):1698–705.
72. Rouleau JL, Roecker EB, Tendera M, Mohacsi P, Krum H, Katus HA, et al. Influence of pretreatment systolic blood pressure on the effect of carvedilol in patients with severe chronic heart failure. J Am Coll Cardiol. 2004;43(8):1423–9.
73. Soläng L, Malmberg K, Rydén L. Diabetes mellitus and congestive heart failure. Further knowledge needed. Eur Heart J. 1999;20(11):789–95.

74. Haas SJ, Vos T, Gilbert RE, Krum H. Are beta-blockers as efficacious in patients with diabetes mellitus as in patients without diabetes mellitus who have chronic heart failure? A meta-analysis of large-scale clinical trials. Am Heart J. 2003;146(5):848–53.
75. Shorr RI, Ray WA, Daugherty JR, Griffin MR. Antihypertensives and the risk of serious hypoglycemia in older persons using insulin or sulfonylureas. JAMA. 1997;278(1):40–3.
76. Rodger JC, Sheldon CD, Lerski RA, Livingstone WR. Intermittent claudication complicating beta-blockade. Br Med J. 1976;1(6018):1125.
77. Radack K, Deck C. Beta-adrenergic blocker therapy does not worsen intermittent claudication in subjects with peripheral arterial disease. A meta-analysis of randomized controlled trials. Arch Intern Med. 1991;151(9):1769–76.
78. Broadley KJ. Beta-adrenoceptor responses of the airways: for better or worse? Eur J Pharmacol. 2006;533(1–3):15–27.
79. McNeill RS. Effect of a beta-adrenergic-blocking agent, propranolol, on asthmatics. Lancet. 1964;2(7369):1101–2.
80. Salpeter SR, Ormiston TM, Salpeter EE. Cardioselective beta-blockers in patients with reactive airway disease: a meta-analysis. Ann Intern Med. 2002;137(9):715–25.
81. Kotlyar E, Keogh AM, Macdonald PS, Arnold RH, McCaffrey DJ, Glanville AR. Tolerability of carvedilol in patients with heart failure and concomitant chronic obstructive pulmonary disease or asthma. J Heart Lung Transplant. 2002;21(12):1290–5.
82. Rutten FH, Zuithoff NPA, Hak E, Grobbee DE, Hoes AW. Beta-blockers may reduce mortality and risk of exacerbations in patients with chronic obstructive pulmonary disease. Arch Intern Med. 2010;170(10):880–7.
83. Salpeter S, Ormiston T, Salpeter E. Cardioselective beta-blockers for chronic obstructive pulmonary disease. Cochrane Database Syst Rev. 2005;(4):CD003566.
84. Jabbour A, Macdonald PS, Keogh AM, Kotlyar E, Mellemkjaer S, Coleman CF, et al. Differences between beta-blockers in patients with chronic heart failure and chronic obstructive pulmonary disease: a randomized crossover trial. J Am Coll Cardiol. 2010;55(17):1780–7.
85. Mentz RJ, Wojdyla D, Fiuzat M, Chiswell K, Fonarow GC, O'Connor CM. Association of beta-blocker use and selectivity with outcomes in patients with heart failure and chronic obstructive pulmonary disease (from OPTIMIZE-HF). Am J Cardiol. 2012;111(4):582–7.
86. Blecker S, Paul M, Taksler G, Ogedegbe G, Katz S. Heart failure associated hospitalizations in the United States. J Am Coll Cardiol. 2013;61(12):1259–67.
87. Weil JV, Chidsey CA. Plasma volume expansion resulting from interference with adrenergic function in normal man. Circulation. 1968;37(1):54–61.
88. Heart Failure Society of America (HFSA) Practice Guidelines. HFSA guidelines for management of patients with heart failure caused by left ventricular systolic dysfunction--pharmacological approaches. J Card Fail. 1999;5(4):357–82.
89. Gattis WA, O'Connor CM, Gallup DS, Hasselblad V, Gheorghiade M. IMPACT-HF Investigators and Coordinators. Predischarge initiation of carvedilol in patients hospitalized for decompensated heart failure: results of the Initiation Management Predischarge: Process for Assessment of Carvedilol Therapy in Heart Failure (IMPACT-HF) trial. J Am Coll Cardiol. 2004;43(9):1534–41.
90. Fonarow GC, Abraham WT, Albert NM, Stough WG, Gheorghiade M, Greenberg BH, et al. Influence of beta-blocker continuation or withdrawal on outcomes in patients hospitalized with heart failure. J Am Coll Cardiol. 2008;52(3):190–9.
91. Fonarow G, Abraham W, Albert N, Stough W, Gheorghiade M, Greenberg B, O'Connor CM, et al. Prospective evaluation of beta-blocker use at the time of hospital discharge as a heart failure performance measure: results from OPTIMIZE-HF. J Card Fail. 2007;13(9):722–31.
92. Gorodeski EZ, Chu EC, Reese JR, Shishehbor MH, Hsich E, Starling RC. Prognosis on chronic dobutamine or milrinone infusions for stage d heart failure. Circ Heart Fail. 2009;2(4):320–4.
93. De Marco T, Chatterjee K. Phosphodiesterase inhibitors in refractory heart failure: bridge to beta-blockade? J Am Coll Cardiol. 1998;31(6):1341–3.

94. Metra M, Nodari S, D'Aloia A, Muneretto C, Robertson AD, Bristow MR, et al. Beta-blocker therapy influences the hemodynamic response to inotropic agents in patients with heart failure: a randomized comparison of dobutamine and enoximone before and after chronic treatment with metoprolol or carvedilol. J Am Coll Cardiol. 2002;40(7):1248–58.
95. Jennings DL, Thompson ML. Use of combination therapy with a beta-blocker and milrinone in patients with advanced heart failure. Ann Pharmacother. 2009;43(11):1872–6.
96. Shakar SF, Abraham WT, Gilbert EM, Robertson AD, Lowes BD, Zisman LS, et al. Combined oral positive inotropic and beta-blocker therapy for treatment of refractory class IV heart failure. J Am Coll Cardiol. 1998;31(6):1336–40.
97. Krum H, Ninio D, MacDonald P. Baseline predictors of tolerability to carvedilol in patients with chronic heart failure. Heart. 2000;84(6):615–9.
98. Parameswaran AC, Tang WHW, Francis GS, Gupta R, Young JB. Why do patients fail to receive beta-blockers for chronic heart failure over time? A "real-world" single-center, 2-year follow-up experience of beta-blocker therapy in patients with chronic heart failure. Am Heart J. 2005;149(5):921–6.
99. Bristow MR, Gilbert EM, Abraham WT, Adams KF, Fowler MB, Hershberger RE, et al. Carvedilol produces dose-related improvements in left ventricular function and survival in subjects with chronic heart failure. MOCHA Investigators. Circulation. 1996;94(11):2807–16.
100. Simon T. Bisoprolol dose–response relationship in patients with congestive heart failure: a subgroup analysis in the Cardiac Insufficiency Bisoprolol Study (CIBIS II). Eur Heart J. 2003;24(6):552–9.
101. Metra M, Torp-Pedersen C, Swedberg K, Cleland JG, Di Lenarda A, Komajda M. Influence of heart rate, blood pressure, and beta-blocker dose on outcome and the differences in outcome between carvedilol and metoprolol tartrate in patients with chronic heart failure: results from the COMET trial. Eur Heart J. 2005;26(21):2259–68.
102. Wikstrand J, Hjalmarson A, Waagstein F, Fagerberg B, Goldstein S, Kjekshus J, et al. Dose of metoprolol CR/XL and clinical outcomes in patients with heart failure: analysis of the experience in metoprolol CR/XL randomized intervention trial in chronic heart failure (MERIT-HF). J Am Coll Cardiol. 2002;40(3):491–8.
103. Fowler MB, Lottes SR, Nelson JJ, Lukas MA, Gilbert EM, Greenberg B, et al. Beta-blocker dosing in community-based treatment of heart failure. Am Heart J. 2007;153(6):1029–36.
104. Lechat P, Hulot JS, Escolano S, Mallet A, Leizorovicz A, Werhlen-Grandjean M, et al. Heart rate and cardiac rhythm relationships with bisoprolol benefit in chronic heart failure in CIBIS II Trial. Circulation. 2001;103(10):1428–33.
105. McAlister FA, Wiebe N, Ezekowitz JA, Leung AA, Armstrong PW. Meta-analysis: beta-blocker dose, heart rate reduction, and death in patients with heart failure. Ann Intern Med. 2009;150(11):784–94.
106. Borlaug BA, Paulus WJ. Heart failure with preserved ejection fraction: pathophysiology, diagnosis, and treatment. Eur Heart J. 2011;32(6):670–9.
107. Benedict CR, Weiner DH, Johnstone DE, Bourassa MG, Ghali JK, Nicklas J, et al. Comparative neurohormonal responses in patients with preserved and impaired left ventricular ejection fraction: results of the Studies of Left Ventricular Dysfunction (SOLVD) registry. J Am Coll Cardiol. 1993;22(Suppl A):146A–53A.
108. Carson P, Johnson G, Fletcher R, Cohn J. Mild systolic dysfunction in heart failure (left ventricular ejection fraction >35 %): baseline characteristics, prognosis and response to therapy in the Vasodilator in Heart Failure Trials (V-HeFT). J Am Coll Cardiol. 1996;27(3):642–9.
109. Flather MD, Shibata MC, Coats AJ, Van Veldhuisen DJ, Parkhomenko A, Borbola J, et al. Randomized trial to determine the effect of nebivolol on mortality and cardiovascular hospital admission in elderly patients with heart failure (SENIORS). Eur Heart J. 2004;26(3):215–25.
110. van Veldhuisen DJ, Cohen-Solal A, Bohm M, Anker SD, Babalis D, Roughton M, et al. Beta-blockade with nebivolol in elderly heart failure patients with impaired and preserved left ventricular ejection fraction. J Am Coll Cardiol. 2009;53(23):2150–8.

111. El-Refai M, Peterson EL, Wells K, Swadia T, Sabbah HN, Spertus JA, et al. Comparison of beta-blocker effectiveness in heart failure patients with preserved ejection fraction versus those with reduced ejection fraction. J Card Fail. 2013;19(2):73–9.
112. Hernandez AF, Hammill BG, O'Connor CM, Schulman KA, Curtis LH, Fonarow GC. Clinical effectiveness of beta-blockers in heart failure. J Am Coll Cardiol. 2009;53(2):184–92.
113. Bohm M, La Rosée K, Schwinger RH, Erdmann E. Evidence for reduction of norepinephrine uptake sites in the failing human heart. J Am Coll Cardiol. 1995;25(1):146–53.
114. Haider N, Baliga RR, Chandrashekhar Y, Narula J. Adrenergic excess, hNET1 down-regulation, and compromised mIBG uptake in heart failure poverty in the presence of plenty. JACC Cardiovasc Imaging. 2010;3(1):71–5.
115. Carrió I, Cowie MR, Yamazaki J, Udelson J, Camici PG. Cardiac sympathetic imaging with mIBG in heart failure. JACC Cardiovasc Imaging. 2010;3(1):92–100.
116. Thackeray JT, Bengel FM. Assessment of cardiac autonomic neuronal function using PET imaging. J Nucl Cardiol. 2013;20(1):150–65.
117. Merlet P, Valette H, Dubois-Randé JL, Moyse D, Duboc D, Dove P, et al. Prognostic value of cardiac metaiodobenzylguanidine imaging in patients with heart failure. J Nucl Med. 1992;33(4):471–7.
118. Jacobson AF, Senior R, Cerqueira MD, Wong ND, Thomas GS, Lopez VA, et al. Myocardial Iodine-123 meta-iodobenzylguanidine imaging and cardiac events in heart failure. J Am Coll Cardiol. 2010;55(20):2212–21.
119. Cohen-Solal A, Rouzet F, Berdeaux A, Le Guludec D, Abergel E, Syrota A, et al. Effects of carvedilol on myocardial sympathetic innervation in patients with chronic heart failure. J Nucl Med. 2005;46(11):1796–803.
120. Kasama S, Toyama T, Hatori T, Sumino H, Kumakura H, Takayama Y, et al. Evaluation of cardiac sympathetic nerve activity and left ventricular remodelling in patients with dilated cardiomyopathy on the treatment containing carvedilol. Eur Heart J. 2007;28(8):989–95.
121. DiFrancesco D. The role of the funny current in pacemaker activity. Circ Res. 2010;106(3):434–46.
122. Frenneaux MP. Autonomic changes in patients with heart failure and in post-myocardial infarction patients. Heart. 2004;90(11):1248–55.
123. Heart rate variability: standards of measurement, physiological interpretation and clinical use. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. Circulation. 1996;93(5):1043–65.
124. Casolo G, Balli E, Taddei T, Amuhasi J, Gori C. Decreased spontaneous heart rate variability in congestive heart failure. Am J Cardiol. 1989;64(18):1162–7.
125. Ponikowski P, Anker SD, Chua TP, Szelemej R, Piepoli M, Adamopoulos S, et al. Depressed heart rate variability as an independent predictor of death in chronic congestive heart failure secondary to ischemic or idiopathic dilated cardiomyopathy. Am J Cardiol. 1997;79(12):1645–50.
126. Bilchick KC, Fetics B, Djoukeng R, Fisher SG, Fletcher RD, Singh SN, et al. Prognostic value of heart rate variability in chronic congestive heart failure (Veterans affairs' survival trial of antiarrhythmic therapy in congestive heart failure). Am J Cardiol. 2002;90(1):24–8.
127. Mortara A, La Rovere MT, Pinna GD, Maestri R, Capomolla S, Cobelli F. Nonselective beta-adrenergic blocking agent, carvedilol, improves arterial baroflex gain and heart rate variability in patients with stable chronic heart failure. J Am Coll Cardiol. 2000;36(5):1612–8.
128. Bullinga JR, Alharethi R, Schram MS, Bristow MR, Gilbert EM. Changes in heart rate variability are correlated to hemodynamic improvement with chronic carvedilol therapy in heart failure. J Card Fail. 2005;11(9):693–9.
129. Strauss HW, Johnson MN, Schöder H, Tamaki N. Metaiodobenzylguanidine imaging comes of age. A new arrow in the prognostic quiver for heart failure patients. J Am Coll Cardiol. 2010;55(20):2222–4.
130. Linde C, Ellenbogen K, McAlister FA. Cardiac resynchronization therapy (CRT): clinical trials, guidelines, and target populations. Heart Rhythm. 2012;9(Suppl):S3–S13.

131. Adamson PB, Kleckner KJ, VanHout WL, Srinivasan S, Abraham WT. Cardiac resynchronization therapy improves heart rate variability in patients with symptomatic heart failure. Circulation. 2003;108(3):266–9.
132. Cha YM, Chareonthaitawee P, Dong YX, Kemp BJ, JK O, Miyazaki C, et al. Cardiac sympathetic reserve and response to cardiac resynchronization therapy. Circ Heart Fail. 2011;4(3):339–44.
133. Fantoni C, Raffa S, Regoli F, Giraldi F, La Rovere MT, Prentice J, et al. Cardiac resynchronization therapy improves heart rate profile and heart rate variability of patients with moderate to severe heart failure. J Am Coll Cardiol. 2005;46(10):1875–82.
134. Sin DD, Fitzgerald F, Parker JD, Newton G, Floras JS, Bradley TD. Risk factors for central and obstructive sleep apnea in 450 men and women with congestive heart failure. Am J Respir Crit Care Med. 1999;160(4):1101–6.
135. Somers VK, Dyken ME, Mark AL, Abboud FM. Sympathetic-nerve activity during sleep in normal subjects. N Engl J Med. 1993;328(5):303–7.
136. Somers VK, Dyken ME, Clary MP, Abboud FM. Sympathetic neural mechanisms in obstructive sleep apnea. J Clin Invest. 1995;96(4):1897–904.
137. Usui K, Bradley TD, Spaak J, Ryan CM, Kubo T, Kaneko Y, et al. Inhibition of awake sympathetic nerve activity of heart failure patients with obstructive sleep apnea by nocturnal continuous positive airway pressure. J Am Coll Cardiol. 2005;45(12):2008–11.
138. Kaneko Y, Floras JS, Usui K, Plante J, Tkacova R, Kubo T, et al. Cardiovascular effects of continuous positive airway pressure in patients with heart failure and obstructive sleep apnea. N Engl J Med. 2003;348(13):1233–41.
139. Kasai T, Narui K, Dohi T, Yanagisawa N, Ishiwata S, Ohno M, et al. Prognosis of patients with heart failure and obstructive sleep apnea treated with continuous positive airway pressure. Chest. 2008;133(3):690–6.
140. McKelvie RS, Teo KK, McCartney N, Humen D, Montague T, Yusuf S. Effects of exercise training in patients with congestive heart failure: a critical review. J Am Coll Cardiol. 1995;25(3):789–96.
141. O'Connor CM, Whellan DJ, Lee KL, Keteyian SJ, Cooper LS, Ellis SJ, et al. Efficacy and safety of exercise training in patients with chronic heart failure: HF-ACTION randomized controlled trial. JAMA. 2009;301(14):1439–50.
142. Gademan MGJ, Swenne CA, Verwey HF, van der Laarse A, Maan AC, van de Vooren H, et al. Effect of exercise training on autonomic derangement and neurohumoral activation in chronic heart failure. J Card Fail. 2007;13(4):294–303.
143. Roveda F, Middlekauff HR, Rondon MUPB, Reis SF, Souza M, Nastari L, et al. The effects of exercise training on sympathetic neural activation in advanced heart failure: a randomized controlled trial. J Am Coll Cardiol. 2003;42(5):854–60.
144. DiMicco JA, Samuels BC, Zaretskaia MV, Zaretsky DV. The dorsomedial hypothalamus and the response to stress: part renaissance, part revolution. Pharmacol Biochem Behav. 2002;71(3):469–80.
145. Akashi YJ, Goldstein DS, Barbaro G, Ueyama T. Takotsubo cardiomyopathy: a new form of acute, reversible heart failure. Circulation. 2008;118(25):2754–62.
146. Wittstein IS, Thiemann DR, Lima JAC, Baughman KL, Schulman SP, Gerstenblith G, et al. Neurohumoral features of myocardial stunning due to sudden emotional stress. N Engl J Med. 2005;352(6):539–48.
147. Yeh GY, McCarthy EP, Wayne PM, Stevenson LW, Wood MJ, Forman D, et al. Tai chi exercise in patients with chronic heart failure: a randomized clinical trial. Arch Intern Med. 2011;171(8):750–7.
148. Yeh GY, Wood MJ, Lorell BH, Stevenson LW, Eisenberg DM, Wayne PM, et al. Effects of tai chi mind-body movement therapy on functional status and exercise capacity in patients with chronic heart failure: A randomized controlled trial. Am J Med. 2004;117(8):541–8.
149. Curiati JA, Bocchi E, Freire JO, Arantes AC, Braga M, Garcia Y, et al. Meditation reduces sympathetic activation and improves the quality of life in elderly patients with

optimally treated heart failure: a prospective randomized study. J Altern Complement Med. 2005;11(3):465–72.
150. Olshansky B, Sabbah HN, Hauptman PJ, Colucci WS. Parasympathetic nervous system and heart failure: pathophysiology and potential implications for therapy. Circulation. 2008;118(8):863–71.
151. Zhang Y, Popovic ZB, Bibevski S, Fakhry I, Sica DA, Van Wagoner DR, et al. Chronic vagus nerve stimulation improves autonomic control and attenuates systemic inflammation and heart failure progression in a canine high-rate pacing model. Circ Heart Fail. 2009;2(6):692–9.
152. De Ferrari GM, Crijns HJGM, Borggrefe M, Milasinovic G, Smid J, Zabel M, et al. Chronic vagus nerve stimulation: a new and promising therapeutic approach for chronic heart failure. Eur Heart J. 2011;32(7):847–55.
153. Hauptman PJ, Schwartz PJ, Gold MR, Borggrefe M, van Veldhuisen DJ, Starling RC, et al. Rationale and study design of the INcrease Of Vagal TonE in Heart Failure study: INOVATE-HF. Am Heart J. 2012;163(6):954–62.
154. Rundqvist B, Elam M, Bergmann-Sverrisdottir Y, Eisenhofer G, Friberg P. Increased cardiac adrenergic drive precedes generalized sympathetic activation in human heart failure. Circulation. 1997;95(1):169–75.
155. Chatterjee S, Biondi-Zoccai G, Abbate A, D'Ascenzo F, Castagno D, Van Tassell B, et al. Benefits of beta blockers in patients with heart failure and reduced ejection fraction: network meta-analysis. Br Med J. 2013;346:f55. doi:10.1136/bmj.f55.

Chapter 7
Management of the Patient with Heart Failure with Preserved Ejection Fraction

Jeffrey D. Wessler and Mathew S. Maurer

Introduction

Since its first formal characterization three decades ago as *congestive heart failure with normal systolic function* [1] heart failure with preserved ejection fraction (HFPEF) has emerged as an increasingly common and challenging entity within the field of heart failure. Several early studies conducted on hypertrophic and infarcted hearts demonstrated diminished diastolic left ventricular (LV) filling and led to coining of the term *diastolic heart failure* [2, 3]. Yet as our understanding of heart failure has grown, the term "diastolic heart failure" was replaced by the nomenclature "heart failure with a preserved ejection fraction" by national guidelines in part because of diverse pathophysiologic mechanisms beyond diastolic dysfunction that contribute to the observed phenotype and are potential targets for therapy [4]. The following chapter will cover the management of patients with HFPEF. After presenting an overview of the scope and pathophysiology of the condition, we will detail the diagnostic approach and treatment options before concluding with a look at the future directions in HFPEF.

J.D. Wessler, MD, MPhil (✉)
Department of Medicine, Columbia University Medical Center,
177 Fort Washington, Milstein Hospital Building, 6th Floor, Center Room 12, New York, NY 10032, USA
e-mail: jdw2170@columbia.edu

M.S. Maurer, MD
Department of Medicine, Columbia University Medical Center, Allen Hospital of New York Presbyterian, 5141 Broadway, 3 Field West, Room 037, New York, NY 10034, USA
e-mail: msm10@columbia.edu

H. Eisen (ed.), *Heart Failure*, DOI 10.1007/978-1-4471-4219-5_7

Epidemiology

HFPEF is a disease primarily effecting older adults. The incidence and prevalence of heart failure are increasing and it has been projected that these rates will continue well into the twenty-first Century. More than six million Americans have been diagnosed with heart failure in the United States [5]. The total number of admissions for heart failure in the United States is greater than one million per year [5]. Readmission rates are as high as 30–60 % within 3–6 months after discharge [6]. The incidence and prevalence of heart failure are strikingly age-dependent, with prevalence rates in adults over 80 years of age approaching 10 % and mortality rates increasing exponentially with advancing age in all major demographic subgroups of the United States population [5]. Although several factors have contributed to the rise in heart failure, principal among them is the progressive aging of the population. The exponential increase in the prevalence of heart failure has been attributed to the increase in prevalence and cumulative duration of systemic hypertension and coronary artery disease with advancing age and age-related changes in cardiac structure and function, which occur even in the absence of overt clinically defined cardiovascular disease [7, 8]. Consistent with the high prevalence and substantial mortality associated with this disorder, heart failure is currently one of the most common reasons for hospital admission in adults older than 65 years of age. It is not only one of the most common diagnosis related group in the Medicare population, it is also the most costly, with estimated annual inpatient expenditures in excess of $15 billion [9].

Of all patients suffering from heart failure, the majority have preserved ejection fraction. While these changes in the heart failure phenotype are thought to be relatively new, the distribution of different ejection fraction consistent with HFREF (<40 %), HFPEF (40–55 %) and with HFNEF (>55 %) in several large epidemiologic studies at the inception of these cohorts demonstrates that most individuals with heart failure in the community have a normal or preserved ejection fraction (see Fig. 7.1). These individuals are more likely to be elderly, female, have higher body mass index (BMI), higher blood pressure, and lower hemoglobin than those with reduced ejection fraction. The rate of hospitalization for HFPEF now exceeds that of heart failure with reduced ejection fraction (HFREF), and 6-month re-hospitalization approaches 50 % [14–16]. Patients with HFPEF are characteristically affected by multiple co-morbidities that contribute to their disease—including obesity, hypertension, anemia, diabetes, coronary artery disease, and chronic kidney disease—as well as multiple non-cardiac comorbidities seen more commonly in older adults—including chronic pulmonary disease, liver disease, thyroid dysfunction, and cancer [14, 17]. Not surprisingly, therefore, though the mortality rates in HFPEF are similar to HFREF, the cause of death in HFPEF is more commonly attributed to non-cardiovascular causes [18], as is the reason for readmission after a hospitalization for acute decompensated heart failure [9].

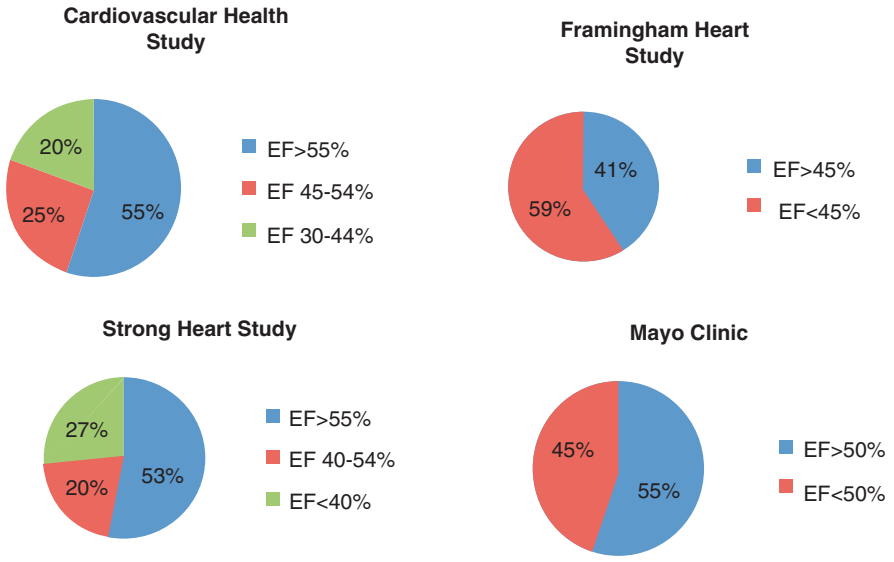


Fig. 7.1 Prevalence of HFPEF in four major epidemiologic cohorts [10–13]

Pathophysiology

The traditional classification of HFPEF as *diastolic heart failure* is based on the premise that a single pathophysiologic mechanism underlies the genesis of HFPEF. Yet as understanding progressed and recognition that HFPEF is a complex clinical syndrome with multiple operative pathophysiologic mechanisms including several different subgroups of patients, it became apparent that diastolic dysfunction was inadequate to explain all cases of HFPEF [19]. Rational sub grouping of patients into cohorts that have operational and targetable pathophysiologic mechanisms can be appreciated by assessment of the pressure-volume (PV) relations that characterize different populations with HFPEF [20, 21]. PV measurements provide a systematic means of characterizing overall, systolic and diastolic properties of the heart, as well as isovolumetric pressure volume area (PVA_{iso}), which when indexed to EDP provides an afterload independent measure of the pump function of the ventricle [22]. End-systolic PV relation (ESPVR) and end-diastolic PV relation (EDPVR) in particular reflect global ventricular chamber pump properties that effect overall cardiac function. These parameters are in turn determined by intrinsic myocardial properties (systolic and diastolic function), but also by muscle mass, chamber architecture (how myocardial fibers are assembled), chamber shape, and sequence of myocardial activation.

Data from PV analyses in both animal and human studies have revealed at least three different phenotypes of HFPEF that are depicted in Fig. 7.2. In the first, patients have a normal ESPVR and upward shifted EDPVR—(e.g. reduced chamber

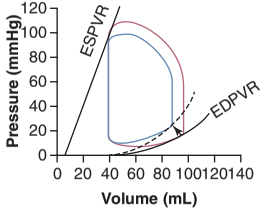
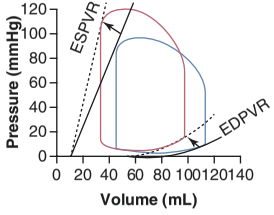
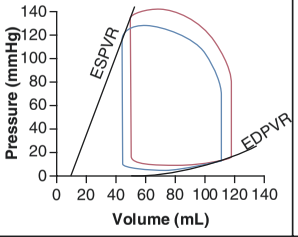
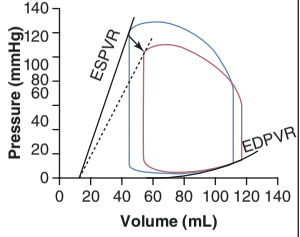
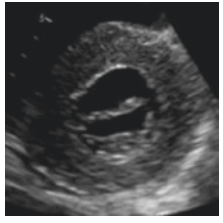
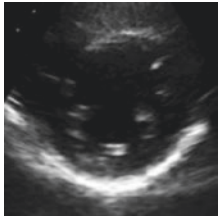
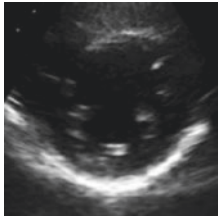
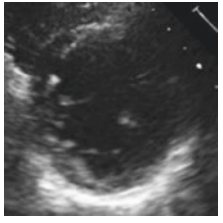
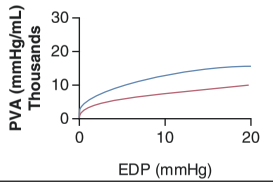
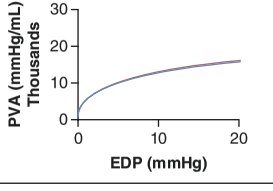
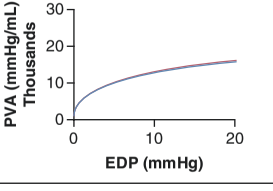
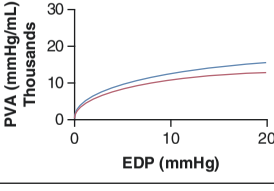
Characteristic	a	b	c	d
PV Loops				
Primary problem	Passive Diastolic dysfunction	Excessive Afterload	Excessive Preload	Systolic Dysfunction
Hypertension	No	Yes	Yes	Variable but usually
Potential Exam findings	S4	AS murmur, S4, widened pulse pressure	Volume overloaded, S3	S3
EF	>50%	>60%	>50%	40-50%
Echo findings				
PVA_{bm} EDP Relationship				

Fig. 7.2 Phenotypic characterization of HFPEF by pressure volume relations with associated clinical characteristics by primary problem. (**a**) Diastolic dysfunction. (**b**) Excessive afterload. (**c**) Excessive preload. (**d**) Systolic dysfunction

capacitance or diastolic dysfunction) with normal chamber contractility (e.g. preserved systolic function) (Fig. 7.2a).

Patients with this classic diastolic heart failure paradigm have intrinsic myocardial disease causing impairment in cardiac relaxation and passive ventricular filling. Such severe and isolated diastolic dysfunction is often found in hypertrophic cardiomyopathy and infiltrative diseases such as cardiac amyloidosis. These patients with isolated diastolic dysfunction can be identified clinically by the presence of heart failure and a normal ejection fraction without concomitant hypertension [23]. Physical exam findings are often notable for signs and symptoms of a stiff ventricle, including an S4 gallop and other classic but non-specific signs of heart failure such as pulmonary congestion and elevated jugular venous distension. In subjects with restrictive cardiomyopathies the jugular venous pressure often has a "double dip" which is indicative of the rapid "x" and "y" descent seen on the right atrial pressure tracing in patients with restriction. Ejection fraction is usually greater than 50 % in the early phases of these conditions, and on echocardiogram Doppler evidence of diastolic dysfunction ranging from impaired relaxation to a restrictive filling pattern can be observed—although Doppler will be notably abnormal and indistinguishable in each of the following phenotypes of HFPEF [24]. Finally, the PVA_{iso} will be lower than normal in these subjects indicative of left ventricular pump dysfunction as a primary pathophysiologic mechanism underlying the phenotype.

In the second paradigm of HFPEF, ESPVR and EDPVR are both shifted upward and leftward, with a resulting decrease in chamber capacitance but with concomitant enhanced chamber systolic function—as evidenced by the upward shift of the ESPVR (Fig. 7.2b). In such subjects, the area between the ESPVR and EDPVR will be unchanged and the PVA_{iso} will remain normal. Examples of clinical conditions that produce this phenotype include increased afterload from chronic hypertension (usually from central conduit artery stiffening) and severe aortic stenosis. These two clinical scenarios are the most common causes of this phenotype in older adults with HFPEF. With normal physiologic aging, increasing central conduit arterial stiffness from collagen crosslinking leads to an increased arterial elastance with concomitant hypertension. Consequent concentric hypertrophy of the left ventricle yields subsequent reliance on atrial filling with corresponding left atrial (LA) enlargement [7, 8, 25, 26] Similarly, concentric remodeling with a small ventricular chamber is seen in patients with aortic stenosis who are characterized by this phenotype according to this paradigm. Ejection fraction is often supranormal in these patients (>60 %) as a result of an increase in end systolic elastance with a similar echocardiographic phenotype characterized by a normal to small LV chamber size, concentric LV hypertrophy and LA enlargement [27].

In the third subtype of HFPEF, patients can display normal ESPVR and normal or slightly rightward and downward shifted EDPVR (e.g. normal or increased capacitance) with increased end diastolic pressures. The latter results from an increased central volume that could be caused by either an expanded blood volume or a shift of the blood volume toward the central circulation from veno-constriction. Indeed, most of the blood volume in mammalian species is in the venous bed, and small changes in venous tone can result in large shift of blood volume back to the

central circulation resulting in left ventricular overfilling [28]. Pathophysiologically, this phenotype is characterized by increased preload without significant alteration in LV systolic or diastolic function (e.g. the ESPVR and EDPVR are not significantly different from normal) (Fig. 7.2c) [29]. Although these patients also have hypertension, the primary operative mechanism is increased preload due conditions that expand the blood volume such as renal dysfunction, obesity, anemia and others. Indeed, age-related changes in non-cardiac systems including renal, pulmonary, endocrine, and autonomic nervous systems have been documented to produce a state of salt sensitive hypertension characterized by excessive salt and water retention [30–32]. The diminished pulmonary vascular capacitance with pulmonary arterial hypertension and endothelial dysfunction coupled with the volume redistribution that accompany advancing age (decreased beta-2 adrenergic responsiveness of the veins reduces venous capacitance) predispose the aging adult to the development of symptomatic pulmonary edema in the setting of normal LV systolic function. Patients display signs of volume overload on physical exam, and can have an S3 gallop. Ejection fraction is commonly >50 % and echocardiography shows a mildly dilated LV that often is unrecognized [33]. LV pump function as indexed by the PVA_{iso} to EDP relation is supranormal in these subjects suggesting that the myocardium is performing more work at any given filling pressure.

Finally, subtle reductions in systolic function as evidenced by a reduction in LV chamber contractile function (either from a downward shifted ESPVR or increased V_0 [volume axis intercept of the ESPVR]) can cause neurohormonal activation that leads to salt and water retention (Fig. 7.2d) [34, 35]. In these subjects, the EF may be low normal or slightly reduced (e.g. ~40–50 %). The primary mechanism in this underappreciated subtype is systolic dysfunction and PVA_{iso} to EDP relation that demonstrates a downward shift compared consistent with reduced chamber contractile strength. These patients are often hypertensive, and on physical exam will appear most similarly to patients with a mild form of systolic heart failure as demonstrated by non-invasive PV analysis [36].

The pathophysiology of HFPEF is heterogeneous, involving multiple physiologic domains in both cardiac and non-cardiac systems—and manifesting in patients with multiple co-morbid conditions. Despite the multifactorial etiology of the syndrome, there are several clinical signs and symptoms consistently present in patients that characterize the phenotype(s) of HFPEF: (i) Labile blood pressure with high resting LVEDP, (ii) predisposition for acute pulmonary edema, and (iii) effort intolerance with diminished exercise capacity [37–39]. Appreciating the distinct pathophysiologic mechanisms that contribute to these phenotypes is essential in guiding therapeutic interventions and in advancing the understanding and management of this condition.

Diagnosis

Diagnosing HFPEF presents a clinical challenge stemming from its diverse etiology. Making the diagnosis of HFPEF is particularly difficult because: (1) there is no specific measure (such as EF in HFREF) to define the syndrome, (2) other disorders

common in older adults (such as obesity with confounding comorbidities) can mimic the clinical syndrome, and (3) precise criteria have not been widely adapted. The original criteria developed to distinguish HFPEF from HFREF called for the presence of a clinical heart failure syndrome, a normal EF, and evidence of diastolic dysfunction by either catheterization or echocardiography [40]. Since then, several guidelines have been published that broaden the requirement of diastolic dysfunction to surrogate markers of diastolic LV dysfunction such as LV hypertrophy, LA enlargement, atrial fibrillation, or elevated plasma natriuretic peptides (NP) levels (Fig. 7.3) [41–45].

In the most recent guideline published by the Heart Failure and Echocardiography Associations of the European Society of Cardiology (ESC), the diagnosis of HFPEF required signs or symptoms of heart failure, a LVEF >50%, a LVEDV Index <97 mL/m^2, and evidence of diastolic LV dysfunction as shown by LVEDP >16 mmHg, pulmonary capillary wedge pressure (PCWP) >12 mmHg or ratio of mitral peak velocity of early filling (E) to early diastolic mitral annular velocity (E/E') >15 alone. Alternatively criteria include an elevated NP with E/E'>8, a mitral flow velocity Doppler signal showing a ratio of early to late flow (E/A) <0.5 with deceleration time (DT) >280 ms, a pulmonary vein flow velocity signal showing a Ard-Ad >30 ms (Ard = duration of reverse pulmonary vein atrial systole flow; Ad = duration of mitral valve atrial wave flow), a LA size >40 mL/m^2, or a LV mass >149 g/m^2 in men or >122 g/m^2 in women [43]. These guidelines represent consensus criteria with ongoing validation studies needed to verify their utility (in particularly for those that are non-invasive). Although invasive measurements with cardiac catheterization remain the gold standard for identifying HFPEF, the invasive nature

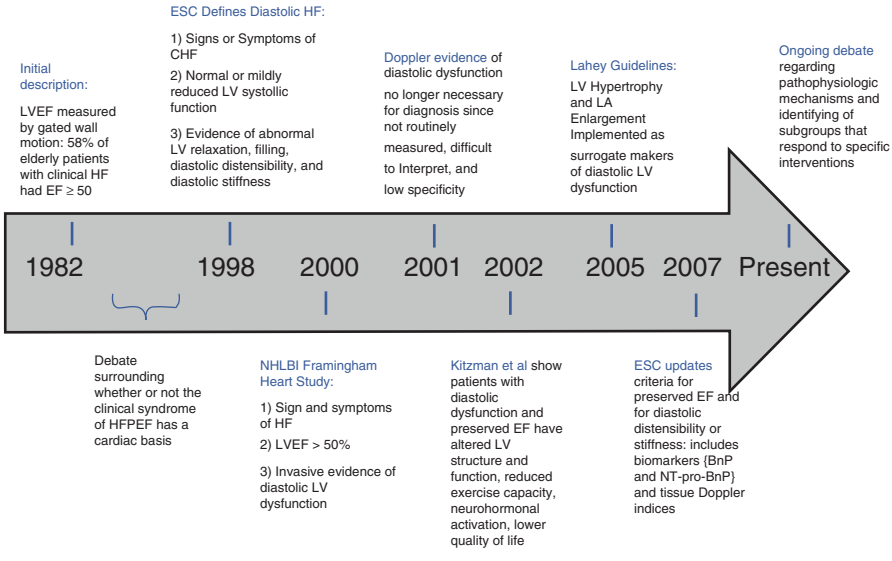


Fig. 7.3 Evolution of HFPEF from initial description to current diagnostic guidelines [41]

of catheterization makes it impractical to obtain during routine evaluation for all patients with the HFPEF phenotype.

The diagnostic criteria above are largely based on the premise that elevated filling pressures remain the primary hemodynamic abnormality in HFPEF. Yet in a recent study assessing the diagnostic utility of these ESC guidelines, only 25 % of patients with HFPEF and unexplained dyspnea who underwent invasive diagnostic testing fulfilled ESC criteria for HFPEF with evidence of elevated filling pressures at rest [46]. Indeed, a significant proportion of the patients demonstrated left ventricular stiffness, dyssynchrony, and dynamic mitral regurgitation, confirming patients with HFPEF can experience heart failure symptoms without demonstrating significant elevated filling pressures at rest or during hand grip exercise (increased afterload), leg lift (increased preload), nitroprusside infusion (decreased afterload), or dobutamine infusion (increased contractility). The specificity of these guidelines was also challenged, with 20–40 % of health controls demonstrating borderline E/E' despite no evidence of heart failure and normal filling pressures [46]. Similarly, in a recent study assessing hemodynamic response to volume challenge in healthy young volunteers, older women, and patients with HFPEF, filling pressures (assessed by PCWP and mean pulmonary artery pressures [MPAP]) rose significantly with volume loading in all of the groups [47]. This raises additional concern for the validity of the cut points utilized to define an elevated filling pressure characteristic of HFPEF, suggesting more testing is needed to determine the threshold at which to classify HFPEF.

Despite these findings, several studies have validated the diagnostic capacity of various non-invasive estimates of elevated filling pressures. Conventional and tissue Doppler echocardiographic indices have been measured against conductance catheter PV loop analyses in patients with diastolic dysfunction (confirmed by invasively measured indices for diastolic relaxation [tau], LVEDP and LVEDV), demonstrating the LV filling index E/E' to have the highest ability to detect diastolic dysfunction (86 % sensitivity) [48]. This measure (E/E') has subsequently been evaluated against LA volume index and LV mass index, demonstrating increased sensitivity of detecting HFPEF in patients with LA size >40 mL/m^2 and LV mass >149 g/m^2 in men or >122 g/m^2 in women [46].Yet when these non-invasive indices were compared with pulmonary capillary wedge pressure (PCWP) assessed by right heart catheterizations, the non-invasive E/E' did not reliably track changes in left-sided filling pressures [49]. This disconnect between patients with HFPEF and non-elevated filling pressures at rest has been examined further by a study of euvolemic patients with exertional dyspnea, preserved EF, and normal cardiac filling pressures at rest: during exercise, patients demonstrated significantly abnormal hemodynamic responses including elevated PCWP [50]. While exercise hemodynamics may lack specificity as abnormal findings can be found in normal aging, it presents an attractive method to yield findings that may not be apparent at rest. The role of exercise hemodynamics in the diagnosis of HFPEF presents an emerging area of potentially improved diagnostic sensitivity. Although further validation of exercise hemodynamics in the diagnosis of HFPEF is necessary, it may be useful in the evaluation of patients who do not meet other established criteria for HFPEF.

Finally, the measurement of circulating natriuretic peptides (NP) has been suggested as an adjunctive diagnostic tool, but is also confounded by the influence of common co-morbidities present in patients with HFPEF on the presence of elevated NP [46]. Recent studies have demonstrated the association between NP and HFPEF, however validation of this marker in the diagnosis of HFPEF needs to be verified in ongoing clinical studies [51, 52].

Given the non-specific nature of the current non-invasive measures and their lack of correlation with invasive measures, the diagnostic utility of the ESC criteria have been called into question [35, 49]. Since many older adults have comorbid conditions that mimic the symptoms of dyspnea, fatigue, paroxysmal nocturnal dyspnea, orthopnea and leg swelling classically associated with heart failure, the specificity of the clinical diagnosis of HFPEF is reduced. Similarly, physical exam findings are both difficult to assess and notoriously non-specific for diagnostic criteria, and the diagnostic EF cutoff defining "preserved EF" has not been consistently used in diagnostic studies [3, 17, 21, 42, 52–54]. The nature of these diagnostic dilemmas has created a clinical challenge for the treating physician. Consequently, many clinicians have opted for an approach to diagnosis that employs a combination of the previous diagnostic strategies that is tailored to specific clinical settings and includes a clinical phenotype consistent with heart failure, a preserved EF, and echocardiographic evidence for LV hypertrophy and LA enlargement [51].

Treatment

Despite advances in our understanding of the causes and mechanisms driving the development of HFPEF, treatment options remain limited. Over the past two decades, clinical trials in HFPEF have primarily focused on drugs that have demonstrated mortality benefit in HFREF. Multiple drug trials have now been completed, yet no single agent has shown mortality benefit, and pharmaceutical options for HFPEF remain elusive. In contrast, lifestyle modifications have exhibited consistent benefit in patients with HFPEF, and novel therapies show promise in targeting several of the non-*diastolic dysfunction* etiologies of HFPEF.

The rationale behind many of the large pharmaceutical trials is that drugs that reduce ventricular hypertrophy or improve myocardial relaxation should benefit patients with HFPEF. This premise is primarily based on improving diastolic function, which as previously mentioned is only one of several mechanistic contributors to HFPEF. The following drug classes have been studied in large randomized placebo-controlled clinical trials (Table 7.1): beta-blockers, angiotensin-converting enzyme inhibitors (ACEi), angiotensin receptor blockers (ARB), aldosterone antagonists, and digoxin.

Each of these trials is notable for including subjects with clinical HFPEF and, with the exception of RAAM-PEF, having greater than 100 and up to 4,128 patients (I-PRESERVE). The trial subjects had a mean age ranging from 63 years to 76 years, and EF cutoffs ranging from ≥35 to ≥50 %. None of these trials demonstrated

Table 7.1 Large pharmacologic trials for HFPEF [55–65]

Trial, year	DIG study (1997) [55, 56]	CHARM-P (2003) [65]	SWEDIC (2004) [57]	PEP-CHF (2006) [58]	SENIORS (2009) [64]
Drug	Digoxin	Candesartan	Carvedilol	Perindopril	Nebivolol
n	988	3023	113	850	752
Mean age (years)	63	67	67	75	76
Inclusion criteria	CHF diagnosis	NYHA II-IV, prior cardiac hospitalization	DHF by echocardiography	HF symptoms, LAE, Impaired LV filling, Cardiac hospitalization in prior 6 mo	HF symptoms, Cardiac hospitalizations in prior 12 mo
EF (%)	>45	>40	>45	≥40	≥35
Primary outcome	Composite death or HF hospitalizations	Composite CV death or HF hospitalization	Regression of diastolic LV dysfunction by Doppler	Composite all-cause mortality or HF hospitalization	Composite all-cause mortality or CV hospitalizations
Results	No mortality benefit (HR 0.82; 95 % CI 0.63–1.07); ↓ 2-year HF Hospitalizations (HR 0.66; 95 % CI 0.47–0.91, p = 0.012)	No mortality benefit (HR 0.89; 95 % CI 0.77–1.03; p=0.118); ↓ 3-year Hospitalizations (p = 0.017)	No significant change in composite diastolic LV function; ↑ E/A (p = <0.05)	No mortality benefit was seen over 2.1 year (HR 0.92; 95 % CI 0.70–1.21, p = 0.545); ↓ 1-year hospitalizations (HR 0.628; 95 % CI 0.408–0.966, p = 0.033)	No reduction (HR (0.81; 95 % CI 0.63–1.04, p = 0.720)

Trial, year	I-PRESERVE (2008) [62]	RAAM-PEF (2011) [60]	ELAND (2012) [59]	Aldo-DHF (2013) [61]	TOPCAT, ongoing [63]
Drug	Irbesartan	Eplerenone	Nebivolol	Spironolactone	Spironolactone
n	4128	44	116	422	3445
Mean age (years)	72	70	66	67	69
Inclusion criteria	NYHA II–IV, Cardiac hospitalization in prior 6 months	NYHA II/III, BNP ≥100 pg/mL	NYHA II/III, ESC criteria of DHF	NYHA II/III, echocardiographic DHF	HF signs and symptoms, HF hospitalization in prior 12 months
EF (%)	≥40	≥50	>45	≥50	≥45
Primary outcome	Composite all-cause mortality or CV hospitalizations	6MWD	6MWD	E/E', peak VO2	Composite CV mortality or HF hospitalizations
Results	No reduction over 49.5 months of follow-up (HR 0.95; 95 % CI 0.86–1.05; p = 0.35)	No improvement (p = 0.91)	No improvement (p = 0.094)	↓ E/E' (adj. mean difference -1.5; 95 % CI -2.0–0.9; p < 0.001); No improvement peak VO2 (p = 0.81)	Reduction in HF hospitalization (HR 0.83; 95 % CI 0.69–0.99; p = 0.04). No reduction in mortality (HR 0.89; 95 % CI 0.77–1.04; p = 0.14)

EF ejection fraction, *NYHA* New York Heart Association, *CHF* congestive heart failure, *DHF* diastolic heart failure, *HF* heart failure, *LAE* left atrial enlargement, *LV* left ventricle, *CV* cardiovascular, *HR* hazard ratio, *CI* confidence interval, *E/E'* ratio of mitral peak velocity of early filling (E) to early diastolic mitral annular velocity (E')

mortality benefit, and most failed to show benefit in the endpoint of heart failure hospitalizations; only candesartan (CHARM-P) and perindopril (PEP-CHF) exhibited decreased hospitalizations. Finally, despite a lack of placebo-controlled trials demonstrating clinical benefit of diuretic use in HFPEF, in the Hong Kong diastolic heart failure study of 150 elderly patients with HFPEF, diuretics significantly reduced heart failure symptoms and improved quality of life, and neither ramipril nor irbesartan demonstrated additional effect [66] Diuretics remain essential therapy in the symptomatic control of volume overloaded states, although their use should be cautioned among preload dependent euvolemic patients. See Table 7.2 [67–77].

Owing in part to the neutral results of pharmacologic therapy but also the increased understanding of the multifactorial etiology of HFPEF, lifestyle modifications have been increasingly studied over the past decade. Evidence-supported interventions include exercise training, weight loss, smoking cessation, cardiac rehabilitation/physical therapy, and low-sodium diet (Table 7.2) [67, 68, 70, 76, 79–83]. Although many of these studies have been limited by a lack of randomization, no placebo-control, small numbers of patients, and less clinically relevant endpoints, they offer valuable insight into the utility of non-pharmacologic treatment in HFPEF. While exercise training, including weight loss and cardiac rehabilitation/physical therapy are now being integrated into clinical guidance for HFPEF [84], salt-restricted diets remain controversial. Low sodium diets have predominantly been studied in the outpatient setting and have been observed to show benefit in vital sign and laboratory measurements [77, 85, 86]. Although most studies have not focused on mortality outcomes, the GAP-HF study demonstrated reduced 30-day combined mortality and readmission with discharge recommendations for a sodium-restricted diet in 443 patients with HFPEF [76]. These findings have been tempered, however, by a recent study in patients with HFREF suggesting low salt diet may increase mortality and HF-related hospitalizations [87]. Whereas these findings raise concern that salt-restriction may be harmful in patients with systolic dysfunction, they may also be viewed as further evidence of the mechanistic and corresponding therapeutic differences between HFPEF and HFREF.

Limited data is available on the use of interventional procedures in the treatment of HFPEF—including percutaneous coronary intervention (PCI), coronary artery bypass grafting (CABG), aortic valve replacement (AVR) and cardiac resynchronization therapy (CRT). Although a study of 46 patients hospitalized with acute pulmonary edema showed that revascularization with PCI or CABG did not effect the recurrence of pulmonary edema [88]. ACC/AHA guidelines recommend revascularization if symptomatic myocardial ischemia is judged to be contributing to worsening of cardiac function [89]. Observations by Hachicha et al., in 331 patients with EF > 50 % and severe aortic stenosis (AS; aortic valve area <0.6) demonstrated that paradoxical low flow states (characteristic of patients with HFPEF) were associated with a worsened 3-year survival [90]. This has contributed to the class I recommendation for AVR in symptomatic patients with HFPEF and AS [91]. Finally, CRT (see Table 7.3) has emerged as a potential therapeutic option for HFPEF based on recent data showing decreased LV dyssynchrony, decreased LVEDP and improved LVESV,

Table 7.2 Lifestyle/exercise interventions in the treatment of HFPEF [67–78]

Study, year	Type of study	n	Population	Age	EF cutpoint	Intervention	Outcome	Results
Exercise								
Gary et al. (2004) [67]	RCT	32	Women, NYHA II/III DHF	68	≥45 %	3 months of home-based low-to-moderate intensity exercise	6MWT, QOL, GDS	6MWT–840 ± 366 ft to 1043 ± 317 ft vs 824 ± 367 ft to 732 ± 408 ft (P = .002); ↑QOL and ↓GDS
Smart et al. (2007) [68]	Non-randomized, non-placebo controlled	26	DHF by delayed relaxation or pseudonormal filling	65	>45 %	16 weeks of supervised cycle ergometer ExT	Peak VO2, E/E', QOL	30 % ↑Peak VO2 ($p < 0.001$); No change E/E' ($p = 0.38$); ↑QOL
Korzeniowska-Kubacka et al. (2010) [69]	RCT	48	Men, Post-MI with mild diastolic dysfunction by TDI	56	≥50 %	18 weeks supervised aerobic training (3 sessions/week)	Exercise capacity, Echocardiography	↑Peak VO2 ($p < 0.0001$); No change E/E'
Kitzman et al. (2010) [70]	Randomized, attention controlled	53	Ambulatory patients with isolated HFPEF (no coronary, pulmonary, valvular disease)	70	≥50 %	16 weeks of supervised aerobic exercise training	Exercise performance, QOL, Echocardiography, Neuroendocrine function	↑ Peak VO2 ($p = 0.0002$); ↑ Physical QOL ($p = 0.03$); No change in doppler echocardiography; No change in BNP ($p = 0.06$)
Edelman et al. (2011) [71]	RCT	64	Outpatients, NYHA II/III, diastolic dysfunction by echocardiogram	65	≥50 %	24 weeks of supervised aerobic cycling	Exercise capacity, Echocardiography, QOL	↑Peak VO2 ($p < 0.001$); ↓ E/E' and LAVI ($p < 0.001$); ↑QOL

(continued)

Table 7.2 (continued)

Study, year	Type of study	n	Population	Age	EF cutpoint	Intervention	Outcome	Results
Fujimato et al. (2012) [72]	Non-randomized, non-controlled	11	HF by Framingham criteria plus e/o pulmonary congestion	75	>45 %	1 year of exercise training (3×/week for 25 min)	RHC, Doppler echocardiography, aterial stiffness, exercise testing, ventricular-arterial coupling	No change in LV compliance or volumes, arterial stiffiness, E/E', peak VO2, or ventricular-arterial coupling
Haykowsky et al. (2012) [73]	Randomized, attention-controlled	40	Ambulatory patients with isolated HFPEF (no coronary, pulmonary, valvular disease)	69	≥50 %	16 weeks of supervised aerobic exercise training	Peak VO2 and echocardiography	↑Peak VO2 ($p = 0.002$; No change in EDV, SV, CO; ↑Peak arterial-venous oxygen difference ($p = 0.03$)
Smart et al. (2012) [74]	RCT	25	Dyspneic clinic patients with delayed relaxation or pseudonormal filling	65	>45 %	16 weeks of supervised, outpatient, cycle ergometer ExT (3×30 min sessions/week)	Peak VO2, Echocardiography, QOL, GDS	25 %↑ Peak VO2 ($p = 0.02$); No change E/E' ($p = 0.52$); No change QOL or GDS
Kitzman et al., 2016 [75]	RCT	100	Older obese patients with chronic, stable HFPEF	67	≥ 50 %	20 wks of exercise, diet or both	Peak VO2, QOL	Peak VO2 ↑ by both interventions. Exercise 1.2 mL/kg body mass/min (95 % CI 0.7-1.7), $p < 0.001$; Diet 1.3 mL/kg body mass/min (95 % CI 0.8-1.8), $p < 0.001$; Combination joint effect 2.5 mL/kg/min. No change QOL.

Salt-restriction								
GAP-HF (2009) [76]	Retrospective cohort	443	Discharge diagnosis of primary HF	75	≥50 %	Discharge recommendation for sodium restricted diet	30-day combined death and readmission	OR 0.43 (95 % CI 0.24–0.79; p = 0.007)
Hummel et al. (2012) [77]	Pilot study, non-randomized, non-controlled	13	Systemic hypertension, e/o diastolic dysfunciton by catheterization or echocardiography	72	≥50 %	21 days of sodium-restricted DASH diet (all food provided)	BP, Laboratory, Echocardiography, Functional testing	↓ Clinic and 24-hr BP (SBP 155–>138, p = 0.02); ↓ Urinary F2-isoprostane and urinary sodium excretion; No change in E/E' (p = 0.45); No change; ↑6MWT (p = 0.006)
GOURMET-HF (2014) [78]	RCT	66	Older adults after hospitalization for ADHF	≥65	≥50 % (stratified, also recruiting <50 %)	4 weeks of preprepared, home-delivered DASH/SRD-compliant meals	QOL, Adherence, Salt taste affinity testing, Echocardiography, Systemic inflammation and oxidative stress reduction, functional testing, adverse events	Results pending

RCT randomized-controlled trial, *NYHA* New York Heart Association, *DHF* diastolic heart failure, *6MWT* 6-min walk test, *HF* heart failure, *QOL* quality of life, *6MWD* 6-min walk distance, *GDS* geriatric depression scale, *VO2* oxygen uptake, *ExT* exercise training, *E/E'* ratio of mitral peak velocity of early filling (E) to early diastolic mitral annular velocity (E'), *TDI* tissue Doppler imaging, *BNP* brain-natriuretic peptide, *LAVI* left atrial volume index, *RHC* right heart catheterization, *EDV* end-diastolic volume, *SV* stroke volume, *CO* cardiac output, *OR* odds ratio, *DASH* dietary approaches to stop hypertension, *SBP* systolic blood pressure, *GOURMET-HF* geriatric out of hospital randomized meal trial in heart failure, *ADHF* acute decompensated heart failure, *SRD* sodium restricted diet

Table 7.3 Additional therapies in HFPEF [92–103]

Therapy	Neutral endopeptidase inhibitors [96]	Recombinant human relaxin-2 [93]	Cardiac resynchronization therapy [92, 98]	Barostimulation [94, 95]	Renal denervation [97, 99]
Summary	Increases plasma concentrations of natriuretic peptides, which inhibit RAA system activity, lower sympathetic drive, and have antiproliferative and antihpertrophic effects	Causes decreased systemic vascular resistance (vasodilation), increased cardiac output (inotropy), and increased renal blood flow	The prevalence of electrical and mechanical ventricular dyssynchrony in HFPEF is less than HFREF but still significant, suggesting a therapeutic role for cardiac resynchronization as a therapeutic target	Reduces the activity of the SNS, leading to diminished hypertension, renal dysfunction, vascular stiffness and myocardial ischemia. Currently being studied to determine carotid baroreceptor stimulation on outcomes in patients with HFPEF	Decreases sodium reabsorbtion and RAA system activity; has been show to reduce blood pressure, renal dysfunction and cardiac hypertrophy in patients with resistant hypertension
Ongoing studies	PARAMOUNT [103], a phase 2 RCT of ARNI LCZ696 in 301 patients with NYHA II/III, EF ≥ 40 %, and NT-proBNP >400 pg/mL, demonstrated reduced NT-proBNP (783–605 pg/mL) compared to valsartan at 12 weeks follow-up	RELAX-AHF [93], a RCT of Serelaxin in 1161 patients with acute HF. Patients with HFPEF (26 % of patients) experienced relief of dyspnea by visual analogue scale through day 5 of treatment	KaRen registry [102], a prospective observational study characterizing the prevalence of electrical or mechanical dyssynchrony in HFPEF with resulting effect on prognosis	HOPE4HF [94], a RCT of Baroreflex Activation Therapy (BAT) in ~540 patients on CV death or HF hospitalizations	SYMPLICITY-HF [100] and SWAN-HF [101], two open-label feasibility and safety/efficacy studies of renal denervation and renal sympathetic modification on patients with HF

however prospective data is ongoing and necessary before clinical CRT guidelines are recommended [104, 105].

In addition to CRT, several other novel therapies have emerged as additional therapeutic possibilities for HFPEF. These include neutral endopeptidase inhibitors [96], recombinant human relaxin-2 [93], barostimulation [94, 95] and renal denervation [97]. Neutral endopeptidase inhibition is based on the hypothesis that reducing the degradation of NP will lower sympathetic drive via the inhibition of the renin-aldosterone-angiotensin (RAA) system, causing antiproliferative and antihypertrophic effects on myocardium. Serelaxin, a recombinant human relaxin-2, causes vasodilation and increased inotropy, and has demonstrated symptomatic relief of dyspnea in patients with HFPEF. Barostimulation has similarly been shown to decrease adrenergic stimulation, leading to reduced ventricular-vascular stiffening with corresponding harmful myocardial remodeling. Finally, renal denervation has demonstrated reduced sodium reabsorption with reduced blood pressure and corresponding ventricular hypertrophy. Recent and ongoing studies are examining the effects of these emerging therapies on various clinical endpoints in HFPEF (See Table 7.3).

In contrast to the above pharmaceutical, lifestyle and interventional therapies that have shown mixed promise in the treatment of HFPEF, several agents have been observed to cause harm and worsen outcomes in HFPEF. Drugs to avoid include those causing fluid retention such as the thiazolinediones (TZDs) pioglitazone or rosiglitazone, and non-steroidal anti-inflammatory drugs (NSAIDS). Such drugs can cause increased sodium and water retention leading to edema and hypertension with subsequent worsening of volume overloaded states. This has led to an AHA Consensus Statement about the increased risk of heart failure with the use of TZDs [106]. Similar caution should be used with drugs causing renal impairment, and in over-diuresis as above in patients with euvolemia for whom preload is essential to maintain cardiac output.

There has been much discussion and several proposed explanations for the apparent disconnect in therapeutic success between HFREF and HFPEF—including differences in myocardial structure [107, 108] flaws in diagnostic methods for inclusion criteria [109] and inappropriate trial design [17]. What is clear is that the success of future of HFPEF treatments will require a novel approach that integrates the multifaceted causes and diverse population that comprise this syndrome distinct from HFREF. In a recent study, however, examining differences in treatment strategies pursued by cardiologists for HF patients according to EF, patients with HFPEF were treated similarly as patients with HFREF, suggesting a lack of integrating known data into current practice [110].

Incorporating the above data together with an appreciation of its multifaceted etiology yields a heterogeneous approach to the management of HFPEF. Clinicians must consider a broad differential diagnosis for the patient presenting with a clinical phenotype consistent with HFPEF. Although data supporting the treatment of comorbid conditions such as anemia, dyslipidemia, chronic renal disease, chronic pain, and diabetes are mixed (including one study showing improved survival with statin use compared to ACEi, beta-blocker, or calcium channel blockers [111] and

another showing no benefit of subcutaneous epoetin alpha [ESA] administration on LVEDV or submaximal exercise but an improvement in peak VO2 in those able to exercise [112], co-morbid conditions should be embraced in the overall treatment strategy with the understanding that peripheral mechanisms of HFPEF may contribute significantly to the clinical phenotype and that non-cardiovascular causes of recurrent hospitalization are the major cause of 30–90 day readmissions [9]. Similar to the multimodal approach championed in the current practice of geriatric medicine, treatment could be aimed at multiple components, including both cardiac and non-cardiac domains.

Conclusion

As the burden of HFPEF rises with our aging population, managing this condition has become increasing complex. Clinicians must take care to understand the multifactorial pathogenesis that defines this syndrome, and the subsequent diagnostic approach used to classify patients. Treatment approaches are evolving, with an emphasis on optimizing volume status, controlling blood pressure and managing comorbid conditions which may exacerbate symptoms. Successful strategies may involve a new approach that does not rely on single interventions but is instead broadly based by addressing targeted goals rather than a single endpoint. Focusing management on improvements in several domains (i.e. vital signs, lifestyle changes, comorbidities, functional limitations and sarcopenia) would direct care at improving target blood pressure control, weight loss, exercise goals and rehabilitation, or diabetes management—based on the understanding that these incremental effects contribute to the overall HFPEF phenotype in a majority of patients. The result would be a treatment approach that addresses the complexity of HFPEF through its fundamental elements. By incorporating a multifaceted approach with our understanding of its complex etiology, further advances in HFPEF trial design will greatly benefit the future management of this condition.

References

1. Dougherty AH, Naccarelli GV, Gray EL, Hicks CH, Goldstein RA. Congestive heart failure with normal systolic function. Am J Cardiol. 1984;54(7):778–82.
2. Hanrath P, DG M, Siegert R, Bleifeld W. Left ventricular relaxation and filling pattern in different forms of left ventricular hypertrophy: an echocardiographic study. Am J Cardiol. 1980;45(1):15–23.
3. JE S, DG G, DJ B, JF G. Left ventricular filling in hypertrophic cardiomyopathy. An angiographic study. Br Heart J. 1977;39(6):661–70.
4. SA H, WT A, MH C, AM F, GS F, TG G, et al. ACC/AHA 2005 Guideline Update for the Diagnosis and Management of Chronic Heart Failure in the Adult: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines

(Writing Committee to Update the 2001 Guidelines for the Evaluation and Management of Heart Failure): developed in collaboration with the American College of Chest Physicians and the International Society for Heart and Lung Transplantation: endorsed by the Heart Rhythm Society. Circulation. 2005;112(12):e154–235.
5. Roger VL, Go AS, Lloyd-Jones DM, Benjamin EJ, Berry JD, Borden WB, et al. Executive summary: heart disease and stroke statistics – 2012 update: a report from the American Heart Association. Circulation. 2012;125(1):188–97.
6. Jencks SF, Williams MV, Coleman EA. Rehospitalizations among patients in the Medicare fee-for-service program. N Engl J Med. 2009;360(14):1418–28.
7. Lakatta EG, Levy D. Arterial and cardiac aging: major shareholders in cardiovascular disease enterprises: part I: aging arteries: a "set up" for vascular disease. Circulation. 2003;107(1):139–46.
8. Lakatta EG, Levy D. Arterial and cardiac aging: major shareholders in cardiovascular disease enterprises: part II: the aging heart in health: links to heart disease. Circulation. 2003;107(2):346–54.
9. Fida N, Pina IL. Trends in heart failure hospitalizations. Curr Heart Fail Rep. 2012;9(4):346–53.
10. Bursi F, Weston SA, Redfield MM, Jacobsen SJ, Pakhomov S, Nkomo VT, et al. Systolic and diastolic heart failure in the community. JAMA. 2006;296(18):2209–16.
11. Devereux RB, Roman MJ, Liu JE, Welty TK, Lee ET, Rodeheffer R, et al. Congestive heart failure despite normal left ventricular systolic function in a population-based sample: the Strong Heart Study. Am J Cardiol. 2000;86(10):1090–6.
12. Kitzman DW, Gardin JM, Gottdiener JS, Arnold A, Boineau R, Aurigemma G, et al. Importance of heart failure with preserved systolic function in patients > or = 65 years of age. CHS Research Group. Cardiovascular Health Study. Am J Cardiol. 2001;87(4):413–9.
13. Lee DS, Gona P, Vasan RS, Larson MG, Benjamin EJ, Wang TJ, et al. Relation of disease pathogenesis and risk factors to heart failure with preserved or reduced ejection fraction: insights from the framingham heart study of the national heart, lung, and blood institute. Circulation. 2009;119(24):3070–7.
14. Lam CS, Donal E, Kraigher-Krainer E, Vasan RS. Epidemiology and clinical course of heart failure with preserved ejection fraction. Eur J Heart Fail. 2011;13(1):18–28.
15. Owan TE, Hodge DO, Herges RM, Jacobsen SJ, Roger VL, Redfield MM. Trends in prevalence and outcome of heart failure with preserved ejection fraction. N Engl J Med. 2006;355(3):251–9.
16. Steinberg BA, Zhao X, Heidenreich PA, Peterson ED, Bhatt DL, Cannon CP, et al. Trends in patients hospitalized with heart failure and preserved left ventricular ejection fraction: prevalence, therapies, and outcomes. Circulation. 2012;126(1):65–75.
17. Bhuiyan T, Maurer MS. Heart failure with preserved ejection fraction: persistent diagnosis. Therapeutic Enigma Curr Cardiovasc Risk Rep. 2011;5(5):440–9.
18. Henkel DM, Redfield MM, Weston SA, Gerber Y, Roger VL. Death in heart failure: a community perspective. Circ Heart Fail. 2008;1(2):91–7.
19. Kliger C, King DL, Maurer MS. A clinical algorithm to differentiate heart failure with a normal ejection fraction by pathophysiologic mechanism. Am J Geriatr Cardiol. 2006;15(1):50–7.
20. Lakatta EG. Cardiovascular regulatory mechanisms in advanced age. Physiol Rev. 1993;73(2):413–67.
21. Maurer MS, Spevack D, Burkhoff D, Kronzon I. Diastolic dysfunction: can it be diagnosed by Doppler echocardiography? J Am Coll Cardiol. 2004;44(8):1543–9.
22. Lakatta EG. Arterial and cardiac aging: major shareholders in cardiovascular disease enterprises: part III: cellular and molecular clues to heart and arterial aging. Circulation. 2003;107(3):490–7.
23. Kawaguchi M, Hay I, Fetics B, Kass DA. Combined ventricular systolic and arterial stiffening in patients with heart failure and preserved ejection fraction: implications for systolic and diastolic reserve limitations. Circulation. 2003;107(5):714–20.
24. Burton A. Physiology and Biophysics of the Circulation. 2nd ed. Chicago: Year Book Medical Publishers; 1972.

25. Duarte D, Santos-Araujo C, Leite-Moreira AF. Hypertension and angiogenesis in the aging kidney: a review. Arch Gerontol Geriatr. 2011;52(3):e93–102.
26. Maurer MS, Kronzon I, Burkhoff D. Ventricular pump function in heart failure with normal ejection fraction: insights from pressure-volume measurements. Prog Cardiovasc Dis. 2006;49(3):182–95.
27. Hotta H, Uchida S. Aging of the autonomic nervous system and possible improvements in autonomic activity using somatic afferent stimulation. Geriatr Gerontol Int. 2010;10(Suppl 1):S127–36.
28. Miller MR. Structural and physiological age-associated changes in aging lungs. Semin Respir Crit Care Med. 2010;31(5):521–7.
29. Abramov D, Helmke S, Rumbarger Lel K, King DL, Maurer MS. Overestimation of left ventricular mass and misclassification of ventricular geometry in heart failure patients by two-dimensional echocardiography in comparison with three-dimensional echocardiography. Echocardiography. 2010;27(3):223–9.
30. He KL, Burkhoff D, Leng WX, Liang ZR, Fan L, Wang J, et al. Comparison of ventricular structure and function in Chinese patients with heart failure and ejection fractions >55% versus 40% to 55% versus <40%. Am J Cardiol. 2009;103(6):845–51.
31. He KL, Dickstein M, Sabbah HN, Yi GH, Gu A, Maurer M, et al. Mechanisms of heart failure with well preserved ejection fraction in dogs following limited coronary microembolization. Cardiovasc Res. 2004;64(1):72–83.
32. Munagala VK, Hart CY, Burnett Jr JC, Meyer DM, Redfield MM. Ventricular structure and function in aged dogs with renal hypertension: a model of experimental diastolic heart failure. Circulation. 2005;111(9):1128–35.
33. Gandhi SK, Powers JC, Nomeir AM, Fowle K, Kitzman DW, Rankin KM, et al. The pathogenesis of acute pulmonary edema associated with hypertension. N Engl J Med. 2001;344(1):17–22.
34. Kitzman DW, Higginbotham MB, Cobb FR, Sheikh KH, Sullivan MJ. Exercise intolerance in patients with heart failure and preserved left ventricular systolic function: failure of the Frank-Starling mechanism. J Am Coll Cardiol. 1991;17(5):1065–72.
35. Zile MR, Gaasch WH, Carroll JD, Feldman MD, Aurigemma GP, Schaer GL, et al. Heart failure with a normal ejection fraction: is measurement of diastolic function necessary to make the diagnosis of diastolic heart failure? Circulation. 2001;104(7):779–82.
36. Vasan RS, Levy D. Defining diastolic heart failure: a call for standardized diagnostic criteria. Circulation. 2000;101(17):2118–21.
37. Lam CS. Heart failure with preserved ejection fraction: invasive solution to diagnostic confusion? J Am Coll Cardiol. 2010;55(16):1711–2.
38. Paulus WJ, Tschope C, Sanderson JE, Rusconi C, Flachskampf FA, Rademakers FE, et al. How to diagnose diastolic heart failure: a consensus statement on the diagnosis of heart failure with normal left ventricular ejection fraction by the Heart Failure and Echocardiography Associations of the European Society of Cardiology. Eur Heart J. 2007;28(20):2539–50.
39. Yturralde RF, Gaasch WH. Diagnostic criteria for diastolic heart failure. Prog Cardiovasc Dis. 2005;47(5):314–9.
40. Penicka M, Bartunek J, Trakalova H, Hrabakova H, Maruskova M, Karasek J, et al. Heart failure with preserved ejection fraction in outpatients with unexplained dyspnea: a pressure-volume loop analysis. J Am Coll Cardiol. 2010;55(16):1701–10.
41. Luchi RJ, Snow E, Luchi JM, Nelson CL, Pircher FJ. Left ventricular function in hospitalized geriatric patients. J Am Geriatr Soc. 1982;30(11):700–5.
42. Bhella PS, Pacini EL, Prasad A, Hastings JL, Adams-Huet B, Thomas JD, et al. Echocardiographic indices do not reliably track changes in left-sided filling pressure in healthy subjects or patients with heart failure with preserved ejection fraction. Circ Cardiovasc Imaging. 2011;4(5):482–9.
43. Emery WT, Jadavji I, Choy JB, Lawrance RA. Investigating the European Society of Cardiology Diastology Guidelines in a practical scenario. Eur J Echocardiogr. 2008;9(5):685–91.
44. Fujimoto N, Borlaug BA, Lewis GD, Hastings JL, Shafer KM, Bhella PS, et al. Hemodynamic responses to rapid saline loading: the impact of age, sex, and heart failure. Circulation. 2013;127(1):55–62.

45. Kasner M, Westermann D, Steendijk P, Gaub R, Wilkenshoff U, Weitmann K, et al. Utility of Doppler echocardiography and tissue Doppler imaging in the estimation of diastolic function in heart failure with normal ejection fraction: a comparative Doppler-conductance catheterization study. Circulation. 2007;116(6):637–47.
46. Jeevanantham V, Shrivastava R, Nannapaneni S, Khan A, Sengodan M, Nautiyal A, et al. Elevated B-type natriuretic peptide level: use with caution in patients with multiple comorbidities and presenting with dyspnea. Indian Heart J. 2007;59(1):64–8.
47. Bishu K, Deswal A, Chen HH, LeWinter MM, Lewis GD, Semigran MJ, et al. Biomarkers in acutely decompensated heart failure with preserved or reduced ejection fraction. Am Heart J. 2012;164(5):763–70 e3.
48. Edelmann F, Schmidt AG, Gelbrich G, Binder L, Herrmann-Lingen C, Halle M, et al. Rationale and design of the 'aldosterone receptor blockade in diastolic heart failure' trial: a double-blind, randomized, placebo-controlled, parallel group study to determine the effects of spironolactone on exercise capacity and diastolic function in patients with symptomatic diastolic heart failure (Aldo-DHF). Eur J Heart Fail. 2010;12(8):874–82.
49. Zile MR, Brutsaert DL. New concepts in diastolic dysfunction and diastolic heart failure: Part I: diagnosis, prognosis, and measurements of diastolic function. Circulation. 2002;105(11):1387–93.
50. Borlaug BA, Nishimura RA, Sorajja P, Lam CS, Redfield MM. Exercise hemodynamics enhance diagnosis of early heart failure with preserved ejection fraction. Circ Heart Fail. 2010;3(5):588–95.
51. Melenovsky V, Borlaug BA, Rosen B, Hay I, Ferruci L, Morell CH, et al. Cardiovascular features of heart failure with preserved ejection fraction versus nonfailing hypertensive left ventricular hypertrophy in the urban Baltimore community: the role of atrial remodeling/dysfunction. J Am Coll Cardiol. 2007;49(2):198–207.
52. Petrie MC, Hogg K, Caruana L, McMurray JJ. Poor concordance of commonly used echocardiographic measures of left ventricular diastolic function in patients with suspected heart failure but preserved systolic function: is there a reliable echocardiographic measure of diastolic dysfunction? Heart. 2004;90(5):511–7.
53. Kindermann M, Reil JC, Pieske B, van Veldhuisen DJ, Bohm M. Heart failure with normal left ventricular ejection fraction: what is the evidence? Trends Cardiovasc Med. 2008;18(8):280–92.
54. Palmieri V, Innocenti F, Pini R, Celentano A. Reproducibility of Doppler echocardiographic assessment of left ventricular diastolic function in multicenter setting. J Am Soc Echocardiogr. 2005;18(2):99–106.
55. The Digitalis Investigation Group. The effect of digoxin on mortality and morbidity in patients with heart failure. N Engl J Med. 1997;336(8):525–33.
56. Ahmed A, Rich MW, Fleg JL, Zile MR, Young JB, Kitzman DW, et al. Effects of digoxin on morbidity and mortality in diastolic heart failure: the ancillary digitalis investigation group trial. Circulation. 2006;114(5):397–403.
57. Bergstrom A, Andersson B, Edner M, Nylander E, Persson H, Dahlstrom U. Effect of carvedilol on diastolic function in patients with diastolic heart failure and preserved systolic function. Results of the Swedish Doppler-echocardiographic study (SWEDIC). Eur J Heart Fail. 2004;6(4):453–61.
58. Cleland JG, Tendera M, Adamus J, Freemantle N, Polonski L, Taylor J. The perindopril in elderly people with chronic heart failure (PEP-CHF) study. Eur Heart J. 2006;27(19):2338–45.
59. Conraads VM, Metra M, Kamp O, De Keulenaer GW, Pieske B, Zamorano J, et al. Effects of the long-term administration of nebivolol on the clinical symptoms, exercise capacity, and left ventricular function of patients with diastolic dysfunction: results of the ELANDD study. Eur J Heart Fail. 2012;14(2):219–25.
60. Deswal A, Richardson P, Bozkurt B, Mann DL. Results of the Randomized Aldosterone Antagonism in Heart Failure with Preserved Ejection Fraction trial (RAAM-PEF). J Card Fail. 2011;17(8):634–42.
61. Edelmann F, Wachter R, Schmidt AG, Kraigher-Krainer E, Colantonio C, Kamke W, et al. Effect of spironolactone on diastolic function and exercise capacity in patients with heart failure with preserved ejection fraction: the Aldo-DHF randomized controlled trial. JAMA. 2013;309(8):781–91.

62. Massie BM, Carson PE, McMurray JJ, Komajda M, McKelvie R, Zile MR, et al. Irbesartan in patients with heart failure and preserved ejection fraction. N Engl J Med. 2008;359(23):2456–67.
63. Shah SJ, Heitner JF, Sweitzer NK, Anand IS, Kim HY, Harty B, et al. Baseline Characteristics of Patients in the Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist (TOPCAT) Trial. Circ Heart Fail. 2013;6:184–92.
64. van Veldhuisen DJ, Cohen-Solal A, Bohm M, Anker SD, Babalis D, Roughton M, et al. Beta-blockade with nebivolol in elderly heart failure patients with impaired and preserved left ventricular ejection fraction: data from SENIORS (Study of Effects of Nebivolol Intervention on Outcomes and Rehospitalization in Seniors With Heart Failure). J Am Coll Cardiol. 2009;53(23):2150–8.
65. Yusuf S, Pfeffer MA, Swedberg K, Granger CB, Held P, McMurray JJ, et al. Effects of candesartan in patients with chronic heart failure and preserved left-ventricular ejection fraction: the CHARM-Preserved Trial. Lancet. 2003;362(9386):777–81.
66. Yip GW, Wang M, Wang T, Chan S, Fung JW, Yeung L, et al. The Hong Kong diastolic heart failure study: a randomised controlled trial of diuretics, irbesartan and ramipril on quality of life, exercise capacity, left ventricular global and regional function in heart failure with a normal ejection fraction. Heart. 2008;94(5):573–80.
67. Gary RA, Sueta CA, Dougherty M, Rosenberg B, Cheek D, Preisser J, et al. Home-based exercise improves functional performance and quality of life in women with diastolic heart failure. Heart Lung. 2004;33(4):210–8.
68. Smart N, Haluska B, Jeffriess L, Marwick TH. Exercise training in systolic and diastolic dysfunction: effects on cardiac function, functional capacity, and quality of life. Am Heart J. 2007;153(4):530–6.
69. Korzeniowska-Kubacka I, Bilinska M, Michalak E, Kusmierczyk-Droszcz B, Dobraszkiewicz-Wasilewska B, Piotrowicz R. Influence of exercise training on left ventricular diastolic function and its relationship to exercise capacity in patients after myocardial infarction. Cardiol J. 2010;17(2):136–42.
70. Kitzman DW, Brubaker PH, Morgan TM, Stewart KP, Little WC. Exercise training in older patients with heart failure and preserved ejection fraction: a randomized, controlled, single-blind trial. Circ Heart Fail. 2010;3(6):659–67.
71. Edelmann F, Gelbrich G, Dungen HD, Frohling S, Wachter R, Stahrenberg R, et al. Exercise training improves exercise capacity and diastolic function in patients with heart failure with preserved ejection fraction: results of the Ex-DHF (Exercise training in Diastolic Heart Failure) pilot study. J Am Coll Cardiol. 2011;58(17):1780–91.
72. Fujimoto N, Prasad A, Hastings JL, Bhella PS, Shibata S, Palmer D, et al. Cardiovascular effects of 1 year of progressive endurance exercise training in patients with heart failure with preserved ejection fraction. Am Heart J. 2012;164(6):869–77.
73. Haykowsky MJ, Brubaker PH, Stewart KP, Morgan TM, Eggebeen J, Kitzman DW. Effect of endurance training on the determinants of peak exercise oxygen consumption in elderly patients with stable compensated heart failure and preserved ejection fraction. J Am Coll Cardiol. 2012;60(2):120–8.
74. Smart NA, Haluska B, Jeffriess L, Leung D. Exercise training in heart failure with preserved systolic function: a randomized controlled trial of the effects on cardiac function and functional capacity. Congest Heart Fail. 2012;18(6):295–301.
75. Kitzman DW, Brubaker P, Morgan T, Haykowsky M, Hundley G, Kraus WE, et al. Effect of caloric restriction or aerobic exercise training on peak oxygen consumption and quality of life in obese older patients with heart failure with preserved ejection fraction: a randomized clinical trial. JAMA. 2016;315(1):36–46.
76. Hummel SL, DeFranco AC, Skorcz S, Montoye CK, Koelling TM. Recommendation of low-salt diet and short-term outcomes in heart failure with preserved systolic function. Am J Med. 2009;122(11):1029–36.
77. Hummel SL, Seymour EM, Brook RD, Kolias TJ, Sheth SS, Rosenblum HR, et al. Low-sodium dietary approaches to stop hypertension diet reduces blood pressure, arterial stiffness, and oxidative stress in hypertensive heart failure with preserved ejection fraction. Hypertension. 2012;60(5):1200–6.

78. Wessler JD, Maurer MS, Hummel SL. Evaluating the safety and efficacy of sodium-restricted/Dietary Approaches to Stop Hypertension diet after acute decompensated heart failure hospitalization: design and rationale for the Geriatric OUt of hospital Randomized MEal Trial in Heart Failure (GOURMET-HF). Am Heart J. 2015;169(3):342–8 e4.
79. Bibbins-Domingo K, Chertow GM, Coxson PG, Moran A, Lightwood JM, Pletcher MJ, et al. Projected effect of dietary salt reductions on future cardiovascular disease. N Engl J Med. 2010;362(7):590–9.
80. Conard MW, Haddock CK, Poston WS, Spertus JA. The impact of smoking status on the health status of heart failure patients. Congest Heart Fail. 2009;15(2):82–6.
81. Hinderliter AL, Babyak MA, Sherwood A, Blumenthal JA. The DASH diet and insulin sensitivity. Curr Hypertens Rep. 2011;13(1):67–73.
82. Meurrens K, Ruf S, Ross G, Schleef R, von Holt K, Schluter KD. Smoking accelerates the progression of hypertension-induced myocardial hypertrophy to heart failure in spontaneously hypertensive rats. Cardiovasc Res. 2007;76(2):311–22.
83. Sacks FM, Svetkey LP, Vollmer WM, Appel LJ, Bray GA, Harsha D, et al. Effects on blood pressure of reduced dietary sodium and the Dietary Approaches to Stop Hypertension (DASH) diet. DASH-Sodium Collaborative Research Group. N Engl J Med. 2001;344(1):3–10.
84. Hunt SA. ACC/AHA 2005 guideline update for the diagnosis and management of chronic heart failure in the adult: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Update the 2001 Guidelines for the Evaluation and Management of Heart Failure). J Am Coll Cardiol. 2005;46(6):e1–82.
85. Hirota S, Sadanaga T, Mitamura H, Fukuda K. Spot urine-guided salt reduction is effective in Japanese cardiology outpatients. Hypertens Res. 2012;35(11):1069–71.
86. Sadanaga T, Ando K, Hirota S, Mitamura H, Tsuchihashi T, Kohsaka S, et al. B-type natriuretic peptide levels are decreased by reducing dietary salt intake in patients with compensated heart failure with preserved ejection fraction. Intern Med J. 2013;43:663–7.
87. Dinicolantonio JJ, Pasquale PD, Taylor RS, Hackam DG. Low sodium versus normal sodium diets in systolic heart failure: systematic review and meta-analysis. Heart. 2013; Epub 2013 March 12.
88. Kramer K, Kirkman P, Kitzman D, Little WC. Flash pulmonary edema: association with hypertension and reoccurrence despite coronary revascularization. Am Heart J. 2000;140(3):451–5.
89. Hunt SA, Abraham WT, Chin MH, Feldman AM, Francis GS, Ganiats TG, et al. 2009 focused update incorporated into the ACC/AHA 2005 Guidelines for the Diagnosis and Management of Heart Failure in Adults: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines: developed in collaboration with the International Society for Heart and Lung Transplantation. Circulation. 2009;119(14):e391–479.
90. Hachicha Z, Dumesnil JG, Bogaty P, Pibarot P. Paradoxical low-flow, low-gradient severe aortic stenosis despite preserved ejection fraction is associated with higher afterload and reduced survival. Circulation. 2007;115(22):2856–64.
91. Bonow RO, Carabello BA, Chatterjee K, de Leon Jr AC, DP F, MD F, et al. 2008 focused update incorporated into the ACC/AHA 2006 guidelines for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to revise the 1998 guidelines for the management of patients with valvular heart disease). Endorsed by the Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. J Am Coll Cardiol. 2008;52(13):e1–142.
92. De Sutter J, Van de Veire NR, Muyldermans L, De Backer T, Hoffer E, Vaerenberg M, et al. Prevalence of mechanical dyssynchrony in patients with heart failure and preserved left ventricular function (a report from the Belgian Multicenter Registry on dyssynchrony). Am J Cardiol. 2005;96(11):1543–8.
93. Filippatos G, Teerlink JR, Farmakis D, Cotter G, Davison BA, Felker GM, et al. Serelaxin in acute heart failure patients with preserved left ventricular ejection fraction: results from the RELAX-AHF trial. Eur Heart J. 2014;35(16):1041–50.

94. Georgakopoulos D, Little WC, Abraham WT, Weaver FA, Zile MR. Chronic baroreflex activation: a potential therapeutic approach to heart failure with preserved ejection fraction. J Card Fail. 2011;17(2):167–78.
95. Lovett EG, Schafer J, Kaufman CL. Chronic baroreflex activation by the Rheos system: an overview of results from European and North American feasibility studies. Conf Proc IEEE Eng Med Biol Soc. 2009;2009:4626–30.
96. Mangiafico S, Costello-Boerrigter LC, Andersen IA, Cataliotti A, Burnett Jr JC. Neutral endopeptidase inhibition and the natriuretic peptide system: an evolving strategy in cardiovascular therapeutics. Eur Heart J. 2013;34:886–893c.
97. Schlaich MP, Krum H, Sobotka PA, Esler MD. Renal denervation and hypertension. Am J Hypertens. 2011;24(6):635–42.
98. Yu CM, Zhang Q, Yip GW, Lee PW, Kum LC, Lam YY, et al. Diastolic and systolic asynchrony in patients with diastolic heart failure: a common but ignored condition. J Am Coll Cardiol. 2007;49(1):97–105.
99. Zile MR, Little WC. Effects of autonomic modulation: more than just blood pressure. J Am Coll Cardiol. 2012;59(10):910–2.
100. ClinicalTrials.gov ID: NCT01392196.
101. ClinicalTrials.gov ID: NCT01402726.
102. Donal E, Lund L, Linde C, Daubert JC. Is cardiac resynchronization therapy an option in heart failure patients with preserved ejection fraction? Justification for the ongoing KaRen project. Arch Cardiovasc Dis. 2010;103(6-7):404–10.
103. Solomon SD, Zile M, Pieske B, Voors A, Shah A, Kraigher-Krainer E, et al. The angiotensin receptor neprilysin inhibitor LCZ696 in heart failure with preserved ejection fraction: a phase 2 double-blind randomised controlled trial. Lancet. 2012;380(9851):1387–95.
104. ES C, RP K, S G, J B, B G, K H, et al. Cardiac resynchronization therapy may benefit patients with left ventricular ejection fraction >35%: a PROSPECT trial substudy. Eur J Heart Fail. 2010;12(6):581–7.
105. Penicka M, Kocka V, Herman D, Trakalova H, Herold M. Cardiac resynchronization therapy for the causal treatment of heart failure with preserved ejection fraction: insight from a pressure-volume loop analysis. Eur J Heart Fail. 2010;12(6):634–6.
106. Nesto RW, Bell D, Bonow RO, Fonseca V, Grundy SM, Horton ES, et al. Thiazolidinedione use, fluid retention, and congestive heart failure: a consensus statement from the American Heart Association and American Diabetes Association. October 7, 2003. Circulation. 2003;108(23):2941–8.
107. van Heerebeek L, Borbely A, Niessen HW, Bronzwaer JG, van der Velden J, Stienen GJ, et al. Myocardial structure and function differ in systolic and diastolic heart failure. Circulation. 2006;113(16):1966–73.
108. Kitzman DW, Little WC, Brubaker PH, Anderson RT, Hundley WG, Marburger CT, et al. Pathophysiological characterization of isolated diastolic heart failure in comparison to systolic heart failure. JAMA. 2002;288(17):2144–50.
109. Paulus WJ, van Ballegoij JJ. Treatment of heart failure with normal ejection fraction: an inconvenient truth! J Am Coll Cardiol. 2010;55(6):526–37.
110. Cohen Solal A, Leurs I, Assyag P, Beauvais F, Clerson P, Contre C, et al. Optimization of heart FailUre medical treatment after hospital discharge according to left ventricUlaR Ejection fraction: the FUTURE survey. Arch Cardiovasc Dis. 2012;105(6-7):355–65.
111. Fukuta H, Sane DC, Brucks S, Little WC. Statin therapy may be associated with lower mortality in patients with diastolic heart failure: a preliminary report. Circulation. 2005;112(3):357–63.
112. Maurer MS, Teruya S, Chakraborty B, Helmke S, Mancini D. Treating Anemia in Older Adults with Heart Failure with a Preserved Ejection Fraction (HFPEF) with Epoetin Alfa: Single Blind Randomized Clinical Trial of Safety and Efficacy. Circ Heart Fail. 2013;6:254–63.

Chapter 8
Acute Decompensated Heart Failure: Classification, Epidemiology and Pathophysiology

Daniel Fishbein

Introduction

Hospitalization for heart failure (HF) has emerged as major worldwide public health problem over the last three decades. Heart failure is the most common cause for hospitalization in patients over the age of 65 years in the United States. There are an estimated one million hospitalizations annually in the US with a primary diagnosis of heart failure accounting for 5–10 % of all hospitalizations. Three million patients are hospitalized annually with a primary or secondary diagnosis of heart failure. Approximately 5.1–5.8 million Americans have HF and it is estimated that the prevalence of heart failure will increase by 46 % from 2012 to 2030 [1–4]. The European Society of Cardiology represents 51 countries with a population of > 900 million people. At least 15 million Europeans have heart failure and an equal number have asymptomatic left ventricular dysfunction [2].

The direct and indirect costs associated with HF in the US in 2009 are estimated to exceed $37 billion. Most of these costs are attributable to hospitalization for HF. The number of hospitalizations for HF has triple in the last three decades. The increase in the prevalence of heart failure appears to be due to a number of factors including: the aging of the U.S. population in association with the increased incidence of heart failure with advancing age; improved survival after myocardial infarction resulting in more patients living with left ventricular dysfunction; and better prevention of arrhythmia-related death in patients with chronic left ventricular systolic dysfunction [5].

D. Fishbein, MD
University of Washington Medical Center, Department of Medicine, Division of Cardiology, 1959 NE Pacific Street, #356422, Seattle, WA 98195, USA
e-mail: dfish@uw.edu

H. Eisen (ed.), *Heart Failure*, DOI 10.1007/978-1-4471-4219-5_8

Definition

Acutely Decompensated Heart Failure (ADHF) can be defined as the new onset or recurrence of heart failure signs and symptoms that require urgent or emergent treatment and that result in hospitalization. A number of other terms have been used in the literature including: Acute Heart Failure Syndromes (AHFS), Acute Heart Failure (AHF) and Acute Decompensation of Chronic Heart Failure (ADCHF). The number of terms used in the literature reflects that ADHF is not a single diagnosis but rather, a group of related syndromes caused by a number of different primary underlying cardiovascular diseases that may be made worse by a variety of cardiac and non-cardiac conditions.

In patients with ADHF, there is significant heterogeneity in the underlying pathophysiology, precipitants, time course, clinical presentation and underlying cause of heart disease. However, pulmonary congestion due to elevated left atrial pressure with associated symptoms of dyspnea with or without clinical evidence of low cardiac output is a consistent finding in patients with this syndrome.

Approximately 80 % of patients hospitalized with ADHF have a previous diagnosis of heart failure, 15 % have new onset heart failure, and 5 % have advanced or refractory heart failure. Underlying cardiovascular diseases including coronary artery disease, hypertension, valvular heart disease and cardiomyopathy are often present. Non-cardiac conditions including kidney dysfunction, pulmonary disease, diabetes, thyroid disease, anemia, substance abuse, obesity, sleep apnea, and infection are often present and may contribute to heart failure decompensation [6].

Epidemiology

The number of hospitalizations with heart failure as a primary or secondary diagnosis tripled from 1979 to 2004, increasing from 1,274,000 in 1974 to 3,860,000 in 2004. Heart failure was the primary diagnosis in 30–35 % of these admissions. Age-adjusted hospitalization rates also increased during this period. More than 80 % of these hospitalizations were in patients age 65 years or older and were paid by Medicare or Medicaid [7].

There has, however, been a recent decline noted in hospitalization rates for ADHF. In an analysis of inpatient National Claims History files from the Centers for Medicare & Medicaid Services (CMS) which identified all fee-for-service Medicare beneficiaries who were hospitalized for HF from 1998 to 2008, the heart failure hospitalization rates adjusted for age, gender and race declined from 2845 per 100,000 person-years in 1998 to 2007 per 100,000 person-years in 2008 (a decline of 29.5 %; $p < 0.001$). Black men had the lowest rate of age-adjusted decline for all race-gender categories. Importantly, risk-adjusted 1-year mortality after hospitalization decreased from 31.7 % in 1999 to 29.6 % in 2008 (a decline of 6.6 %; $p < 0.001$) [8].

Several large multicenter observational registries in the United States and Europe have significantly improved our understanding of the demographics, clinical characteristics, comorbidities, management patterns and outcomes of patients admitted with ADHF. Prior to these registries, our understanding of ADHF came largely from studies of younger patients with moderate to severe systolic dysfunction that were enrolled in single-center or multicenter randomized controlled clinical trials conducted predominantly at academic heart failure centers. The observational registries were designed to enroll a more representative sample of patients with ADHF that included all patients admitted with heart failure at geographically diverse academic and non-academic medical centers.

The Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure (OPTIMIZE-HF) used HF case ascertainment methods to identify 48,612 patients hospitalized at 259 centers in the United States for new or worsening HF as the primary cause of admission or who developed significant HF symptoms during hospitalization for a different diagnosis. Using a web-based registry, detailed data were collected including demographics, medical history, signs and symptoms, medications, laboratories, diagnostic testing procedures, discharge status, outcomes and adherence to performance indicators. A pre-specified subgroup that was $\geq$ 10 % of the total number of patients was followed for 60–90 days after discharge for the collection of outcomes data [9].

The Acute Decompensated Heart Failure National Data Registry (ADHERE) database was a prospective observational registry that was developed to provide a large national database to describe clinical characteristics, management and outcomes of patients hospitalized with heart failure at 285 hospitals in the United States. Thirty one percent of the participating institutions were academic hospitals. From 2002 to 2004, data were collected from 159,168 hospitalizations beginning with the point of initial care and ending with the patients' discharge or in-hospital death [10–12].

The EuroHeart Failure Survey I (EHFS I) was a retrospective registry in which deaths or discharges from 115 hospitals (50 % university hospitals) from 24 European countries were screened to identify patients with known or suspected heart failure. Demographics, clinical characteristics, evaluation, treatment and outcomes were assessed [13–15]. The EuroHeart Failure Survey II (EHFS II) was a prospective observational registry that recruited 3580 patients hospitalized for HF at 133 centers (47 % university hospitals) in 30 European countries. Using a web based registry, detailed data were collected including demographics, clinical characteristics, etiology, treatment and outcome [16].

The findings from the U.S. and European trials are largely concordant. ADHF disproportionately affects the elderly; the mean age in the registries was 73 years. One quarter of the patients in OPTIMIZE-HF were more than 83 years old [17]. Men and women were equally represented in the U.S. registries while men represented two thirds of the hospitalized patients in EHFS II [16]. Women with ADHF tend to be older, are less likely to have coronary artery disease and are more likely to have hypertension and preserved systolic function [17].

Over 70 % of patients with ADHF in the U.S. registries had a history of hypertension. A history of hypertension was reported in 63 % of patients in EHFS II [16]. Elevation of systolic blood pressure is common at the time of presentation to the emergency department (ED). Mean initial systolic blood pressure on presentation to the emergency department (ED) was 143 mmHg in OPTIMIZE-HF and 144 mmHg in ADHERE. Half of the patients in ADHERE and OPTIMIZE-HF had an initial systolic pressure of greater than 140 mmHg [10, 18]. Renal dysfunction is common. The mean serum creatinine was 1.8 mg/dL in both ADHERE and OPTIMIZE; 20 % of patients in ADHERE had a serum creatinine of greater than 2.0 mg/dL [10, 18].

Approximately half of patients in ADHERE and OPTIMIZE had normal or near normal systolic function defined as a left ventricular ejection fraction (LVEF) ≥ 40 % [19, 20]. Patients with heart failure with preserved ejection fraction (HFpEF) were more likely to be older, female, Caucasian, and have a higher systolic blood pressure on admission and less likely to have had a prior myocardial infarction when compared with patients with heart failure with reduced ejection fraction (HFrEF). In-hospital mortality was lower in patients with HFpEF compared to patients with HFrEF in both ADHERE (2.8 % vs. 3.9 %) and OPTIMIZE-HF (2.9 % vs. 3.9 %). In ADHERE, patients with HFpEF had a similar length of stay and duration of intensive care unit stay when compared with patients with HFrEF [19]. In OPTIMIZE-HF, patients with HFpEF and HFrEF had similar 60–90 day post-discharge mortality (9.5 % vs. 9.8 %, respectively) and rehospitalization rates (29.2 % vs. 29.9 %, respectively). Findings were similar when patients with an LVEF between 40–50 % were compared with patients with an LVEF ≥ 50 % [20]. In an analysis of the data from EHFS I, mortality during the 12-week post-discharge follow-up period was higher in patients with HFrEF compared to patients with HFpEF (12 % vs 10 %). There were no differences in readmission rates during the 12 week follow up period [21].

Eighteen percent of patients in OPTIMIZE-HF and 20 % of patients in ADHERE were African American. African American patients in OPTIMIZE-HF were younger (mean age 63.6 years compared with 75.2 years for non-African American patients), were more likely to have systolic dysfunction and a hypertensive etiology of heart failure and significantly less likely to have ischemic heart disease than non- African American patients. African American patients were more likely to receive evidence-based medications but less likely to receive discharge instructions and smoking cessation counseling. African American race was an independent predictor of lower in-hospital mortality but not of hospital length of stay or multivariable adjusted post-discharge outcomes [22].

In ADHERE, 75 % of patients had a prior history of HF and 33 % had a HF admission within the prior 6 months. Eighty eight percent of patients in OPTIMIZE-HF had a prior history of heart failure. Thirty seven percent of patients in EHFS II had new onset HF; 42 % of these patients presented with an acute coronary syndrome [10, 16, 17].

Comorbid conditions are common in patients admitted with ADHF. A history of hypertension was present in over 70 % of patients in the U.S. registries and 53 % and 62.5 % in EHFS I and II, respectively. Over 40 % of patients had diabetes in the

U.S. registries (27 % and 32.8 % in EHFS I and II, respectively). Renal insufficiency was present in 30 % of patients and chronic lung disease was present in 30 % of patients in the U.S. registries.

Outcomes

There are significant differences in length of stay, in-hospital mortality, rehospitalization rates and post-discharge mortality when registry data from the US and Europe are compared. Median length of stay is 4 days in the U.S [10, 17] compared with 9–11 days in Europe [13, 16]. In-hospital mortality is approximately 4 % in the U.S. [10, 17] and 6.7 % in Europe [16].

The 60–90 day post-discharge mortality reported in OPTIMIZE-HF was 10.4 % [17]. In EHFS I, 13 % of patients died between admission and the 12-week follow-up visit. 6.9 % of patients died during the index hospitalization [13]. Readmission rate 60–90 days after discharge was approximately 30 % in OPTIMIZE and 24 % in EHFS I. An analysis of Medicare claims data found that 26.9 % of Medicare beneficiaries who were hospitalized for heart failure were rehospitalized within 30 days. However, only 37 % of patients who were rehospitalized were rehospitalized for heart failure [23].

Two large, retrospective observational studies have demonstrated reductions in hospital length of stay, in-hospital mortality, and 30-day mortality and an increase in 30 day readmission rates. An analysis from the Veterans Affairs Health Care System of 50,125 patients with a first hospitalization for HF from 2002–2006 showed a decrease in in-hospital, 30 day and 1 year mortality from 4.7, 7.1, and 27.7 % in 2002 to 2.8, 5.0, and 24.3 % in 2006, respectively ($p < 0.0001$). Thirty-day readmission rate for heart failure increased from 5.6 in 2002 to 6.1 % in 2006 ($p = 0.11$) [24]. Another analysis of 6,955,461 Medicare fee-for-service hospitalizations for heart failure between 1993 and 2006 demonstrated a decrease in in-hospital mortality from 8.5 % in 1993 to 4.3 % in 2006 and a decrease in 30-day mortality from 12.8 to 10.7 % over the same time period. Thirty-day readmission rates increased from 17.2 to 20.1 % over the same time period. The risk adjusted 30-day mortality risk ratio was 0.92 and the 30-day readmission risk ratio was 1.11 in 2005–2006 compared with 1993–1994 [25].

A large prospective observational study reported outcomes in 69,958 beneficiaries of the French national health insurance general scheme who were hospitalized with heart failure in 2009 [26]. Patients who were hospitalized for heart failure and did not have a previous diagnosis of HF or prior HF hospitalization were included in the analysis. The in-hospital mortality was 6.4 %. The 1-month, 1-year and 2-year survival rates were 89 %, 71 %, and 60 %, respectively. Heart failure and all-cause readmission free rates were 55 % and 43 % at 1 year and 27 % and 17 % at 2 years, respectively. Factors associated with a better 2 year survival rate in patients less than 70 years who survived 1 month after discharge were: female gender, age < 55 years, absence of comorbidities, and use of an angiotensin converting enzyme inhibitor or

angiotensin receptor blocker, beta-blocker, lipid-lowering agent or oral anticoagulant during the month following discharge.

Classification of ADHF

Heart failure is the final common pathway for a broad range of cardiovascular disorders. Patients with ADHF have diverse underlying causes of cardiac dysfunction, time course of symptom development, co-morbid conditions and precipitants, and underlying pathophysiology. A number of attempts have been made to classify ADHF based on onset, underlying heart disease, underlying hemodynamic abnormalities and clinical profiles.

The International Working Group on Acute Heart Failure Syndromes [6] emphasized the time course of development of HF and the American College of Cardiology/American Heart Association (ACC/AHA) stage in their classification of ADHF:

1. Worsening chronic heart failure: with reduced or preserved LVEF. ACC/AHA Stage C heart failure. Seventy percent of all admissions.
2. De novo heart failure: most commonly caused by acute coronary syndrome (ACS); also, acute myocarditis or sudden increase in blood pressure in a patient with a non-compliant left ventricle. Many with either ACC/AHA Stage A (risk factors but no structural heart disease) or Stage B (pre-existing structural heart disease but without signs or symptoms of heart failure). Twenty five percent of all admissions.
3. Advanced heart failure: severe LV systolic dysfunction, associated with progressively worsening low output state, refractory to conventional heart failure therapy and requiring specialized therapies (LVAD, heart transplant, hospice). ACC/AHA Stage D 5 % of all admissions.

The 2009 ACCF/AHA Guidelines for the Diagnosis and Management of Heart Failure in Adults [27] have described three clinical profiles of patients with ADHF that focus on clinical manifestations of congestion and systemic perfusion:

1. The patient with volume overload, manifested by pulmonary and/or systemic congestion, frequently precipitated by an acute increase in chronic hypertension
2. The patient with profound depression of cardiac output manifested by hypotension, renal insufficiency, and/or shock syndrome
3. The patient with signs and symptoms of both fluid overload and shock.

The European Society of Cardiology (ESC) has described six clinical scenarios for patients presenting with ADHF in their 2008 Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure [2]. EHFS II used a modification of the ESC scenarios to characterize patients included in the registry [16]:

1. Worsening or decompensated chronic heart failure: history of progressive worsening of known chronic heart failure. Signs and symptoms of worsening heart failure with evidence of pulmonary and systemic venous congestion. Patients can have either reduced or preserved ejection fraction. (65 % of patients in EHFS II).
2. Pulmonary edema: Patients who present with severe respiratory distress, tachypnea with diffuse pulmonary rales, hypoxia with oxygen saturation < 90 % (without supplemental oxygen) with alveolar edema on chest X-ray. (16 % of patients in EHFS II)
3. Hypertensive heart failure: Patients have signs and symptoms of heart failure with high blood pressure (generally ≥ 180/100 mmHg). There is commonly evidence of high sympathetic tone with tachycardia and signs of vasoconstriction. Patients are more likely to have preserved systolic function. Frequently, these patients present with evidence of pulmonary congestion without signs of systemic congestion. The response to HF therapy is generally rapid and the in-hospital mortality is low (1.5 % in EHFS II). (11 % of patients in EHFS II).
4. Cardiogenic shock: Patients with evidence of end-organ hypoperfusion due to heart failure with adequate or elevated LV end-diastolic pressure. Typically, these patients have a reduced systolic blood pressure (<90 mmHg), oliguria, and low cardiac index (<2.2 L/min/m2). Many patients will also have severe pulmonary congestion. Mortality in this population is high. (4 % of patients in EHFS II)
5. Isolated right heart failure: evidence of systemic venous congestion, elevated jugular venous pressure and low cardiac output without evidence of pulmonary congestion.
6. Acute coronary syndrome complicated by heart failure: (This was not included as a separate classification in EHFS II) heart failure with a clinical picture and laboratory evidence of an acute coronary syndrome. Approximately 13.6 % of patients with ACS have associated signs and symptoms of heart failure [28, 29]. In EHFS II, ACS was the precipitating factor in 42 % of patients who presented with new onset or de novo heart failure and 23 % of patients who had preexisting heart failure.

A recent American Heart Association Scientific Statement on Acute Heart Failure Syndromes has also emphasized the concept of clinical profiles of patients presenting with ADHF [30].

ADHF has also been characterized by the presence or absence of systolic dysfunction. Patients with heart failure with normal or near normal left ventricular ejection fraction are described as having heart failure with preserved ejection fraction (HFpEF). Patients with heart failure with significant reduction in LVEF (and generally with left ventricular dilation) are characterized as having heart failure with reduced ejection fraction (HFrEF). Patients with HFpEF are more likely to be female, older, Caucasian, have hypertension and atrial fibrillation and less likely to have coronary artery disease. Length of stay for patients with HFpEF is similar to patients with HFrEF but in-hospital mortality is lower. Long-term survival is

somewhat better in patients with HFpEF but readmission rates and functional class are similar in patients with HFpEF compared with patients with HFrEF [20, 21, 31].

Pathophysiology

ADHF is a syndrome due to a broad range of cardiovascular disorders. The underlying pathophysiology is heterogeneous and depends on the nature, time course and severity of the underlying cardiac disease and the presence and severity of non-cardiac precipitating factors. The heterogeneity of patients with ADHF makes it difficult to develop a single pathophysiologic model. Despite this heterogeneity, there are some important themes in patients with ADHF that guide the approach to patient management.

Neurohormonal Activation and Salt and Water Retention

In heart failure, there is a decrease in cardiac output that results in activation of baroreceptors in the central circulation in response to "vascular under-filling". This causes activation of the sympathetic nervous system resulting in an increase in sympathetic outflow to the kidney and systemic vasoconstriction.

Decreased renal blood flow and sympathetic stimulation of the kidney cause release of renin from the juxtaglomerular apparatus which, in turn, results in conversion of angiotensinogen to angiotensin I which is converted to angiotensin II by angiotensin converting enzyme (ACE) and other tissue proteases. Angiotensin II is a potent vasoconstrictor that causes systemic vasoconstriction, renal arterial efferent > afferent vasoconstriction, activation of the sympathetic nervous system, stimulation of sodium retention in the proximal tubule of the kidney, release of aldosterone, release of arginine vasopressin, and stimulation of thirst centers in the brain.

Aldosterone increases sodium and water reabsorption in the distal tubule and collecting duct contributing to extracellular fluid expansion and systemic congestion. Aldosterone also increases sodium and water absorption in the colon. Hepatic congestion in the setting of elevated right atrial pressure decreases aldosterone metabolism leading to higher aldosterone levels. In heart failure, patients do not have "aldosterone escape" so that, unlike patients with isolated hyperaldosteronism, the distal tubule continues to reabsorb sodium in response to elevated aldosterone levels.

Stimulation of central baroreceptors and increased angiotensin II levels stimulate the non-osmotic release of arginine vasopressin from the posterior pituitary gland. This leads to increased free water reabsorption in the collecting ducts which worsens volume overload and leads to the development of hyponatremia.

In heart failure, retention of sodium and water is mediated by decreased systemic and renal perfusion, activation of the sympathetic nervous system and activation of the renin angiotensin aldosterone system (RAAS). In many patients, salt and water retention cannot be reversed by pharmacologic blockade of the RAAS and sympathetic nervous system suggesting that neurohormonal activation is not the only mechanism responsible for salt and water retention [32–34]. Increases in sodium and water intake are mediated by an increase in thirst caused by stimulation of central thirst centers mediated by activation of baroreceptors in the central circulation and excessive production angiotensin II. Systemic congestion is a result of an increase in total body salt and water mediated by a decrease in sodium and water excretion and an increase in intake.

Activation of the sympathetic nervous system and RAAS cause systemic vasoconstriction and an increase in systemic vascular resistance (SVR). Increases in SVR result in a decrease in stroke volume and cardiac output in patients with systolic dysfunction and an increase in functional mitral regurgitation in patients with ventricular dilation.

Pulmonary Congestion

Most patients with ADHF present with the primary symptom of dyspnea either at rest or with activity. This is true for patients with new-onset or chronic heart failure and for patients with and without systolic dysfunction. Many patients have evidence on physical exam of pulmonary and systemic venous congestion [10, 17].

Dyspnea in patients with ADHF is caused by an elevation in left atrial and pulmonary capillary pressure. The movement of fluid from the pulmonary capillary space to the pulmonary interstitium is determined by a balance between hydrostatic and oncotic pressures in the pulmonary capillary and the pulmonary interstitial space. The major factor that causes fluid to move out of the capillary is a difference between the higher hydrostatic pressure within the pulmonary capillary and the lower hydrostatic pressure in the surrounding interstitium. This movement of fluid is opposed by the difference between the colloid osmotic pressure (which is mainly provided by the concentration of albumin) in the capillary space and the interstitium, which reduces the transudation of fluid out of the capillary. In normal physiology, lymphatic washout of albumin that enters the interstitium results in an increase in the osmotic gradient between the interstitium and pulmonary capillary which reduces transudation of fluid. In normal physiology, fluid continuously moves from the capillary space into the interstitium and is then removed by the lymphatic system. When hydrostatic pressure in the pulmonary capillary significantly increases, transudation of fluid into the interstitium increases with potential for “spillover” into the alveolar space [35].

There are several protective mechanisms that prevent the development of pulmonary edema (fluid entering the alveolar space). First, the alveolar-capillary

unit is composed of a thin and thick side. The thin side is made up of a capillary closely opposed to the alveolar air space. The capillary endothelium and alveolar epithelium are attenuated, the basal laminae of the alveolar epithelium and capillary endothelium are fused and the permeability to salt and water is low. The thick portion of the alveolar capillary unit contains an interstitial matrix with a gel-like protein component that separates the alveolar epithelium from the capillary endothelium. With a rise in capillary hydrostatic pressure, edema first forms in the interstitial compartment away from areas of gas exchange. Second, as fluid enters the interstitial compartment, hydrostatic pressure rises and oncotic pressure falls, which serves to oppose further movement into the interstitial space. Third, fluid that forms in the interstitium travels along a negative pressure gradient to the interlobular septae, the bronchovascular space and the hila. Edema fluid also collects in the pleural space. Lymphatic vessels in the interlobular septae, peribronchovascular sheath and pleura facilitate clearance of lung water. Pulmonary lymphatics are highly recruitable and, over time, are able to increase clearance of lung water by more than tenfold. Fourth, active Na+ transport across the alveolar-capillary barrier by type II alveolar epithelial cells lining the alveoli is responsible for clearance of alveolar edema. Na+ enters the alveolar epithelial cells through apical amiloride sensitive Na+ channels and other Na+ channels and, by a process that consumes energy, is pumped out of the cell by the Na+,K+-ATPase located in the basolateral membrane [35–40].

In patients with HFpEF or HFrEF, the LV filling pressure required to support a given amount of left ventricular work is increased. As left ventricular end-diastolic pressure (LVEDP) rises, so do left atrial and pulmonary capillary pressures. As pulmonary capillary pressure increases, there is an increase in the transmural filtration of fluid into the pulmonary interstitium. There is a point at which the capacity of the lymphatic system to remove fluid from the interstitium is exceeded and fluid begins to accumulate in the alveoli. Animal data suggest that there is a threshold beyond which interstitial fluid begins to accumulate and that the rate of fluid accumulation is linearly related to pulmonary capillary wedge pressure.

The accumulation of extravascular fluid in the pulmonary interstitium and alveoli is associated with symptoms of dyspnea, orthopnea, paroxysmal dyspnea, and impaired gas exchange. Symptoms and pulmonary function are influenced by water content of the lungs. The underlying pathophysiology of dyspnea in ADHF is multifactorial and complex with contributions from: decreased lung volume; airflow obstruction from reflex bronchoconstriction; geometric decrease in airway size from decreased lung volumes, intraluminal edema fluid and mucosal swelling; decreased lung compliance; decreased alveolar-capillary membrane conductance with acute and chronic decreases in DLCO; impaired gas exchange due to alveolar edema; arterial hypoxemia; increased work of breathing; respiratory muscle weakness in the chronically ill patient; activation of chest wall sensors, an increase in the elastic work of breathing due to vascular engorgement and cardiac enlargement with chest wall expansion past the usual or physiologic position; and stimulation of nerve endings in response to vascular distention and interstitial edema [35].

Transition from Compensated to Decompensated Heart Failure

A traditional understanding of why patients with chronic heart failure develope ADHF suggests that patients with chronic heart failure commonly experience a gradual increase in total body salt and water reflected by gradual weight gain and the gradual development of signs and symptoms of pulmonary and systemic venous congestion. While this paradigm occurs in some patients with chronic heart failure, it may not be applicable to the majority of patients with ADHF. A nested case-control study of patients referred to a home monitoring system by managed care organizations matched 134 case patients with HF hospitalization with 134 control patients without HF hospitalization [41]. Case patients experienced gradual weight gain beginning approximately 30 days before hospitalization. Within 7 days of hospitalization, weight patterns between case and control patients began to diverge more substantially with greater weight gain strongly associated with a greater odds ratio for hospitalization for ADHF (>2–5 lbs HR 2.77; >5–10 lbs HR 4.46; >10 lbs HR 5.65). However, only 46 % of case patients hospitalized for ADHF gained more than two pounds suggesting that in approximately half of patients, weight gain was not the precipitating cause of hospitalization.

Implantable hemodynamic monitor data in patients with chronic heart failure from the Chronicle Offers Management to Patients with Advanced Signs and Symptoms of Heart Failure (COMPASS-HF) trial provide insight into the time course and pathophysiology of the transition from stable heart failure to ADHF. Earlier studies demonstrated that daily activity, exercise and change in body position caused rapid, large and transient increases in estimated pulmonary artery diastolic pressure (ePADP) in the range of 10–40 mmHg. Increases in ePADP could occur over seconds to minutes with change in body position and exercise. Although these activities could be associated with transient dyspnea, they did not lead to hospitalization for ADHF [42–45]. In a sub-study from COMPASS-HF, ambulatory patients with NYHA FC III – IV heart failure due to either systolic or diastolic dysfunction transmitted hemodynamic data at least weekly. The investigators found that estimated pulmonary artery diastolic pressure (ePADP), right ventricular systolic pressure (RVSP) and right ventricular diastolic pressure (RVDP) were elevated in ambulatory patients with systolic and diastolic heart failure. In patients with systolic and diastolic heart failure, increases in median and minimum ePADP, RVSP and RVDP were seen several weeks (and especially within a week) prior to a hypervolemic heart failure-related event (unexpected hospitalization, emergency room visit, or urgent clinic visit requiring intravenous therapy). These changes were not seen in patients free of a heart failure related event (HFRA). Interestingly, no significant change in weight was seen in patients with an HFRA [46].

A subsequent analysis from the COMPASS-HF study looked at the relationship between three pressure variables measured by an implantable hemodynamic monitor and the development of a HFRE in ambulatory patients with NYHA FC III-IV heart failure. Pressure variables assessed included peak ePADP at the time of a HFRE, change in ePADP from baseline to peak ePADP, and the area under the

ePAD pressure-time curve from baseline to peak pressure. Peak ePAD and change in ePAD were not closely associated with the development of an HFRA. However, the area under the ePAD pressure-time curve was strongly associated with the development of a HFRE. It appears that small changes in ePAD sustained over time most strongly correlated with an HFRE [47]. This data suggests that the accumulation of lung water rather than total body salt and water results in hospitalization for ADHF.

These studies do not negate the importance of following serial weights in patients at risk for ADHF. Although it is common to have patients present with ADHF without an antecedent gain in weight, patients with heart failure who do gain weight are at a significantly increased risk of hospitalization.

Hypertension, Increased Systemic Vascular Resistance and Arterial Stiffness

Elevated blood pressure is found in 50 % of patients with ADHF on initial presentation. In the ADHERE registry the mean first systolic blood pressure was 144 mmHg and 50 % of patients had an initial systolic blood pressure greater than 140 mmHg [10]. In OPTIMIZE-HF, the mean systolic pressure at admission was 143 mmHg and 25 % of patients had an initial systolic pressure >161 mmHg [18]. Admission hypertension was associated with female gender, black race, HFpEF and a non-ischemic etiology of heart failure. [18] Some of the patients in each of these registries received medical therapy by emergency medical services before arriving to the ED suggesting that initial blood pressure prior to treatment was actually higher than reported in the registries. In a study of all patients seen for ADHF at a single city hospital over a 3 month period, first blood pressure was recorded before initiation of therapy at the first patient encounter either in the ambulance or ED. Mean blood pressure was 164/88. Seventy five percent of patients had a systolic BP >140 mmHg. Fifty percent of patients had a mean blood pressure >113 mmHg and the mean systolic blood pressure in the highest quartile of mean blood pressures was 212 mmHg [48].

A study of patients who presented with acute pulmonary edema followed hemodynamic parameters using a pulmonary artery catheter for 24 hours after presentation. Patients who developed recurrent pulmonary edema after initial stabilization were noted to have a marked, rapid increase in systemic vascular resistance and decrease in cardiac index that preceded an increase in pulmonary capillary wedge pressure. These hemodynamic changes were not seen in patients who did not have recurrent pulmonary edema. The only hemodynamic variable at baseline that predicted recurrent pulmonary edema was low cardiac power index (CPI = cardiovascular flow x mean forward pressure = cardiac index x mean arterial pressure) [49].

These data suggest that high blood pressure and elevated systemic vascular resistance play an important role in the development of ADHF. Many patients with

hypertension at the time of hospitalization have a prompt reduction in blood pressure and improvement in symptoms shortly after receiving intravenous diuretics [50, 51]. Some of these patients may have reactive hypertension driven by a response to increased filling pressures and activation of the RAAS and the sympathetic nervous system in the setting of contractile reserve. Some patients may develop acute heart failure in response to elevated blood pressure and systemic vascular resistance in the setting of significant impairment of systolic function that results in an acute decrease in stroke volume, increase in mitral regurgitation, a rapid increase in left atrial pressure and pulmonary congestion in the absence of systemic congestion. It is also possible that an acute decrease in venous capacitance mediated by sympathetic nervous system activation could acutely increase venous return to the heart causing an acute increase in filling pressures.

Balmain compared arterial compliance, microvascular function and venous capacitance in patients with HFpEF, HFrEF, and normal controls [52]. Arterial compliance was significantly lower in patients with HFpEF than in patients with HFrEF and normal controls. Patients with HFpEF and HFrEF had impaired endothelial dependent and independent microvascular vasodilation. Patients with HFrEF had higher venous capacitance than either patients with HFpEF or controls. Higher venous capacitance may result in a greater capacity for the circulation to accommodate greater blood volume without an increase in right atrial and left ventricular end-diastolic pressures. The "normal" venous capacitance of patients with HFpEF may be pathologic and contribute to the development of pulmonary congestion in these patients.

It is unclear what mediates the dynamic change in systemic vascular resistance (and possible acute decrease in venous capacitance) in some patients with ADHF. Age and disease-related increases in arterial stiffness, activation of the RAAS and the sympathetic nervous system, and acute inflammatory activation may all contribute to the transient increase in systemic vascular resistance. This increase in SVR may cause "afterload mismatch" with a decline in stroke volume, and increase in functional mitral regurgitation and an acute rise in left atrial pressure that leads to volume redistribution into the lungs and pulmonary congestion [30, 52–54].

An analysis from the OPTIMIZE-HF registry looked at the impact of admission systolic blood pressure on in-hospital mortality in the entire cohort (48,612 patients) and on post-discharge outcomes in the pre-specified subgroup who were followed for 60–90 days after discharge (5791 patients) [18]. Patients were divided into quartiles by SBP at time of hospital admission (<120, 120–139, 140–161, >161 mmHg). Higher systolic blood pressure at admission was associated with lower in-hospital mortality rates (7.2 %, 3.6 %, 2.5 %, and 1.7 %, respectively by quartile of increasing blood pressure). Post-discharge mortality rates in the follow-up cohort were similarly lower in patients with higher admission systolic BP (14, 8.4, 6.0 and 5.4 % by quartile of increasing blood pressure). A number of other studies have also demonstrated the prognostic importance of systolic blood pressure in ADHF across a broad range of blood pressures [55–57] In these studies, the adjusted relative risk

for mortality have ranged from 0.76 to 0.9 for each 10 mmHg increase in systolic blood pressure.

The consistent relationship between systolic blood pressure and survival suggests an important difference in the pathophysiology of ADHF in patients with high vs. normal or low systolic blood pressure. High blood pressure is more common in advanced age, women, blacks, patients with a non-ischemic cause of heart failure and patients with HFpEF. Patients with elevated SBP on presentation have more pulmonary congestion and respiratory compromise than patients with normal SBP but have more rapid improvement with treatment. Elevated SBP tends to improve rapidly in patients with high admission SBP. Congestive symptoms, which are more common in patients with elevated SBP at admission, become less common prior to discharge when compared to patients with normal or low admission SBP. Elevated SBP is an important reflection of contractile reserve which, like maximum oxygen consumption during cardiopulmonary exercise testing, is a powerful predictor of survival. These observations have led to the suggestion that initial treatment of ADHF be based on presenting SBP with patients divided into three groups: hypertensive (SBP >140 mmHg); normotensive (SBP 100–140 mmHg); and hypotensive (SBP <100 mmHg) based on the initial BP in the ambulance or ED [18, 30, 58, 59].

Pulmonary Manifestations of Acute Vs. Chronic Heart Failure

89 % of patients with ADHF have dyspnea on presentation [8]. Two thirds of patients admitted to the hospital with ADHF have pulmonary rales [8, 18]. Two thirds of patients have lower extremity edema (LE) [8, 18]. However, most patients admitted to the hospital do not have reduced oxygen saturation and only a small percentage of patients with ADHF present with acute pulmonary edema (16 % in EHFS II). Patients with chronic heart failure may have symptoms of dyspnea without evidence of pulmonary congestion on exam or chest radiograph despite having a high pulmonary capillary wedge pressure (PCWP). Patients with new onset heart failure develop pulmonary edema at pulmonary capillary wedge pressures of approximately 25 mmHg while some patients with chronic heart failure are ambulatory without pulmonary rales despite having wedge pressures of 35–40 mmHg [35, 36, 60].

A number of mechanisms have been proposed to explain the disparity in pulmonary manifestations in patients with acute or recent onset heart failure and patients with chronic heart failure. It has been suggested that lymphatic enlargement seen on post-mortem examination of patients with chronic heart failure may protect from the development of alveolar edema although data supporting this concept has been inconsistent [37, 38].

Pathologic specimens from patients with chronic heart failure, especially studies of patients with mitral stenosis, help explain the difference in presentation in patients with new onset versus longstanding heart failure. At a microscopic level, many

specimens demonstrate alveolar fibrosis. Electron micrographs show thickening of the capillary endothelial and alveolar epithelial cell basement membranes. These changes are thought to reduce the permeability of the alveolar-capillary membrane to water and prevent the formation of pulmonary edema. In addition, pulmonary arteries and arterioles develop intimal fibrosis and medial hypertrophy with extension to the small arterioles. Pulmonary veins are thick-walled and lymphatic vessels are dilated and occasionally muscularized [35, 36, 61].

In experimental models of chronic heart failure, there is thickening of the alveolar and capillary basal laminae with pericyte and type IV collagen infiltration of the alveolar-capillary barrier. Alveolar-capillary remodeling leads to a chronic reduction in alveolar capillary membrane conductance, capillary filtration and lung diffusion capacity [35, 36, 40, 62–64]. Wall thickness-lumen ratio is increased in small pulmonary arterioles and venules with an increase in arterial and venous resistance. The vascular remodeling leads to increased vascular resistance [35, 36, 62–64]. These remodeling changes may protect against alveolar edema on the one hand but may impede gas exchange on the other.

There is also likely a difference in alveolar fluid clearance in acute versus chronic heart failure which protects against the development of alveolar edema in chronic heart failure. Alveolar fluid clearance is decreased in the setting of acutely elevated left atrial pressure. However, with chronic elevation of PCWP, alveolar fluid clearance is increased likely secondary to upregulation of active sodium transport [36, 39, 40].

Lower Extremity Edema

Lower extremity edema is a manifestation of severe fluid retention with an increase in total body salt and water and transfer of fluid into the tissues. Tissue edema forms when capillary hydrostatic pressure is greater than plasma colloid pressure by an amount sufficient to cause transudation from the capillary space into the interstitial space at a rate that exceeds the rate at which lymphatics can drain away the interstitial fluid. The rate of edema formation depends on capillary pressure (which is affected by position and right atrial pressure) and capillary permeability [32].

Myocardial Injury

Coronary artery disease (CAD) is present in 50–70 % of patients who present with ADHF [10, 11, 14, 15]. In OPTIMIZE-HF, patients with CAD had a higher inpatient mortality rate (3.7 % vs. 2.9 %) and a higher 60–90 day post-discharge mortality rate (9.2 % vs 6.9 %) [65]. In EHFS II, ACS was the precipitating factor in 42 % of patients who presented with new onset heart failure and 23 % of patients who had preexisting heart failure [16]. Approximately 10–20 % of patients with ACS have

associated heart failure on presentation and another 10 % develop heart failure during hospitalization [66].

Cardiac troponin (either T or I) has a high clinical sensitivity and near absolute specificity for myocardial injury [67, 68]. The presence of measurable cardiac troponin (cTn) is abnormal and indicative of myocardial injury. Typically, the patient with ACS precipitating heart failure will have precordial pain, characteristic ST segment elevations on ECG and significant cTn elevations (cTn I >1.0 ng/ml or mcg/L). However, in ADHF, troponin elevation may be seen in patients with or without ACS and with or without significant obstructive coronary artery disease. There has been a consistent association between elevate cTn and in-hospital mortality.

The reported prevalence of detectable troponin in ADHF has been variable and has depended on the population studied, cTn assay used and cTn threshold considered positive. An analysis from the ADHERE Registry found that an elevated troponin I ≥ 1.0 mcg/L or a troponin T ≥ 0.1 mcg/liter was found in 6.2 % of 67,924 patients who had a troponin an admission and a creatinine <2.0 mg/dL. 53 % of troponin positive patients and 52 % of troponin negative patients had ischemic heart disease reported as the cause of ADHF. Ischemic heart failure was not a useful discriminator of troponin status. Patients who had a positive troponin had lower systolic blood pressure on admission, lower ejection fraction and higher in-hospital mortality (8.0 % vs 2.7 %) compared to patients with a negative troponin. The risk adjusted odds ratio for death among patients with a positive troponin was 2.55 ($P < 0.001$). When mortality was assessed by quartiles of cardiac troponin, there was a progressive increase in in-hospital mortality from quartile one to quartile four (from the lowest to highest troponin quartile) [69].

The Enhanced Feedback for Effective Cardiac Treatment (EFFECT) study was a population-based quality improvement initiative that evaluated patients hospitalized with heart failure at 103 acute care hospitals in Ontario, Canada. The EFFECT investigators looked at the relationship between troponin I >0.5 mcg/L and all-cause mortality in 2025 patients hospitalized for heart failure. Elevated troponin occurred in 34.5 % of patients and was an independent predictor of mortality with an adjusted hazard ratio of 1.49 ($p < 0.001$). Adjustment for the presence of reduced ejection fraction had no significant impact on the estimate of risk. As in the analysis from ADHERE, there was a relationship between troponin I level and mortality that persisted after adjusting for confounding variables such that the hazard ratio for mortality increased with each quartile of troponin elevation. In addition, the association between troponin and mortality was similar for patients with and without other clinical features of acute myocardial ischemia [70].

This data demonstrates that myocardial injury, independent of ACS, occurs in a significant number of patients with ADHF with or without coronary artery disease and that myocardial injury plays an important role in the development of acute heart failure. A number of mechanisms underlying cTn release have been proposed. The Carvedilol Hibernation Reversible Ischemia (CHRISTMAS) trial reported that 60 % of patients with heart failure and CAD had hibernating myocardium [71]. Hibernating myocardium may be at risk for injury due to focal myocardial ischemia

(especially subendocardial ischemia) in the setting of elevated left ventricular end-diastolic pressure, hypotension with reduced myocardial perfusion, tachycardia, or medications that increase contractility. Patients without CAD may be at risk for injury due to the same hemodynamic conditions. Proposed mechanisms of myocardial injury other than myocardial ischemia in patients with and without CAD include: cardiomyocyte damage from inflammatory cytokines or oxidative stress, altered calcium handling, apoptosis, and release of intact troponin or troponin fragments from viable cardiomyocytes [69, 70, 72].

Conclusions

Acute decompensated heart failure is defined as the new onset or recurrence of heart failure signs and symptoms that require urgent or emergent treatment and that result in hospitalization. This syndrome is common and expensive. Recent large multicenter observational registries have improved our understanding of the demographics, clinical characteristics, comorbidities, management patterns and outcomes of patients admitted with ADHF. ADHF disproportionately affects the elderly. Most patients have a history of hypertension and half of patients have an elevated systolic blood pressure on presentation. Approximately half of the patients with ADHF have normal or near normal left ventricular ejection fraction. Coronary artery disease (CAD) is present in 50–70 % of patients who present with ADHF and ACS is the most common precipitating factor in patients who presented with de novo heart failure.

ADHF is a syndrome due to a broad range of cardiovascular disorders. The underlying causes are heterogeneous but most patients seek medical attention because of dyspnea due to elevated left atrial and pulmonary capillary wedge pressure. The pathophysiology of dyspnea in ADHF is complex and multifactorial and impacted by the time course of volume overload, the presence of rapid elevations in systemic vascular resistance and left atrial pressure, and the chronicity of elevated PCWP.

References

1. Go AS, Mozaffarian D, Roger VL, Benjamin EJ, Berry JD, Blaha MJ, et al; American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics – 2014 update: a report from the American Heart Association. Circulation. 2014;129(3):e28–e292. doi: 10.1161/01.cir.0000441139.02102.80. Epub 2013 Dec 18.
2. Dickstein K, Cohen-Solal A, Filippatos G, McMurray JJ, Ponikowski P, Poole-Wilson PA, et al; ESC Committee for Practice Guidelines (CPG). ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2008: the Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2008 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association of the ESC (HFA) and endorsed by the European Society of Intensive Care Medicine (ESICM). Eur Heart J. 2008;29(19):2388–442. doi: 10.1093/eurheartj/ehn309. Epub 2008 Sep 17.

3. National Heart Lung and Blood Institute. People Science Health. What is heart failure? Available from: http://www.nhlbi.nih.gov/health/health-topics/topics/hf/. Accessed Feb 2012.
4. Hall MJ, DeFrances CJ, Williams SN, et al. National Hospital Discharge Survey: 2007 summary. National health statistics reports; no 29. Hyattsville: National Center for Health Statistics. 2010. Available from: http://www.cdc.gov/nchs/data/nhsr/nhsr029.pdf.
5. Gheorghiade M, Pang PS. Acute heart failure syndromes. J Am Coll Cardiol. 2009;53(7):557–73. doi:10.1016/j.jacc.2008.10.041.
6. Gheorghiade M, Zannad F, Sopko G, Klein L, Piña IL, Konstam MA, et al. International Working Group on acute heart failure syndromes. Acute heart failure syndromes: current state and framework for future research. Circulation. 2005;112(25):3958–68.
7. Fang J, Mensah GA, Croft JB, Keenan NL. Heart failure-related hospitalization in the U.S., 1979 to 2004. J Am Coll Cardiol. 2008;52(6):428–34. doi:10.1016/j.jacc.2008.03.061.
8. Chen J, Normand SL, Wang Y, Krumholz HM. National and regional trends in heart failure hospitalization and mortality rates for Medicare beneficiaries, 1998–2008. JAMA. 2011;306(15):1669–78. doi:10.1001/jama.2011.1474.
9. Fonarow GC, Abraham WT, Albert NM, Gattis WA, Gheorghiade M, Greenberg B, et al. Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure (OPTIMIZE-HF): rationale and design. Am Heart J. 2004;148(1):43–51.
10. Adams KF, Fonarow GC, Emerman CL, LeJemtel TH, Costanzo MR, Abraham WT, et al; ADHERE Scientific Advisory Committee and Investigators. Characteristics and outcomes of patients hospitalized for heart failure in the United States: rationale, design, and preliminary observations from the first 100,000 cases in the Acute Decompensated Heart Failure National Registry (ADHERE). Am Heart J. 2005;149(2):209–16.
11. Fonarow GC, Heywood JT, Heidenreich PA, Lopatin M, CW Y, ADHERE Scientific Advisory Committee and Investigators. Temporal trends in clinical characteristics, treatments, and outcomes for heart failure hospitalizations, 2002 to 2004: findings from Acute Decompensated Heart Failure National Registry (ADHERE). Am Heart J. 2007;153(6):1021–8.
12. Fonarow GC, Corday E, ADHERE Scientific Advisory Committee. Overview of acutely decompensated congestive heart failure (ADHF): a report from the ADHERE registry. Heart Fail Rev. 2004;9(3):179–85.
13. Cleland JG, Swedberg K, Cohen-Solal A, Cosin-Aguilar J, Dietz R, Follath F, et al; The Euro Heart Failure Survey of the EUROHEART survey programme. A survey on the quality of care among patients with heart failure in Europe. The Study Group on Diagnosis of the Working Group on Heart Failure of the European Society of Cardiology. The Medicines Evaluation Group Centre for Health Economics University of York. Eur J Heart Fail. 2000;2(2):123–32.
14. Cleland JG, Swedberg K, Follath F, Komajda M, Cohen-Solal A, Aguilar JC, et al; Study Group on Diagnosis of the Working Group on Heart Failure of the European Society of Cardiology. The EuroHeart Failure survey programme – a survey on the quality of care among patients with heart failure in Europe. Part 1: patient characteristics and diagnosis. Eur Heart J. 2003;24(5):442–63.
15. Komajda M, Follath F, Swedberg K, Cleland J, Aguilar JC, Cohen-Solal A, et al; Study Group on Diagnosis of the Working Group on Heart Failure of the European Society of Cardiology. The EuroHeart Failure Survey programme – a survey on the quality of care among patients with heart failure in Europe. Part 2: treatment. Eur Heart J. 2003;24(5):464–74.
16. Nieminen MS, Brutsaert D, Dickstein K, Drexler H, Follath F, Harjola VP, et al; EuroHeart Survey Investigators; Heart Failure Association, European Society of Cardiology. EuroHeart Failure Survey II (EHFS II): a survey on hospitalized acute heart failure patients: description of population. Eur Heart J. 2006;27(22):2725–36. Epub 2006 Sep 25.
17. Fonarow GC, Abraham WT, Albert NM, Stough WG, Gheorghiade M, Greenberg BH, et al; OPTIMIZE-HF Investigators and Hospitals. Age- and gender-related differences in quality of care and outcomes of patients hospitalized with heart failure (from OPTIMIZE-HF). Am J Cardiol. 2009;104(1):107–15. doi: 10.1016/j.amjcard.2009.02.057.

18. Gheorghiade M, Abraham WT, Albert NM, Greenberg BH, O'Connor CM, She L, et al; OPTIMIZE-HF Investigators and Coordinators. Systolic blood pressure at admission, clinical characteristics, and outcomes in patients hospitalized with acute heart failure. JAMA. 2006;296(18):2217–26.
19. CW Y, Lopatin M, LW S, De Marco T, GC F, ADHERE Scientific Advisory Committee and Investigators. Clinical presentation, management, and in-hospital outcomes of patients admitted with acute decompensated heart failure with preserved systolic function: a report from the Acute Decompensated Heart Failure National Registry (ADHERE) database. J Am Coll Cardiol. 2006;47(1):76–84. PubMed PMID 16386668
20. Fonarow GC, Stough WG, Abraham WT, Albert NM, Gheorghiade M, Greenberg BH, et al; OPTIMIZE-HF Investigators and Hospitals. Characteristics, treatments, and outcomes of patients with preserved systolic function hospitalized for heart failure: a report from the OPTIMIZE-HF Registry. J Am Coll Cardiol. 2007;50(8):768–777. PubMed PMID 17707182.
21. Lenzen MJ, op Reimer WJ S, Boersma E, PJ V, Follath F, Swedberg K, et al. Differences between patients with a preserved and a depressed left ventricular function: a report from the EuroHeart Failure Survey. Eur Heart J. 2004;25(14):1214–20.
22. Yancy CW, Abraham WT, Albert NM, Clare R, Stough WG, Gheorghiade M, et al. Quality of care of and outcomes for African Americans hospitalized with heart failure: findings from the OPTIMIZE-HF (Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients With Heart Failure) registry. J Am Coll Cardiol. 2008;51(17):1675–84. doi:10.1016/j.jacc.2008.01.028.
23. Jencks SF, Williams MV, Coleman EA. Rehospitalizations among patients in the Medicare fee-for-service program. N Engl J Med. 2009;360(14):1418–28. doi:10.1056/NEJMsa0803563.
24. Heidenreich PA, Sahay A, Kapoor JR, Pham MX, Massie B. Divergent trends in survival and readmission following a hospitalization for heart failure in the Veterans Affairs health care system 2002 to 2006. J Am Coll Cardiol. 2010;56(5):362–8. doi:10.1016/j.jacc.2010.02.053.
25. Bueno H, Ross JS, Wang Y, Chen J, Vidán MT, Normand SL, et al. Trends in length of stay and short-term outcomes among Medicare patients hospitalized for heart failure, 1993–2006. JAMA. 2010;303(21):2141–7. doi:10.1001/jama.2010.748.
26. Tuppin P, Cuerq A, de Peretti C, Fagot-Campagna A, Danchin N, Juillière Y, et al. Two-year outcome of patients after a first hospitalization for heart failure: a national observational study. Arch Cardiovasc Dis. 2014;107(3):158–68. doi:10.1016/j.acvd.2014.01.012. Epub 2014 Mar 21.
27. Jessup M, Abraham WT, Casey DE, Feldman AM, Francis GS, Ganiats TG, et al. 2009 focused update: ACCF/AHA guidelines for the diagnosis and management of heart failure in adults: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines: developed in collaboration with the International Society for Heart and Lung Transplantation. Circulation. 2009;119(14):1977–2016. doi:10.1161/CIRCULATIONAHA.109.192064. Epub 2009 Mar 26.
28. Kaul P, Ezekowitz JA, Armstrong PW, Leung BK, Savu A, Welsh RC, et al. Incidence of heart failure and mortality after acute coronary syndromes. Am Heart J. 2013;165(3):379–85.e2. doi:10.1016/j.ahj.2012.12.005. Epub 2013 Jan 22.
29. Steg PG, Dabbous OH, Feldman LJ, Cohen-Solal A, Aumont MC, López-Sendón J, et al; Global Registry of Acute Coronary Events Investigators. Determinants and prognostic impact of heart failure complicating acute coronary syndromes: observations from the Global Registry of Acute Coronary Events (GRACE). Circulation. 2004;109(4):494–9. Epub 2004 Jan 26.
30. Weintraub NL, Collins SP, Pang PS, Levy PD, Anderson AS, Arslanian-Engoren C, et al; American Heart Association Council on Clinical Cardiology and Council on Cardiopulmonary, Critical Care, Perioperative and Resuscitation. Acute heart failure syndromes: emergency department presentation, treatment, and disposition: current approaches and future aims: a scientific statement from the American Heart Association. Circulation. 2010;122(19):1975–96. doi: 10.1161/CIR.0b013e3181f9a223. Epub 2010 Oct 11.

31. Campbell RT, Jhund PS, Castagno D, Hawkins NM, Petrie MC, McMurray J. What have we learned about patients with heart failure and preserved ejection fraction from DIG-PEF, CHARM-preserved, and I-PRESERVE? J Am Coll Cardiol. 2012;60(23):2349–56. doi:10.1016/j.jacc.2012.04.064. Epub 2012 Nov 7.
32. Clark AL, Cleland JG. Causes and treatment of oedema in patients with heart failure. Nat Rev Cardiol. 2013;10(3):156–70. doi:10.1038/nrcardio.2012.191. Epub 2013 Jan 15.
33. ter Maaten JM, Valente MA, Damman K, Hillege HL, Navis G, AA V. Diuretic response in acute heart failure-pathophysiology, evaluation, and therapy. Nat Rev Cardiol. 2015;12(3):184–92. doi:10.1038/nrcardio.2014.215. Epub 2015 Jan 6.
34. Ronco C, Cicoira M, McCullough PA. Cardiorenal syndrome type 1: pathophysiological crosstalk leading to combined heart and kidney dysfunction in the setting of acutely decompensated heart failure. J Am Coll Cardiol. 2012;60(12):1031–42. doi:10.1016/j.jacc.2012.01.077. Epub 2012 Jul 25.
35. Gehlbach BK, Geppert E. The pulmonary manifestations of left heart failure. Chest. 2004;125(2):669–82.
36. Guazzi M. Alveolar gas diffusion abnormalities in heart failure. J Card Fail. 2008;14(8):695–702. doi:10.1016/j.cardfail.2008.06.004. Epub 2008 Jul 18.
37. Uhley HN, Leeds SE, Sampson JJ, Friedman M. Role of pulmonary lymphatics in chronic pulmonary edema. Circ Res. 1962;11:966–70.
38. Mackersie RC, Christensen J, Lewis FR. The role of pulmonary lymphatics in the clearance of hydrostatic pulmonary edema. J Surg Res. 1987;43(6):495–504.
39. Hochberg I, Abassi Z, Azzam ZS. Patterns of alveolar fluid clearance in heart failure. Int J Cardiol. 2008;130(2):125–30. doi:10.1016/j.ijcard.2008.03.015. Epub 2008 Jun 24.
40. Guazzi M, Phillips SA, Arena R, Lavie CJ. Endothelial dysfunction and lung capillary injury in cardiovascular diseases. Prog Cardiovasc Dis. 2015;57(5):454–62. doi:10.1016/j.pcad.2014.11.003. Epub 2014 Nov 12.
41. Chaudhry S, Wang Y, Concato J, Gill TM, Krumholz HM. Patterns of weight change preceding hospitalization for heart failure. Circulation. 2007;116(14):1549–54. Epub 2007 Sep 10.
42. Adamson PB, Magalski A, Braunschweig F, Böhm M, Reynolds D, Steinhaus D, et al. Ongoing right ventricular hemodynamics in heart failure: clinical value of measurements derived from an implantable monitoring system. J Am Coll Cardiol. 2003;41(4):565–71.
43. Ohlsson A, Steinhaus D, Kjellström B, Ryden L, Bennett T. Central hemodynamic responses during serial exercise tests in heart failure patients using implantable hemodynamic monitors. Eur J Heart Fail. 2003;5(3):253–9.
44. Adamson PB, Kjellström B, Braunschweig F, Magalski A, Linde C, Kolodiezj A, et al. Ambulatory hemodynamic monitoring from an implanted device: components of continuous 24-hour pressures that correlate to supine resting conditions and acute right heart catheterization. Congest Heart Fail. 2006;12(1):14–9.
45. Aaron MF, Aranda JM, Renlund DG, Fonarow GC, Feldman DS, Cho YK, et al. The effect of postural changes on intracardiac filling pressures[abstract]. J Card Fail. 2008;14:S28.
46. Zile MR, Bennett TD, St John Sutton M, Cho YK, Adamson PB, Aaron MF, et al. Transition from chronic compensated to acute decompensated heart failure: pathophysiological insights obtained from continuous monitoring of intracardiac pressures. Circulation. 2008;118(14):1433–41. doi:10.1161/CIRCULATIONAHA.108.783910. Epub 2008 Sep 15.
47. Zile MR, Adamson PB, Cho YK, Bennett TD, Bourge RC, Aaron MF, et al. Hemodynamic factors associated with acute decompensated heart failure: part 1 – insights into pathophysiology. J Card Fail. 2011;17(4):282–91. doi:10.1016/j.cardfail.2011.01.010. Epub 2011 Feb 26.
48. Milo-Cotter O, Adams KF, O'Connor CM, Uriel N, Kaluski E, Felker GM, et al. Acute heart failure associated with high admission blood pressure – a distinct vascular disorder? Eur J Heart Fail. 2007;9(2):178–83. Epub 2006 Jul 31.
49. Cotter G, Moshkovitz Y, Milovanov O, Salah A, Blatt A, Krakover R, et al. Acute heart failure: a novel approach to its pathogenesis and treatment. Eur J Heart Fail. 2002;4(3):227–34.

50. Kaluski E, Kobrin I, Zimlichman R, Marmor A, Krakov O, Milo O, et al. RITZ-5: randomized intravenous TeZosentan (an endothelin-A/B antagonist) for the treatment of pulmonary edema: a prospective, multicenter, double-blind, placebo-controlled study. J Am Coll Cardiol. 2003;41(2):204–10.
51. Mebazaa A, Pang PS, Tavares M, Collins SP, Storrow AB, Laribi S, et al. The impact of early standard therapy on dyspnoea in patients with acute heart failure: the URGENT-dyspnoea study. Eur Heart J. 2010;31(7):832–41. doi:10.1093/eurheartj/ehp458. Epub 2009 Nov 11.
52. Balmain S, Padmanabhan N, Ferrell WR, Morton JJ, McMurray JJ. Differences in arterial compliance, microvascular function and venous capacitance between patients with heart failure and either preserved or reduced left ventricular systolic function. Eur J Heart Fail. 2007;9(9):865–71. Epub 2007 Jul 19.
53. Cotter G, Metra M, Milo-Cotter O, Dittrich HC, Gheorghiade M. Fluid overload in acute heart failure – re-distribution and other mechanisms beyond fluid accumulation. Eur J Heart Fail. 2008;10(2):165–9. doi:10.1016/j.ejheart.2008.01.007.
54. Cotter G, Felker GM, Adams KF, Milo-Cotter O, O'Connor CM. The pathophysiology of acute heart failure – is it all about fluid accumulation? Am Heart J. 2008;155(1):9–18.
55. Felker GM, Leimberger JD, Califf RM, Cuffe MS, Massie BM, Adams Jr KF, et al. Risk stratification after hospitalization for decompensated heart failure. J Card Fail. 2004;10(6):460–6.
56. Fonarow GC, Adams Jr KF, Abraham WT, Yancy CW, Boscardin WJ, ADHERE Scientific Advisory Committee, Study Group, Investigators. Risk stratification for in-hospital mortality in acutely decompensated heart failure: classification and regression tree analysis. JAMA. 2005;293(5):572–80.
57. Lee DS, Austin PC, Rouleau JL, Liu PP, Naimark D, JV T. Predicting mortality among patients hospitalized for heart failure: derivation and validation of a clinical model. JAMA. 2003;290(19):2581–7.
58. Collins S, Storrow AB, Kirk JD, Pang PS, Diercks DB, Gheorghiade M. Beyond pulmonary edema: diagnostic, risk stratification, and treatment challenges of acute heart failure management in the emergency department. Ann Emerg Med. 2008;51(1):45–57. Epub 2007 Sep 14.
59. Collins S, Storrow AB, Albert NM, Butler J, Ezekowitz J, Felker GM, et al; SAEM/HFSA Acute Heart Failure Working Group. Early management of patients with acute heart failure: state of the art and future directions. A consensus document from the society for academic emergency medicine/heart failure society of America acute heart failure working group. J Card Fail. 2015;21(1):27–43. doi: 10.1016/j.cardfail.2014.07.003. Epub 2014 Jul 18.
60. Stevenson LW, Perloff JK. The limited reliability of physical signs for estimating hemodynamics in chronic heart failure. JAMA. 1989;261(6):884–8. PubMed PMID 2913385
61. Kay JM, Edwards FR. Ultrastructure of the alveolar-capillary wall in mitral stenosis. J Pathol. 1973;111(4):239–45.
62. Kingsbury MP, Huang W, Donnelly JL, Jackson E, Needham E, Turner MA, Sheridan DJ. Structural remodelling of lungs in chronic heart failure. Basic Res Cardiol. 2003;98(5):295–303. Epub 2003 May 16.
63. Huang W, Kingsbury MP, Turner MA, Donnelly JL, Flores NA, Sheridan DJ. Capillary filtration is reduced in lungs adapted to chronic heart failure: morphological and haemodynamic correlates. Cardiovasc Res. 2001;49(1):207–17.
64. Davies SW, Bailey J, Keegan J, Balcon R, Rudd RM, Lipkin DP. Reduced pulmonary microvascular permeability in severe chronic left heart failure. Am Heart J. 1992;124(1):137–42.
65. Rossi JS, Flaherty JD, Fonarow GC, Nunez E, Gattis Stough W, Abraham WT, et al. Influence of coronary artery disease and coronary revascularization status on outcomes in patients with acute heart failure syndromes: a report from OPTIMIZE-HF (Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure). Eur J Heart Fail. 2008;10(12):1215–23. doi:10.1016/j.ejheart.2008.09.009. Epub 2008 Nov 8.
66. Flaherty JD, Bax JJ, De Luca L, Rossi JS, Davidson CJ, Filippatos G, et al. Acute Heart Failure Syndromes International Working Group. Acute heart failure syndromes in patients with coro-

nary artery disease early assessment and treatment. J Am Coll Cardiol. 2009;53(3):254–63. PubMed PMID 19147042.
67. Thygesen K, Alpert JS, White HD, Joint ESC/ACCF/AHA/WHF Task Force for the Redefinition of Myocardial Infarction, AS J, FS A, Galvani M, HA K, LK N, Ravkilde J, et al. Universal definition of myocardial infarction. Circulation. 2007;116(22):2634–53. Epub 2007 Oct 19.
68. Kociol RD, Pang PS, Gheorghiade M, Fonarow GC, O'Connor CM, Felker GM. Troponin elevation in heart failure prevalence, mechanisms, and clinical implications. J Am Coll Cardiol. 2010;56(14):1071–8. doi:10.1016/j.jacc.2010.06.016.
69. Peacock 4th WF, De Marco T, Fonarow GC, Diercks D, Wynne J, Apple FS, Wu AH; ADHERE Investigators. Cardiac troponin and outcome in acute heart failure. N Engl J Med 2008; 358(20):2117-2126. doi: 10.1056/NEJMoa0706824. PMID: 18480204 [PubMed - indexed for MEDLINE].
70. You JJ, Austin PC, Alter DA, Ko DT, Tu JV. Relation between cardiac troponin I and mortality in acute decompensated heart failure. Am Heart J. 2007;153(4):462–70.
71. Cleland JG, Pennell DJ, Ray SG, Coats AJ, Macfarlane PW, Murray GD, et al; Carvedilol Hibernating Reversible Ischaemia Trial: Marker of Success Investigators. Myocardial viability as a determinant of the ejection fraction response to carvedilol in patients with heart failure (CHRISTMAS trial): randomised controlled trial. Lancet. 2003;362(9377):14–21.
72. Beohar N, Erdogan AK, Lee DC, Sabbah HN, Kern MJ, Teerlink J, et al. Acute heart failure syndromes and coronary perfusion. J Am Coll Cardiol. 2008;52(1):13–6. doi:10.1016/j.jacc.2008.03.037.

Chapter 9
Acute Decompensated Heart Failure: Presentation, Physical Exam, and Laboratory Evaluation

Daniel Fishbein

Presentation of Patients with ADHF

ADHF may be a manifestation of any abnormality of cardiovascular function. Most patients have a prior history of heart failure. Patients with chronic heart failure may have a history of gradually worsening symptoms of pulmonary and systemic venous congestion over several days to weeks or may have more rapid development of symptoms commonly associated with a clear precipitant (examples: new onset atrial fibrillation with rapid ventricular response in a patient with HFpEF; ACS in a patient with an ischemic cardiomyopathy). Approximately 25 % of patients with ADHF have new onset or *de novo* heart failure – many of these patients have associated ACS or poorly controlled hypertension [1].

A minority of patients present with acute pulmonary edema. Patients with pulmonary edema have severe respiratory distress, tachypnea, tachycardia, hypoxemia, pulmonary rales, and radiographic evidence of pulmonary congestion. Some patients may need mechanical ventilation. The onset is frequently acute and associated with severe hypertension or atrial tachyarrhythmia (especially in patients with preserved systolic function) In EHFS II 16 % of patients presented with acute pulmonary edema [2]. In OPTIMIZE-HF, 2.5 % of patients presented in acute pulmonary edema [3]. In the ADHERE Registry, 4.5 % of patients required mechanical ventilation during hospitalization [4]. In ADHERE, the percentage of patients who required mechanical ventilation decreased from 5.3 to 3.4 % over 3 years (January 2002 to December 2004) [5].

A minority of patients present with cardiogenic shock. Cardiogenic shock is generally associated with heart failure complicating ACS. The ADHERE and

D. Fishbein, MD
Department of Medicine, Division of Cardiology, University of Washington Medical Center, 1959 NE Pacific Street, #356422, Seattle, WA 98195, USA
e-mail: dfish@uw.edu

H. Eisen (ed.), *Heart Failure*, DOI 10.1007/978-1-4471-4219-5_9

OPTIMIZE registries did not specifically describe patients as having cardiogenic shock. In OPTIMIZE, 10 % of patients had a systolic BP <105 mmHg [6]. In ADHERE, 3 % of patients had an initial systolic BP <90 mmHg [5]. In EHFS II, 4 % of patients admitted with heart failure presented with cardiogenic shock [7].

Symptoms

Patients with heart failure commonly present with dyspnea at rest or with exertion. Other common symptoms include lower extremity edema, fatigue, orthopnea and paroxysmal dyspnea. In ADHERE, 89 % of patients had dyspnea, 34 % of patients had dyspnea at rest, 65 % had peripheral edema and 31 % of patients had fatigue [4]. In OPTIMIZE-HF, 61 % of patients had dyspnea on exertion, 44 % of patients had dyspnea at rest, and 65 % of patients had edema [6].

Patients may be unable to sleep flat because of shortness of breath (orthopnea) and some patients may have an acute increase in dyspnea with any degree of recumbence. Orthopnea is a sensitive and specific symptom of elevated filling pressures. In a study of patients with chronic heart failure, orthopnea was reported by 39/43 patients who had a PCWP ≥22 mmHg [8]. In the Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization (ESCAPE) trial, orthopnea ≥2 pillows was the only finding on history that was associated with a PCWP ≥30 mmHg [9]. The symptom of orthopnea can also be seen in patients with central obesity, ascites, esophageal reflux, obstructive airway disease or emphysema. Paroxysmal nocturnal dyspnea (PND) may be a more specific symptom of decompensated heart failure and pulmonary congestion. Typically, the patient with PND is awakened acutely several hours after retiring by symptoms of severe shortness of breath and air hunger. Patients often feel the need to sit up, get out of bed, or seek fresh air from an open window. Symptoms generally resolve within 10–20 min. Nocturnal or exertional cough or wheezing may also be a manifestation of pulmonary congestion.

Patients with systemic venous congestion may have symptoms of lower extremity edema, abdominal fullness or distention, early satiety, nausea, poor appetite and right upper quadrant abdominal pain. Edema is a common finding in patients with ADHF. Edema is, however, not a specific finding for heart failure as patients may have edema from other causes (see below under “Physical Examination”) [10, 11].

Patients with low cardiac output may have symptoms of severe fatigue, poor appetite, exertional light headedness and manifestations of cerebral hypoperfusion including impaired mentation, agitation, and irritability [12]. Some patients complain of very bright or very “white” vision in association with low blood pressure and/or low cardiac output. Exertional pre-syncope or syncope may also be a manifestation of low cardiac output.

Physical Examination

A careful physical examination is an essential component of the evaluation of the patient presenting with shortness of breath. The physical examination is critical in establishing the diagnosis of heart failure and in assessing the severity of disease, the presence and severity of systemic and pulmonary venous congestion, the adequacy of cardiac output and end-organ perfusion, the severity of respiratory compromise and the need for emergent intervention. In addition, the exam provides insights into the underlying cause of heart failure and the presence of reversible conditions that may have contributed to heart failure decompensation.

An assessment should be made of the patient's general appearance, vital signs including O2 saturation by finger oximetry and neurologic status. In addition, an examination of the heart, neck veins, lungs, abdomen, lower extremities and carotid and peripheral pulses should be performed.

General Examination and Vital Signs

General examination and vital signs provide insight into the presence and severity of heart failure. Patients may have evidence of respiratory distress with tachypnea, hypoxemia on pulse oximetry, inability to speak in full sentences, inability to lie flat, agitation, and use of accessory muscles of respiration. Observation of coughing or wheezing, especially with walking or while recumbent suggests the presence of pulmonary congestion. Respiratory rate is important and should be counted rather than estimated. Tachypnea may reflect severe pulmonary congestion, pulmonary edema and/or respiratory failure. The presence of Cheyne-Stokes respirations suggests that the patient has chronic severe heart failure.

Tachycardia may reflect low cardiac output, sympathetic nervous system activation, or a supraventricular arrhythmia that may be a heart failure precipitant. An irregular pulse may be due to premature ventricular beats or preexisting or new onset atrial fibrillation. An elevated temperature suggests infection as a possible contributor to heart failure decompensation. Temperature < 36 °C has been shown to be associated with a 51 % higher risk of the composite of HF rehospitalization or CV death when compared with the index group of patients with temperature >36.5 °C in the Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study with Tolvaptan (EVEREST) trial [13].

In acute heart failure, systolic and mean blood pressures are important in guiding the choice of initial therapies including vasodilators, inotropic agents, vasopressors, intra-aortic balloon pump therapy or mechanical circulatory support. Low blood pressure, especially if associated with low pulse pressure, tachycardia and cool distal extremities, is a sign of low cardiac output and inadequate systemic perfusion. Low blood pressure is unusual in patients with ADHF but when present,

identifies a patient at high risk of in-hospital mortality who may need more intensive care including admission to the CCU, treatment with inotropic agents (or vasopressors), and/or support with an intra-aortic balloon pump [6, 14]. As heart failure progresses, systolic blood pressure decreases, diastolic blood pressure is unchanged and pulse pressure (systolic blood pressure-diastolic blood pressure) decreases. A pulse pressure/systolic pressure ratio (referred to as the "proportional pulse pressure") of less than 0.25 suggests that the patient has a cardiac index of less than 2.2 L/min/m^2 [15].

Approximately half of patients with ADHF have an initial systolic blood pressure of >140 mmHg. Patients who present with hypertension may have pulmonary congestion related to volume redistribution due to a mismatch between rapidly increasing blood pressure and impaired contractile reserve rather than total body fluid accumulation. These patients may have more severe pulmonary congestion and less volume overload than normotensive patients with ADHF. These patients generally benefit from parenteral diuretics but may also benefit from early initiation of vasodilator therapy [16–22].

Agitation or altered mental status should raise concern about brain hypoperfusion due to severely reduced cardiac output, even in the setting of normal blood pressure. Patients with low cardiac output may also have cool distal extremities, diaphoresis, pallor, tachypnea, dyspnea at rest, low systolic blood pressure, low pulse pressure, and low proportional pulse pressure. Feeling the skin of the hands and feet can give important information about systemic perfusion and the presence of systemic vasoconstriction. The temperature of the hands/feet should be compared to that of the upper arm/leg. Relative coolness of the distal extremities suggests low cardiac output [15, 23]. Some authors have suggested that feeling the temperature of the forearms and calves rather than hands and feet (which may be cool from anxiety) may be more specific for assessment of systemic perfusion [15].

Assessment for Pulmonary and Systemic Venous Congestion

An important goal of the initial physical exam is to identify and quantitate pulmonary and systemic venous congestion. Historically, four signs have been used to determine whether cardiac filling pressures are elevated including the presence of: jugular venous distention, pulmonary rales, a ventricular gallop (S3) and lower extremity edema.

Lung examination provides insight into the cause of dyspnea, volume status and the presence of pulmonary congestion. Percussion of the posterior chest may elicit dullness at one or both bases indicating the presence of a pleural effusion. Patients may also have associated decreased breath sounds. Pleural effusion is generally a manifestation of elevated right and left sided filling pressures. Bilateral pleural effusions are more common than unilateral effusions. When a unilateral effusion is present in a patient with ADHF, it is generally on the right. An isolated left pleural effusion is an unusual manifestation of decompensated heart failure.

Pulmonary crackles (or rales) are caused by transudation of fluid from the pulmonary capillaries into the alveolar space. Crackles due to heart failure generally are audible from the base upward and do not clear with cough or deep inspiration. Patients with chronic heart failure may not have rales despite significantly elevated pulmonary capillary wedge pressure and clinical decompensation [8]. The absence of rales in patients with chronic heart failure does not exclude decompensated heart failure as a cause of worsening dyspnea. Rales may be due to other pulmonary pathology. Rales associated with atelectasis are generally coarse and clear with cough or deep inspiration. Rales associated with pneumonia may be heard at locations other than the bases, are frequently unilateral and commonly associated with fever, leukocytosis, and other findings of pulmonary consolidation such as bronchial breath sounds and egophony. Patients with ADHF may present with "cardiac asthma" with wheezing and decreased airflow. Cardiac asthma is probably caused by a combination of reflex bronchoconstriction in response to elevated pulmonary and bronchial vascular pressure, obstruction from intraluminal edema fluid, and bronchial mucosal swelling [24].

Lower extremity edema is a common finding in patients with ADHF. In patients with chronic heart failure, edema may be absent despite symptoms of dyspnea and elevated pulmonary capillary wedge pressure [8]. Edema is not a specific finding for heart failure as patients may have edema from other causes including venous insufficiency, cirrhosis, hypoalbuminemia, kidney disease including nephrotic syndrome, pregnancy, and treatment with a number of medications including calcium channel blockers (particularly dihydropyridines, e.g. amlodipine, nifedipine), thiazolidinediones, docetaxel, gabapentin, pregabalin, nonsteroidal anti-inflammatory drugs (NSAIDs), glucocorticoids, fludrocortisone, and vasodilators (hydralazine, minoxidil, diazoxide; less frequent – alpha1 blockers, and methyldopa). However, edema is a specific finding of heart failure when associated with elevated jugular venous pressure [10, 11].

The jugular venous pressure (JVP) is the single most important finding in the assessment of intravascular volume status. JVP provides a direct measurement of right atrial (RA) pressure, an estimate of right ventricular filling pressure and some insight into pulmonary capillary wedge and left atrial pressures. JVP is measured as the vertical distance from the mid right atrium to the top of the observable column of blood (or meniscus) in the internal jugular vein and is expressed in centimeters of water.

A number of methods have been suggested to estimate JVP. Assessment of JVP may be made with the upper torso of the patient elevated at 30–45°. When assessing JVP, it is important that the height of the meniscus of the internal jugular vein be clearly identified. In patients with ADHF, a meniscus may not be seen at 30–45° because of high JVP. It is recommended that JVP be assessed at both 30–45° and 90° (sitting upright) to avoid underestimating filling pressures [15, 25]. The position of the right atrium can be estimated to be at the intersection of the fourth or fifth intercostal space and the mid-axillary line. The JVP can be estimated by measuring the vertical distance from the position of the right atrium to the top of the meniscus. Alternatively, the position of the right atrium can be estimated to be 5 cm below the

angle of Louis. Using this method, JVP can be estimated to be the vertical distance from the angle of Louis to the meniscus plus 5 cm of water.

Another alternative is to measure JVP in the upright sitting position. In most patients, the distance from the right atrium to the clavicle is 10 cm in the upright position. If a meniscus is seen above the clavicle, the patient has an elevated JVP. The JVP is 10 cm plus the measured distance from the clavicle to the observed meniscus. This method gives JVP <10 cm of water, 10–12 cm, 12–14 cm, etc. This method is less cumbersome, is more accurate, and has less intra- and inter-observer variability and avoids underestimating JVP. If a meniscus is not observed in the upright position, assessment of JVP should then be made at progressively decreasing elevations of the torso above supine. If a meniscus is not seen while lying flat, the patient may be volume depleted [15, 25].

Some studies have found poor inter-observer reliability in the assessment of JVP by ED physicians [26]. A study of patients with heart failure that compared estimates of JVP by exam, estimates of RA pressure by echo and RA pressure measured by a pulmonary artery catheter in patients with heart failure found that clinical assessment of JVP accurately estimated normal RA pressure but tended to underestimate RA pressure in patients with elevated RA pressure [27]. Others have suggested that physical examination is helpful in determining whether central venous pressure is high or low but not in assessing a specific pressure [28, 29].

In the ESCAPE trial, estimates of JVP by physical exam recorded on initial history and physical exam were compared with RA pressure on invasive hemodynamic monitoring in 194 patients with chronic severe symptomatic heart failure randomized to the PA catheter group [9]. Estimated JVP (in cm of water) was converted to RA pressure (in mmHg) by multiplying JVP (in cm of water) by 0.736, the ratio of the density of water relative to the density of mercury. (1 cm of water equals 0.736 mmHg.) Measured right atrial pressure was less than 8 mmHg in 82 % of patients (9/11) who had an estimated JVP of less than 8 mmHg. Measured RA pressure was ≥8 mmHg in 82 % (149/181) of patients who had an estimated JVP ≥8 mmHg. Measured right atrial pressure was >12 mmHg in 70 % (80 of 114) of patients who had an estimated JVP of >12 mmHg.

Elevated JVP is helpful in predicting elevated pulmonary capillary wedge pressure. In the ESCAPE trial, estimated RA pressure ≥12 mmHg was strongly associated with PCWP ≥30 mmHg with an odds ratio of 4.6 [9]. In a study of 1000 patients with advanced heart failure undergoing transplant evaluation, 79 % of patients had concordance of right atrial and pulmonary capillary wedge pressures defined as an RAP ≥10 mmHg with a PCWP ≥22 mmHg [30]. An RA pressure of ≥10 mmHg had a positive predictive value of 88 % to identify a PCWP ≥22 mmHg. In another study of 4079 potential transplant candidates, elevated pressures were defined as RAP ≥10 mmHg and PCWP ≥22 mmHg. Pressures were described as "concordant" if the RA and PCWP were both either high or low. The frequency of concordant pressures over three sequential 4 year periods was 74 %, 72 %, and 73 % [31]. In another study of 537 patients hospitalized for ADHF who underwent right heart catheterization, 36 % of patients had concordant low filling pressures (RA <10 mmHg; PCWP <22 mmHg) and 36 % of patients had concordant high

filling pressures (RA ≥10 mmHg; PCWP ≥22 mmHg [32]. Fifteen percent of patients had RA <10 with PCWP ≥22 mmHg ("High-Left Mismatch") and 13 % of patients had RA ≥10 mmHg and PCWP <22 mmHg ("High-Right Mismatch").

On multivariate analysis, patients with a history of symptomatic heart failure who were enrolled in the Studies of Left Ventricular Function (SOLVD) treatment trial and who had elevated JVP had an increased risk of hospitalization for heart failure, death or hospitalization for heart failure, and death from pump failure [33].

In patients with chronic severe heart failure, findings of volume overload (rales, elevated JVP and lower extremity edema) identify patients with an elevated PCWP. However, rales, elevated JVP and rales may be absent despite an elevated PCWP. In a study of 50 patients with chronic heart failure, physical findings of heart failure were compared with hemodynamic measurements. All 10 patients with lower extremity edema had an RA pressure ≥10 mmHg. All patients with an RA pressure ≥10 mmHg had an elevated PCWP ≥22 mmHg. JVP was the most sensitive finding on exam for elevated PCWP. No patient with edema, rales or elevated JVP had a wedge pressure <22 mmHg. However, 18/43 patients (42 %) with PCWP ≥22 mmHg and 8/18 (44 %) of patients with PCWP ≥35 mmHg had no findings of volume overload on physical exam [8].

In ADHF, the apical impulse may be displaced leftward indicating cardiac enlargement. A late diastolic gallop (S4) may be heard, especially in patients with heart failure with preserved systolic function in sinus rhythm. An early diastolic gallop (S3) may be heard in patients with heart failure and systolic dysfunction. There is conflicting evidence whether an S3 is specific for elevated LVEDP [8, 34] but its presence reliably predicts the presence of left ventricular dysfunction [8, 34]. A holosystolic murmur of functional mitral regurgitation is common in patients with ADHF and systolic dysfunction. Patients with biventricular dysfunction, pulmonary hypertension or isolated right heart failure may have a murmur of tricuspid regurgitation. This can be distinguished from a murmur of mitral regurgitation by the location of the murmur at the left sternal border and an increase in the intensity of the murmur with inspiration.

Wang et al. reviewed 22 studies of patients who presented to the emergency department with dyspnea to assess the usefulness of history, symptoms, physical findings, and routine diagnostic studies (chest radiograph, electrocardiogram and serum B-type natriuretic peptide) to differentiate heart failure from other causes of dyspnea. Many clinical characteristics increased the probability that dyspnea was caused by heart failure. The finding in each category that best predicted that dyspnea was due to heart failure was the *presence* of: a past history of heart failure; the symptom of paroxysmal nocturnal dyspnea; sign of a third heart sound; chest radiograph showing pulmonary venous congestion; and electrocardiogram showing atrial fibrillation. The finding in each category that best predicted that dyspnea was *not* due to heart failure was the *absence* of: a past history of heart failure; the symptom of dyspnea on exertion; rales on physical exam; chest radiograph showing cardiomegaly; and any abnormality on electrocardiogram [35].

Many heart failure practitioners have found a 2 × 2 dichotomous matrix based on a clinical assessment of volume status (congestion/no congestion) ("wet" or "dry")

and systemic perfusion (adequate perfusion/clinically important hypoperfusion) ("warm" or "cold") to be useful in characterizing the clinical status of patients with ADHF and in developing a therapeutic plan [36]. See Fig. 2.1 in Chap. 2 [37]. Signs, symptoms and laboratory data that suggest a patient is congested or "wet" include: orthopnea, jugular venous distention, rales, ascites, peripheral edema, dyspnea at rest or with exertion, orthopnea, PND, peripheral edema, abdominal distention, unexplained weight gain, rales, jugular venous distention, hepatojugular reflux, hepatomegaly, and elevated B-type natriuretic peptide (BNP) or n-terminal pro-BNP. Signs and symptoms that suggest a patient has compromised perfusion or is "cold" include: a narrow pulse pressure, a proportional pulse pressure of <0.25, pulsus alternans, symptomatic hypotension (without orthostasis), cool distal extremities, anxiety and impaired mentation.

A prospective analysis of 452 patients admitted to an academic heart failure service found that clinical assessment of a patient's hemodynamic profile could be used to predict outcomes. Patients with initial "warm-wet" and "cold-wet" profiles had an increased risk of death or urgent transplant on multivariate analysis (HR 2.48; P = 0.003). These profiles were also associated with an increased risk of death or urgent transplant when patients with NHYA FC III (HR 2.23, p = 0.026) and NYHA FC IV (HR 2.73, p = 0.009) symptoms were analyzed separately [23]. In the ESCAPE trial, clinician determined "cold" vs. "warm" profile was associated with a lower median measured cardiac index in the "cold" patients (1.75 vs. 2.0 L/min/m^2; p = 0.004). On Cox regression analysis, "cold" or "wet" profiles at the time of discharge conveyed a 50 % increased risk of death or rehospitalization [9].

Patients with right heart failure may have a right-sided S3, increased intensity of the pulmonic component of the second heart sound (in patients with pulmonary hypertension), a murmur of tricuspid regurgitation, hepatomegaly and ascites. A pulsatile liver may be palpable in patients with severe tricuspid regurgitation.

Initial Laboratory Evaluation

The initial evaluation of the patient presenting with ADHF should include laboratory studies which help confirm heart failure as the cause of the presenting symptoms; identify underlying conditions that may be a cause of heart failure or may precipitate heart failure decompensation; help assess the severity of underlying end-organ dysfunction; and identify conditions which may be immediately life threatening and require urgent treatment.

Serum Electrolytes

Minor abnormalities of serum electrolytes are common in patients with ADHF and may be due to neurohormonal activation, low cardiac output, or heart failure medications. The reported incidence of hyponatremia defined as a serum sodium

≤ 135 mEq/L varies widely between 7.7 and 45 % [38, 39]. In EHFS I, 20 % of patients were hyponatremic [37]. Hypokalemia is common in patients treated with loop diuretics. Hyperkalemia occurs in approximately 8 % of patients with ADHF in the setting of chronic heart failure and is associated with treatment with angiotensin converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), mineralocorticoid antagonists (MRAs), potassium supplementation, potassium sparing diuretics, and chronic or acute renal insufficiency [39, 40]. Diabetes is common in patients with ADHF (44 % in ADHERE; 41.5 % in OPTIMIZE) and poor glycemic control may accompany or contribute to ADHF [41].

Blood Urea Nitrogen (BUN) and Creatinine

Renal dysfunction is common in patients with ADHF. In the ADHERE Registry, chronic renal insufficiency was reported in 30 % of patients. 9 % of patients had a creatinine on admission of >3.0 mg/dL and 21 % had a creatinine >2.0 mg/dL. Five percent were on chronic dialysis [1]. In OPTIMIZE-HF, the mean creatinine was 1.8 mg/dL [6]. In EHFS I, renal dysfunction was reported to have complicated management in 18 % of patients. Serum creatinine was ≥150 μmol/l (1.7 mg/dL) in 16 % of patients and ≥200 μmol/l (2.3 mg/dL) in 7 % [2]. In a nationwide, prospective, observational study of 206 cardiology centers with intensive cardiac care units in Italy, 47 % of patients admitted with acute heart failure had renal dysfunction defined as creatinine ≥1.5 mg % (mg/dL) [39].

Patients with HF commonly have risk factors associated with both heart and kidney disease including diabetes mellitus, hypertension and vascular disease. Elevated BUN and creatinine may be manifestations of renal hypoperfusion in the setting of low cardiac output or in the setting of marked neurohormonal activation even in the face of normal cardiac output and normal or elevated filling pressures. Elevated BUN and creatinine may also be a manifestation of hypovolemia with low filling pressures in the setting of diuretic therapy. The BUN/creatinine ratio may be elevated in the setting of low cardiac output, neurohormonal activation or volume depletion. In each of these conditions, the proximal tubular absorption of sodium is increased. This is accompanied by reabsorption of BUN but not creatinine. Treatment with ACEIs or ARBs may also contribute to renal dysfunction particularly in the setting of renal artery stenosis, severe chronic heart failure or volume depletion [42, 43]. It has been our observation that lower urinary tract obstruction is a common reversible cause of abnormal renal function in older men with ADHF.

Hematologic Measures

Anemia is common in patients with ADHF. The World Health Organization defines anemia as hemoglobin (Hgb) <13.0 g/dL in men and <12.0 g/dL in women. In clinical trials and large HF registries, the prevalence of anemia has ranged from 15 to

61 % overall and from 14 to 70 % among hospitalized patients [44]. In a meta-analysis of 34 cohort studies or retrospective analyses of randomized controlled trials in HF which included 153,180 patients, 37.2 % of patients were anemic. Anemia was associated with an increased risk of mortality in patients with HFrEF and HFpEF with an adjusted hazard ratio of 1.46 [45].

In the OPTIMIZE – HF registry, half of the patients had a hemoglobin <12.1 g/dL and 25 % had a hemoglobin of 5–10.7 g/dL. Patients with low hemoglobin tended to be older, female, and Caucasian and more commonly had preserved systolic function and elevated creatinine. Low hemoglobin was associated with higher in-hospital mortality, longer hospital length of stay and more readmissions at 90 days [46]. In EHFS I, a hemoglobin <11 g/dL was reported in 18 % of men and 23 % of women [2]. In patients with ADHF in Italy, a hemoglobin <12 g/dL was present in 46 % of patients [39]. In a large population-based cohort of Canadian patients discharged after hospitalization for new onset HF, 17 % had anemia, 58 % of whom had anemia of chronic disease. Anemic patients were more likely to be older, female, and have a history of chronic renal insufficiency or hypertension. Anemic patients had a significantly greater risk-adjusted mortality (HR = 1.34) compared with non-anemic patients [47]. In the EVEREST Trial, 34 % of patients with systolic dysfunction hospitalized for ADHF were anemic at baseline. 73 % of patients who were anemic at baseline were anemic at discharge or day 7 and 6 % of patients without anemia developed anemia by discharge or day7. Anemia at discharge but not on admission was associated with an increased risk of long-term all-cause mortality and short-term (≤100 days post-discharge) cardiovascular mortality or CHF hospitalization [48].

Anemia in heart failure is multifactorial [44]. In patients with acute decompensation, plasma expansion due to salt and water overload may cause dilutional anemia [49, 50]. Anemia may also be caused by renal dysfunction with inappropriate erythropoietin production, pro-inflammatory cytokine activation with anemia of chronic disease, iron deficiency and defective iron utilization [44, 51]. In a community based study of patients with HF due to systolic dysfunction, the relationship between anemia and renal insufficiency was explored. Anemia was present in 32 % of patients. Low serum iron or low ferritin was found in 43 % of patients with anemia. Renal dysfunction (defined as a glomerular filtration rate <60 ml/min by the Modification of Diet in Renal Disease (MDRD) equation) was present in 54 % of patients. 41 % of patients with renal dysfunction and 22 % of patients without renal dysfunction were anemic. Anemia and renal dysfunction independently predicted mortality and the effects were additive [52]. In patients hospitalized for ADHF who had a thorough evaluation for underlying causes of anemia (defined as hemoglobin <12 g/dL in men and <11.5 g/dL in women), iron deficiency was the most common cause of anemia with depleted iron stores found in 73 % of anemic patients on bone marrow aspiration. Serum ferritin was not a reliable marker of iron deficiency in this study [53].

Low “relative lymphocyte count” or “lymphocyte ratio” (total number of lymphocytes/total number of leukocytes × 100) is an independent predictor of mortality in outpatients with heart failure [54]. In the EVEREST trial, patients with low

relative lymphocyte count tended to be older, more likely to be male, had higher rates of comorbid disease and were more likely to have a history of prior myocardial infarction and coronary revascularization. Patients with low relative lymphocyte ratio had significantly lower presenting systolic and diastolic blood pressure, higher mean heart rates, lower serum sodium levels, higher blood urea nitrogen, and higher natriuretic peptide levels. These patients were less likely to receive evidence-based HF medications. After adjusting for multiple risk factors, relative lymphocyte count <15.4 % was an independent predictor of all-cause mortality and cardiovascular mortality or HF hospitalization in the first 100 days following discharge [55].

In the Preliminary study of RELAXin in Acute Heart Failure (Pre-RELAX-AHF), patients admitted with acute heart failure, SBP ≥125 mmHg, and BNP ≥350 pg/ml were randomized to the vasodilator relaxin or placebo. Patients with a lymphocyte ratio <13 % had similar baseline characteristics as patients with a lymphocyte ratio >13 % but had less improvement in dyspnea, greater worsening of HF, longer initial length of stay, fewer days alive and out of the hospital and greater risk for all-cause mortality at 60 and 180 days [56].

Liver Function Tests (LFTs)

Up to 60 % of patients hospitalized with ADHF have mild liver function test abnormalities. Elevation of all liver function tests, and especially γ-glutamyl transferase (GGT) and total bilirubin (Tbili), are associated with high central venous pressure (CVP). Only elevated transaminases and Tbili are associated with both high CVP and low cardiac output [57].

In the EVEREST trial, the most common LFT abnormality was an elevation in GGT which occurred in 60 % of patients. Other LFT abnormalities were common and included elevation of alanine aminotransferase (ALT) in 21 % of patients, aspartate aminotransferase (AST) in 21 %, alkaline phosphatase in 23 %, and total bilirubin (Tbili) in 26 % and decreased albumin in 17 %. LFT abnormalities were minor in most patients. Tbili was the only LFT abnormality to decrease from admission to discharge. All LFTs except albumin improved following discharge. Lower baseline ALB and elevated Tbili were both associated with an increased risk for all-cause mortality. In-hospital decreases in albumin or increases in Tbili were associated with higher rates of both all-cause mortality and HF rehospitalization [58].

Two specific conditions affecting the liver, congestive hepatopathy and ischemic hepatitis (or “shock liver”) have been described in patients with heart failure. Congestive hepatopathy refers to a spectrum of chronic liver injury that is caused by chronic passive hepatic congestion in the setting of elevated right atrial pressure. Congestive hepatopathy occurs most commonly in conditions associated with chronically elevated right atrial pressure including: severe right-sided or biventricular heart failure, severe tricuspid regurgitation, cor pulmonale, severe pulmonary hypertension, restrictive cardiomyopathy, pericardial constriction, and congenital heart disease with Fontan reconstruction. Untreated congestion can result in hepatic fibrosis

and, eventually cardiac cirrhosis. Laboratory testing generally shows mild non-specific increases in transaminases generally not more than 2–3 times the upper limit of normal, mildly increased Tbili generally <3 mg/dL (predominantly unconjugated), and normal or slightly elevated alkaline phosphatase (which helps differentiate congestion from biliary obstruction). Hepatic synthetic function is usually normal or only slightly impaired. Serum albumin is usually normal or slightly reduced. The international normalized ratio (INR) is rarely increased above 1.5 [59, 60].

Ischemic hepatitis (or "shock liver") refers to a condition of diffuse hepatocellular injury caused by impaired perfusion to the liver. This most commonly occurs in the setting of cardiogenic shock. It can also occur in patients without hypotension but with severe heart failure, marked reduction in cardiac output and elevated right sided filling pressures. The diagnosis is defined by the appropriate clinical setting of cardiac, circulatory or pulmonary failure, marked increases in serum aminotransferase levels generally greater than 20 times the upper limit of normal, and exclusion of other causes of acute liver injury. AST, ALT and lactic dehydrogenase (LDH) levels are markedly elevated. The ALT/LDH ratio is generally less than 1.5 which helps distinguish ischemic injury from other forms of acute hepatic injury. Tbili is also increased but generally not above 4 times the upper limit of normal. Alkaline phosphatase may be normal or mildly elevated. INR, which is a marker of synthetic liver function, may be elevated in the setting of severe liver injury. ALT, AST and LDH generally peak 1–3 days after the precipitating event and return to normal in 7–10 days after improvement in systemic perfusion. Patients who present with ADHF and marked elevation of AST, ALT, and LDH generally require hemodynamic monitoring, support with inotropes, and consideration of IABP or other mechanical circulatory support [59, 60].

Natriuretic Peptides

B-type natriuretic peptide (BNP) is a member of a family of three natriuretic hormones that share a common 17-amino-acid ring structure. BNP is primarily synthesized in the ventricles although can be synthesized in the atria. BNP is synthesized and released in response to increased wall stress resulting from an increase in intracardiac filling pressures. In response to increased wall stress, pre-proBNP is synthesized in cardiac myocytes and cleaved to $proBNP_{1\text{-}108}$ which is released from the myocyte. $ProBNP_{1\text{-}108}$ is subsequently cleaved to $BNP_{1\text{-}32}$ which is biologically active and N-terminal proBNP (NT-proBNP) which is biologically inactive. The biologic actions of BNP are mediated by membrane bound natriuretic peptide receptors. The biologic effects of BNP include vasodilation, natriuresis, diuresis and antagonism of activation of the renin-angiotensin-aldosterone system (RAAS). Both BNP an NT-proBNP are elevated in ADHF and the magnitude of the elevation parallels the elevation of left ventricular filling pressure [61, 62].

Both BNP and NT-proBNP levels have been shown to be useful in identifying heart failure as the underlying cause of symptoms in patients who present to the

emergency department (ED) with shortness of breath. The Breathing Not Properly (BNP) study was a large multicenter observational evaluation of 1586 patients who presented to the ED with acute dyspnea who had a prospective BNP level obtained. ED physicians, who were blinded to the results of the BNP measurement, assessed the probability that heart failure was the cause of the patient's symptoms. Two cardiologists (also blinded to the results of the BNP measurements) reviewed all medical records and independently classified the diagnosis as: dyspnea due to congestive heart failure; acute dyspnea due to non-cardiac causes in a patient with a history of left ventricular dysfunction; or dyspnea not due to congestive heart failure. Using a BNP cutoff of 100 pg/mL, BNP had a sensitivity, specificity, negative predictive and positive predictive value of 90 %, 76 %, 79 %, and 89 %, respectively. BNP had a higher diagnostic accuracy than the ED physician with an area under the receiver-operator curve of 0.91. In multiple logistic regression analysis, an elevated BNP was the strongest predictor of heart failure with an odds ratio of 29.5. BNP was predictive of heart failure in patients with reduced or preserved ventricular function [63].

The ProBNP Investigation of Dyspnea in the ED (PRIDE) was a similar study using NT-proBNP in 600 patients who presented to a single institution with dyspnea. NT-proBNP levels at cut points of >450 pg/ml for patients <50 years of age and >900 pg/ml for patients ≥50 years of age were highly sensitive and specific for the diagnosis of acute heart failure. An NT-proBNP <300 pg/ml was best for ruling out heart failure and had a negative predictive value of 99 %. NT-proBNP was the strongest independent predictor of a final diagnosis of heart failure with an odds ratio of 44 and was superior to clinical judgment alone. NT-proBNP combined with clinical judgment was superior to either alone in diagnosing heart failure. The investigators suggested a single cut point of <300 pg/ml to rule out heart failure and two cut points based on age to rule in a diagnosis of heart failure (>450 pg/ml in patients <50 years of age and >900 pg/ml in patients ≥50 years of age) [64]. Other authors have suggested using either an age-independent cut point of >900 pg/ml or a more accurate age-stratified approach of 450/900/1800 for patients ages <50, 50–75, and >75 years [65–67].

Patients with chronic heart failure may have elevated BNP or NT-proBNP levels despite normal volume status. Increases above an established patient-specific "euvolemic" BNP or NT-proBNP level may help identify worsening volume overload in individual patients. However, the biologic variability of both markers complicates interpreting serial BNPs. BNP may need to change by 70 % and NT-proBNP by 50 % to be helpful diagnostically [66, 68, 69].

In general, BNP and NT-proBNP have similar diagnostic utility. Both are particularly good at ruling out heart failure at levels <100 pg/ml for BNP and <300 pg/ml for NT-proBNP. NT-proBNP levels are increased to a greater degree in advanced age and renal insufficiency. Both can be elevated in the absence of heart failure in a number of conditions including: acute coronary syndromes, chronic heart failure without volume overload, advanced age, renal dysfunction, pulmonary disease, acute hemodynamically significant pulmonary embolism, high output states including sepsis, cirrhosis and hyperthyroidism, and atrial fibrillation. BNP and

NT-proBNP are commonly not elevated in obese patients with volume overload. Other conditions in which levels are lower than expected include heart failure from mitral stenosis, acute mitral regurgitation, cardiac tamponade and pericardial constriction [61, 66].

Troponins

Measurement of circulating cardiac troponin (cTn) plays an important role in the diagnosis of ACS and should be obtained in all patients with ADHF on presentation to the emergency department [70]. Cardiac troponin (either T or I) has near absolute specificity for myocardial injury and high clinical sensitivity [71, 72]. The presence of measurable cTn is abnormal and indicative of myocardial injury. Typically, a patient with an acute coronary syndrome (ACS) precipitating heart failure will have precordial pain, characteristic ST segment elevations on ECG and significant cTn elevations (cTn I >1.0 ng/ml). However, in acute heart failure, troponin elevation may be seen in patients with and without ACS and with and without significant obstructive coronary artery disease suggesting that mechanisms other than focal myocardial ischemia/injury may be responsible for troponin release in some patients. The reported prevalence of elevated (defined as "detectable") troponin has varied widely in patients with ADHF depending on the population studied and on the sensitivity of the assay used [72]. See section on "Heart Failure Mechanisms".

Electrocardiography (ECG)

One of the primary goals of the initial evaluation of patients with ADHF is to promptly identify an acute coronary syndrome using history, electrocardiography and serum biomarkers. In EHFS II, 11.1 % of patients had evidence of an ST segment elevation myocardial infarction, 10.0 % had a non-STEMI and 9.1 % had unstable angina [2]. The presence of ST segment elevation and elevated troponin is diagnostic for an acute coronary syndrome [73]. ACS may be more difficult to diagnose in the setting of non-specific ST-T wave abnormalities [74].

The electrocardiogram is abnormal in many patients with ADHF. An abnormal ECG defined as the presence of atrial fibrillation or flutter, left or right bundle branch block, evidence of past myocardial infarction or ST-segment deviation had a sensitivity of 58 % and specificity of 78 % to identify HF in a group of 880 patients who presented to the ED with acute dyspnea at one of 7 academic medical centers [75].

Sinus tachycardia is common. Atrial fibrillation (AF) is present in approximately 30–40 % of patients admitted with ADHF [6, 7, 39, 76–80].

QRS prolongation (QRS >120 ms) is also common. Of 2962 patients enrolled in the EVEREST Trial without a pacemaker or implantable cardioverter-defibrillator (ICD), 1321 (45 %) had a QRS duration ≥120 ms. LBBB was present in 909 patients

(30.6 %). QRS prolongation was independently associated with an increased risk of all-cause mortality and cardiovascular death or HF hospitalization (HR = 1.24 and 1.28, respectively) [81]. The incidence of LBBB has been reported to be lower (16–17 %) in other reports [82, 83].

Electrocardiography may offer clues to the cause of heart failure. Patients may have pathologic Q waves indicative of an ischemic cardiomyopathy. Evidence of left ventricular hypertrophy may be present in patients with hypertensive heart disease, aortic stenosis or hypertrophic cardiomyopathy. Patients with cardiac amyloidosis may have low voltage with or without pathologic Q waves ("pseudo-infarction" pattern).

Chest Radiography

A chest radiograph should be obtained in all patients presenting with acute shortness of breath or suspicion of ADHF. A number of radiographic findings may be present in patients with ADHF including cardiomegaly, cephalization of the pulmonary vasculature, interstitial lung edema, alveolar edema, and pleural effusion(s). Heart size on chest radiography is assessed by calculating the cardiothoracic ratio (CTR) which is determined by dividing the largest horizontal width of the heart by the widest internal diameter of the thorax on a posterior-anterior chest film. A normal CTR is less than 0.5. CTR is abnormal in 57–71 % of patients with chronic heart failure due to systolic dysfunction [84]. CTR may be less predictive of cardiomegaly in patients with chronic obstructive lung disease as the lung volumes are increase and the diaphragms are flattened.

Evaluation of the pulmonary vasculature and parenchyma is important in patients presenting with acute shortness of breath. It is best to evaluate pulmonary vascularity in the upright position. If the lung is divided into three zones vertically from the mediastinum to the periphery (chest wall), the major pulmonary arteries are located centrally around the hila, the midsize pulmonary arteries are easily visualized in the mid-zone and the small arteries and arterioles are located in the outer zone and are generally not visualized on chest radiograph. Normally, the visible small and mid-size arteries in the mid-zone have sharp definable margins. The lungs may also be divided into three regions horizontally from the diaphragms to the apices. In the upright position, the arteries in the lower region of the lung are generally larger than those in the upper region. This finding is related to the effect of gravity on the distribution of pulmonary blood flow and is not seen on supine CXR. In the setting of elevated left atrial pressure, especially in patients with chronic heart failure, there is redistribution of lung perfusion toward the apical regions. The lower zone vessels appear equal or smaller in diameter compared to the upper zone vessels. This finding is called "cephalization" or "inversion", is best correlated with measures of pulmonary vascular resistance and is likely due to vasoconstriction of lower zone vessels [85, 86].

As PCWP increases, the mid-zone vessels become less distinct due to extravasation of fluid into the pulmonary interstitium. Interstitial fluid may also be seen as

small well-defined reticulonodular (reticular, nodular or both) infiltrates seen in both the central and peripheral zones. Fine horizontal pleural-based linear densities may be seen in the periphery of the lung and represent interstitial fluid that accumulates in the septae between anatomic lung lobules (referred to as "Kerley B" or septal lines). This pattern of interstitial edema may progress to alveolar edema characterized by alveolar filling by transudated fluid. Alveolar edema is a bilateral process but may only involve parts of each lung. Alveolar edema causes poorly defined but homogeneous lung opacities that become progressively denser as edema worsens. Air bronchograms may be present as fluid filled alveoli outline air filled bronchi [87].

Pleural effusions may also be present. Effusions are generally bilateral. When unilateral, the effusion is more commonly present on the right.

The characteristic findings of heart failure on chest radiograph may not be present in all patients with ADHF. In patients with emphysema or pulmonary fibrosis, the pulmonary vascular pattern is abnormal at baseline and may not change in a predictable way in the setting of volume overload. Patients with chronic heart failure and chronically elevated pulmonary capillary wedge pressure may not have an abnormal pulmonary vascular pattern and may not develop interstitial or alveolar edema despite significantly elevated pulmonary capillary wedge pressure [88].

In the ADHERE Registry, 18.7 % of 85,376 patients (approximately one of every five patients) with a hospital discharge diagnosis of heart failure had no radiographic findings of heart failure (interstitial edema, pulmonary edema, or vascular congestion) on initial chest radiograph. Patients without signs of congestion on initial ED radiograph were more likely to have an ED non-heart failure diagnosis than patients with signs of congestion (13.0 vs 23.3 %) [89].

An analysis of 880 patients presenting with acute dyspnea to the emergency departments of seven teaching hospitals found that elevated BNP and radiographic findings of cardiomegaly, cephalization and interstitial edema added significant predictive information in the diagnosis of heart failure. Radiographic findings that were assessed included: cardiomegaly, cephalization, interstitial edema, alveolar edema, pleural effusion, hyperinflated lungs, and evidence of pneumonia. Of the patients evaluated for shortness of breath, 68 % were diagnosed with acute heart failure. The radiographic finding of cardiomegaly had a sensitivity of 79 % and specificity of 80 %. Cephalization, interstitial edema and alveolar edema were all highly specific (96–99 %) but insensitive (6–41 %). Cardiomegaly, cephalization, interstitial edema and alveolar edema all added significant, predictive information to historical and clinical predictors of heart failure [75].

Conclusions

Most patients with heart failure present with dyspnea at rest or with exertion and lower extremity edema. Some patients present with symptoms and ECG findings consistent with an acute coronary syndrome. A small percentage of patients present with acute pulmonary edema or cardiogenic shock.

The physical examination is critical in establishing the diagnosis of heart failure and in assessing the severity of disease, the presence and severity of systemic and pulmonary venous congestion, the adequacy of cardiac output and end-organ perfusion, the severity of respiratory compromise and the need for emergent intervention. In addition, the exam provides insights into the underlying cause of heart failure and the presence of reversible conditions that may have contributed to heart failure decompensation. Assessment of mental status, respiratory rate, oxygen saturation, blood pressure, jugular venous pressure, presence of pulmonary rales and presence of lower extremity edema are especially important components of the exam.

An ECG and measurement of circulating cardiac troponin are important in the diagnosis of ACS. BNP and NT-proBNP are useful in identifying heart failure as the underlying cause of symptoms in patients who present to the emergency department with shortness of breath.

References

1. Adams KF, Fonarow GC, Emerman CL, LeJemtel TH, Costanzo MR, Abraham WT, et al; ADHERE Scientific Advisory Committee and Investigators. Characteristics and outcomes of patients hospitalized for heart failure in the United States: rationale, design, and preliminary observations from the first 100,000 cases in the Acute Decompensated Heart Failure National Registry (ADHERE). Am Heart J 2005;149(2):209–16.
2. Cleland JG, Swedberg K, Follath F, Komajda M, Cohen-Solal A, Aguilar JC, et al; Study Group on Diagnosis of the Working Group on Heart Failure of the European Society of Cardiology. The EuroHeart Failure survey programme-- a survey on the quality of care among patients with heart failure in Europe. Part 1: patient characteristics and diagnosis. Eur Heart J. 2003;24(5):442–63.
3. Fonarow GC, Stough WG, Abraham WT, Albert NM, Gheorghiade M, Greenberg BH, et al; OPTIMIZE-HF Investigators and Hospitals. Characteristics, treatments, and outcomes of patients with preserved systolic function hospitalized for heart failure: a report from the OPTIMIZE-HF Registry. J Am Coll Cardiol. 2007;50(8):768–777. PubMed PMID 17707182.
4. Fonarow GC, Corday E, ADHERE Scientific Advisory Committee. Overview of acutely decompensated congestive heart failure (ADHF): a report from the ADHERE registry. Heart Fail Rev. 2004;9(3):179–85.
5. Fonarow GC, Heywood JT, Heidenreich PA, Lopatin M, Yancy CW, ADHERE Scientific Advisory Committee and Investigators. Temporal trends in clinical characteristics, treatments, and outcomes for heart failure hospitalizations, 2002 to 2004: findings from Acute Decompensated Heart Failure National Registry (ADHERE). Am Heart J. 2007;153(6):1021–8.
6. Gheorghiade M, Abraham WT, Albert NM, Greenberg BH, O'Connor CM, She L, et al; OPTIMIZE-HF Investigators and Coordinators. Systolic blood pressure at admission, clinical characteristics, and outcomes in patients hospitalized with acute heart failure. JAMA 2006;296(18):2217–2226.
7. Nieminen MS, Brutsaert D, Dickstein K, Drexler H, Follath F, Harjola VP, et al; EuroHeart Survey Investigators; Heart Failure Association, European Society of Cardiology. EuroHeart Failure Survey II (EHFS II): a survey on hospitalized acute heart failure patients: description of population. Eur Heart J. 2006 27(22):2725–36. Epub 2006 Sep 25.
8. Stevenson LW, Perloff JK. The limited reliability of physical signs for estimating hemodynamics in chronic heart failure. JAMA. 1989;261(6):884–8 PubMed PMID 2913385.

9. Drazner MH, Hellkamp AS, Leier CV, Shah MR, Miller LW, Russell SD, et al. Value of clinician assessment of hemodynamics in advanced heart failure: the ESCAPE trial. Circ Heart Fail. 2008;1(3):170–7. doi:10.1161/CIRCHEARTFAILURE.108.769778.
10. Ely JW, Osheroff JA, Chambliss ML, Ebell MH. Approach to leg edema of unclear etiology. J Am Board Fam Med. 2006;19(2):148–60.
11. Heart Failure Society of America, Lindenfeld J, Albert NM, Boehmer JP, Collins SP, Ezekowitz JA, Givertz MM, et al. HFSA 2010 Comprehensive Heart Failure Practice Guideline. Section 12: Evaluation and Management of Patients with Acute Decompensated Heart Failure. J Card Fail. 2010;16(6):e131–56. doi:10.1016/j.cardfail.2010.04.004.
12. Leier CV, Silver MA, Massie BM, Young JB, Fowler MB, Ventura HO, Hershberger RE. Nuggets, pearls, and vignettes of master heart failure clinicians. Part 1 – the medical history. Congest Heart Fail. 2001;7(5):245–9.
13. Payvar S, Spertus JA, Miller AB, Casscells SW, Pang PS, Zannad F, et al; Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study with Tolvaptan (EVEREST) Investigators. Association of low body temperature and poor outcomes in patients admitted with worsening heart failure: a substudy of the Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study with Tolvaptan (EVEREST) trial. Eur J Heart Fail 2013;15(12):1382–1389. doi: 10.1093/eurjhf/hft113. Epub 2013 Jul 15.
14. Gheorghiade M, Vaduganathan M, Ambrosy A, Böhm M, Campia U, Cleland JG, et al. Current management and future directions for the treatment of patients hospitalized for heart failure with low blood pressure. Heart Fail Rev. 2013;18(2):107–22. doi:10.1007/s10741-012-9315-1.
15. Leier CV, Young JB, Levine TB, Pina I, Armsrtrong W, Fowler MB, et al. Nuggest, pearls, and vignettes of master heart failure clinicians. Part 2—the physical examination. Congest Heart Fail. 2001;7(6):297–308 PubMed PMID 11828174.
16. Weintraub NL, Collins SP, Pang PS, Levy PD, Anderson AS, Arslanian-Engoren C, et al; American Heart Association Council on Clinical Cardiology and Council on Cardiopulmonary, Critical Care, Perioperative and Resuscitation. Acute heart failure syndromes: emergency department presentation, treatment, and disposition: current approaches and future aims: a scientific statement from the American Heart Association. Circulation. 2010;122(19):1975–96. doi:10.1161/CIR.0b013e3181f9a223. Epub 2010 Oct 11.
17. Cotter G, Metra M, Milo-Cotter O, Dittrich HC, Gheorghiade M. Fluid overload in acute heart failure--re-distribution and other mechanisms beyond fluid accumulation. Eur J Heart Fail. 2008;10(2):165–9. doi:10.1016/j.ejheart.2008.01.007.
18. Cotter G, Felker GM, Adams KF, Milo-Cotter O, O'Connor CM. The pathophysiology of acute heart failure--is it all about fluid accumulation? Am Heart J. 2008;155(1):9–18.
19. Collins S, Storrow AB, Albert NM, Butler J, Ezekowitz J, Felker GM, et al; SAEM/HFSA Acute Heart Failure Working Group. Early management of patients with acute heart failure: state of the art and future directions. A consensus document from the society for academic emergency medicine/heart failure society of America acute heart failure working group. J Card Fail 2015;21(1):27–43. doi: 10.1016/j.cardfail.2014.07.003. Epub 2014 Jul 18.
20. Peacock WF, Chandra A, Char D, Collins S, Der Sahakian G, Ding L, et al. Clevidipine in acute heart failure: Results of the A Study of Blood Pressure Control in Acute Heart Failure-A Pilot Study (PRONTO). Am Heart J. 2014;167(4):529–36. doi:10.1016/j.ahj.2013.12.023 .Epub 2014 Jan 15
21. Cotter G, Metzkor E, Kaluski E, Faigenberg Z, Miller R, Simovitz A, et al. Randomised trial of high-dose isosorbide dinitrate plus low-dose furosemide versus high-dose furosemide plus low-dose isosorbide dinitrate in severe pulmonary oedema. Lancet. 1998;351(9100):389–93.
22. Levy P, Compton S, Welch R, Delgado G, Jennett A, Penugonda N, et al. Treatment of severe decompensated heart failure with high-dose intravenous nitroglycerin: a feasibility and outcome analysis. Ann Emerg Med. 2007;50(2):144–52 . Epub 2007 May 23.
23. Nohria A, Tsang SW, Fang JC, Lewis EF, Jarcho JA, Mudge GH, et al. Clinical assessment identifies hemodynamic profiles that predict outcomes in patients admitted with heart failure. J Am Coll Cardiol. 2003;41(10):1797–804 PubMed PMID 12767667.

24. Gehlbach BK, Geppert E. The pulmonary manifestations of left heart failure. Chest. 2004;125(2):669–82.
25. Leier CV, Chatterjee K. The physical examination in heart failure--Part I. Congest Heart Fail. 2007;13(1):41–7.
26. Chaudhry A, Singer AJ, Chohan J, Russo V, Lee C. Interrater reliability of hemodynamic profiling of patients with heart failure in the ED. Am J Emerg Med. 2008;26(2):196–201. doi:10.1016/j.ajem.2007.04.029.
27. Stein JH, Neumann A, Marcus RH. Comparison of estimates of right atrial pressure by physical examination and echocardiography in patients with congestive heart failure and reasons for discrepancies. Am J Cardiol. 1997;80(12):1615–8.
28. McGee SR. Physical examination of venous pressure: a critical review. Am Heart J. 1998;136(1):10–8.
29. Cook DJ, Simel DL. The Rational Clinical Examination. Does this patient have abnormal central venous pressure? JAMA. 1996;275(8):630–4.
30. Drazner MH, Hamilton MA, Fonarow G, Creaser J, Flavell C, Stevenson LW, et al. Relationship between right and left-sided filling pressures in 1000 patients with advanced heart failure. J Heart Lung Transplant. 1999;18(11):1126–32 PubMed PMID 10598737.
31. Drazner MH, Brown RN, Kaiser PA, Cabuay B, Lewis NP, Semigran MJ, et al. Relationship of right-and left-sided filling pressures in patients with advanced heart failure: a 14-year multi-institutional analysis. J Heart Lung Transplant. 2012;31(1):67–72 PubMed PMID 22071240.
32. Campbell P, Drazner MH, Kato M, Lakdawala N, Palardy M, Nohria A, et al. Mismatch of right- and left-sided filling pressures in chronic heart failure. J Card Fail. 2011;17(7):561–8 PubMed PMID 21703528.
33. Drazner MH, Rame JE, Stevenson LW, Dries DL. Prognostic importance of elevated jugular venous pressure and a third heart sound in patients with heart failure. N Engl J Med. 2001;345(8):574–81 . PubMed PMID 11529211.
34. Marcus GM, Gerber IL, McKeown BH, Vessey JC, Jordan MV, Huddleston M, et al. Association between phonocardiographic third and fourth heart sounds and objective measures of left ventricular function. JAMA. 2005;293(18):2238–44.
35. Wang CS, FitzGerald JM, Schulzer M, Mak E, Ayas NT. Does this dyspneic patient in the emergency department have congestive heart failure? JAMA. 2005;294(15):1944–56.
36. Grady KL, Dracup K, Kennedy G, Moser DK, Piano M, Stevenson LW, et al. Team management of patients with heart failure: A statement for healthcare professionals from The Cardiovascular Nursing Council of the American Heart Association. Circulation. 2000;102(19):2443–56 PubMed PMID 11067802.
37. Dickstein K, Cohen-Solal A, Filippatos G, McMurray JJ, Ponikowski P, Poole-Wilson PA, et al; ESC Committee for Practice Guidelines (CPG). ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2008: the Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2008 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association of the ESC (HFA) and endorsed by the European Society of Intensive Care Medicine (ESICM). Eur Heart J. 2008;29(19):2388–442. doi: 10.1093/eurheartj/ehn309. Epub 2008 Sep 17.
38. Hauptman PJ, Burnett J, Gheorghiade M, Grinfeld L, Konstam MA, Kostic D, et al. Everest Investigators.Clinical course of patients with hyponatremia and decompensated systolic heart failure and the effect of vasopressin receptor antagonism with tolvaptan. J Card Fail. 2013;19(6):390–7. doi:10.1016/j.cardfail.2013.04.001 .Epub 2013 May 14.PMID:23743487 [PubMed – indexed for MEDLINE]
39. Tavazzi L, Maggioni AP, Lucci D, Cacciatore G, Ansalone G, Oliva F, Porcu M; Italian survey on Acute Heart Failure Investigators. Nationwide survey on acute heart failure in cardiology ward services in Italy. Eur Heart J. 2006;27(10):1207–15. Epub 2006 Apr 7. PMID:16603579 [PubMed – indexed for MEDLINE 1.
40. Juurlink DN, Mamdani MM, Lee DS, Kopp A, Austin PC, Laupacis A, Redelmeier DA. Rates of hyperkalemia after publication of the Randomized Aldactone Evaluation Study. N Engl J Med. 2004;351(6):543–51.

41. Greenberg BH, Abraham WT, Albert NM, Chiswell K, Clare R, Stough WG, et al. Influence of diabetes on characteristics and outcomes in patients hospitalized with heart failure: a report from the Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure (OPTIMIZE-HF). Am Heart J. 2007;154(2):277.e1–8.
42. Ronco C, Haapio M, House AA, Anavekar N, Bellomo R. Cardiorenal syndrome. J Am Coll Cardiol. 2008;52(19):1527–39. doi:10.1016/j.jacc.2008.07.051.
43. McCullough PA, Kellum JA, Haase M, Müller C, Damman K, PT M, et al. Pathophysiology of the cardiorenal syndromes: executive summary from the eleventh consensus conference of the Acute Dialysis Quality Initiative (ADQI). Contrib Nephrol. 2013;182:82–98. doi:10.1159/000349966 .Epub 2013 May 13
44. Anand IS. Anemia and chronic heart failure implications and treatment options. J Am Coll Cardiol. 2008;52(7):501–11. doi:10.1016/j.jacc.2008.04.044.
45. Groenveld HF, Januzzi JL, Damman K, van Wijngaarden J, Hillege HL, van Veldhuisen DJ, van der Meer P. Anemia and mortality in heart failure patients a systematic review and meta-analysis. J Am Coll Cardiol. 2008;52(10):818–27. doi:10.1016/j.jacc.2008.04.061.
46. Young JB, Abraham WT, Albert NM, Gattis Stough W, Gheorghiade M, Greenberg BH, et al; OPTIMIZE-HF Investigators and Coordinators. Relation of low hemoglobin and anemia to morbidity and mortality in patients hospitalized with heart failure (insight from the OPTIMIZE-HF registry). Am J Cardiol 2008;101(2):223-230. doi: 10.1016/j.amjcard.2007.07.067.
47. Ezekowitz JA, McAlister FA, Armstrong PW. Anemia is common in heart failure and is associated with poor outcomes: insights from a cohort of 12 065 patients with new-onset heart failure. Circulation. 2003;107(2):223–5.
48. Mentz RJ, Greene SJ, Ambrosy AP, Vaduganathan M, Subacius HP, Swedberg K, et al. Clinical profile and prognostic value of anemia at the time of admission and discharge among patients hospitalized for heart failure with reduced ejection fraction: findings from the EVEREST trial. Circ Heart Fail. 2014;7(3):401–8. doi:10.1161/CIRCHEARTFAILURE.113.000840 .Epub 2014 Apr 15
49. Abramov D, Cohen RS, Katz SD, Mancini D, Maurer MS. Comparison of blood volume characteristics in anemic patients with low versus preserved left ventricular ejection fractions. Am J Cardiol. 2008;102(8):1069–72. doi:10.1016/j.amjcard.2008.05.058 .Epub 2008 Jul 31
50. Androne AS, Katz SD, Lund L, LaManca J, Hudaihed A, Hryniewicz K, Mancini DM. Hemodilution is common in patients with advanced heart failure. Circulation. 2003;107(2):226–9 PMID:12538419 [PubMed – indexed for MEDLINE].
51. Okonko DO, Mandal AK, Missouris CG, Poole-Wilson PA. Disordered iron homeostasis in chronic heart failure: prevalence, predictors, and relation to anemia, exercise capacity, and survival. J Am Coll Cardiol. 2011;58(12):1241–51. doi:10.1016/j.jacc.2011.04.040.
52. de Silva R, Rigby AS, Witte KK, Nikitin NP, Tin L, Goode K, et al. Anemia, renal dysfunction, and their interaction in patients with chronic heart failure. Am J Cardiol. 2006;98(3):391–8 Epub 2006 Jun 12.
53. Nanas JN, Matsouka C, Karageorgopoulos D, Leonti A, Tsolakis E, Drakos SG, et al. Etiology of anemia in patients with advanced heart failure. J Am Coll Cardiol. 2006;48(12):2485–9 Epub 2006 Nov 28. PMID: 17174186.
54. Huehnergarth KV, Mozaffarian D, Sullivan MD, Crane BA, Wilkinson CW, Lawler RL, et al. Usefulness of relative lymphocyte count as an independent predictor of death/urgent transplant in heart failure. Am J Cardiol. 2005;95(12):1492–5.
55. Vaduganathan M, Ambrosy AP, Greene SJ, Mentz RJ, Subacius HP, et al; EVEREST trial investigators. Predictive value of low relative lymphocyte count in patients hospitalized for heart failure with reduced ejection fraction: insights from the EVEREST trial. Circ Heart Fail 2012;5(6):750–758. doi: 10.1161/CIRCHEARTFAILURE.112.970525. Epub 2012 Oct 9.
56. Milo-Cotter O, Teerlink JR, Metra M, Felker GM, Ponikowski P, Voors AA, et al. Low lymphocyte ratio as a novel prognostic factor in acute heart failure: results from the Pre-RELAX-AHF study. Cardiology. 2010;117(3):190–6. doi:10.1159/000321416 .Epub 2010 Nov 17

57. van Deursen VM, Damman K, Hillege HL, van Beek AP, van Veldhuisen DJ, Voors AA. Abnormal liver function in relation to hemodynamic profile in heart failure patients. J Card Fail. 2010;16(1):84–90. doi:10.1016/j.cardfail.2009.08.002 .Epub 2009 Sep 26
58. Ambrosy AP, Vaduganathan M, Huffman MD, Khan S, Kwasny MJ, Fought AJ, et al; EVEREST trial investigators. Clinical course and predictive value of liver function tests in patients hospitalized for worsening heart failure with reduced ejection fraction: an analysis of the EVEREST trial. Eur J Heart Fail 2012;14(3):302–311.
59. Weisberg IS, Jacobson IM. Cardiovascular diseases and the liver. Clin Liver Dis. 2011;15(1): 1–20. doi:10.1016/j.cld.2010.09.010 .Review. PMID: 21111990
60. Kavoliuniene A, Vaitiekiene A, Cesnaite G. Congestive hepatopathy and hypoxic hepatitis in heart failure: a cardiologist's point of view. Int J Cardiol. 2013;166(3):554–8. doi:10.1016/j.ijcard.2012.05.003 .Epub 2012 May 30. Review. PMID: 22656043
61. Daniels LB, Maisel AS. Natriuretic peptides. J Am Coll Cardiol. 2007;50(25):2357–68.
62. Silver MA, Maisel A, Yancy CW, McCullough PA, Burnett Jr JC, GS F, et al. BNP Consensus Panel BNP Consensus Panel 2004: A clinical approach for the diagnostic, prognostic, screening, treatment monitoring, and therapeutic roles of natriuretic peptides in cardiovascular diseases. Congest Heart Fail. 2004;10(5 Suppl 3):1–30.
63. Maisel AS, Krishnaswamy P, Nowak RM, McCord J, Hollander JE, Duc P, et al; Breathing Not Properly Multinational Study Investigators. Rapid measurement of B-type natriuretic peptide in the emergency diagnosis of heart failure. N Engl J Med 2002;347(3):161–167.
64. Januzzi Jr JL, Camargo CA, Anwaruddin S, Baggish AL, Chen AA, Krauser DG, et al. The N-terminal Pro-BNP investigation of dyspnea in the emergency department (PRIDE) study. Am J Cardiol. 2005;95(8):948–54.
65. Januzzi Jr JL, Chen-Tournoux AA, Moe G. Amino-terminal pro-B-type natriuretic peptide testing for the diagnosis or exclusion of heart failure in patients with acute symptoms. Am J Cardiol. 2008;101(3A):29–38. doi:10.1016/j.amjcard.2007.11.017.
66. Maisel A, Mueller C, Adams Jr K, Anker SD, Aspromonte N, Cleland JG, et al. State of the art: using natriuretic peptide levels in clinical practice. Eur J Heart Fail. 2008;10(9):824–39. doi:10.1016/j.ejheart.2008.07.014 .Epub 2008 Aug 29
67. Gopal DJ, Iqbal MN, Maisel A. Updating the role of natriuretic peptide levels in cardiovascular disease. Postgrad Med. 2011;123(6):102–13. doi:10.3810/pgm.2011.11.2500.
68. O'Hanlon R, O'Shea P, Ledwidge M, O'Loughlin C, Lange S, Conlon C, et al. The biologic variability of B-type natriuretic peptide and N-terminal pro-B-type natriuretic peptide in stable heart failure patients. J Card Fail. 2007;13(1):50–5.
69. Wu AH. Serial testing of B-type natriuretic peptide and NTpro-BNP for monitoring therapy of heart failure: the role of biologic variation in the interpretation of results. Am Heart J. 2006;152(5):828–34.
70. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE Jr, Drazner MH,et al; American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. Circulation 2013;128(16):e240–e327. doi: 10.1161/CIR.0b013e31829e8776. Epub 2013 Jun 5.
71. Thygesen K, Alpert JS, White HD; Joint ESC/ACCF/AHA/WHF Task Force for the Redefinition of Myocardial Infarction, Jaffe AS, Apple FS, Galvani M, Katus HA, Newby LK, Ravkilde J, et al. Universal definition of myocardial infarction. Circulation 2007;116(22):2634–2653. Epub 2007 Oct 19.
72. Kociol RD, Pang PS, Gheorghiade M, Fonarow GC, O'Connor CM, Felker GM. Troponin elevation in heart failure prevalence, mechanisms, and clinical implications. J Am Coll Cardiol. 2010;56(14):1071–8. doi:10.1016/j.jacc.2010.06.016.
73. O'Gara PT, Kushner FG, Ascheim DD, Casey DE Jr, Chung MK, et al; American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines.

2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation. 2013;127(4):e362–425. doi: 10.1161/CIR.0b013e3182742cf6. Epub 2012 Dec 17. No abstract available. Erratum in: Circulation. 2013 Dec 24;128(25):e481.

74. Anderson JL, Adams CD, Antman EM, Bridges CR, Califf RM, Casey DE Jr, et al.; American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. 2012 ACCF/AHA focused update incorporated into the ACCF/AHA 2007 guidelines for the management of patients with unstable angina/non-ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation. 2013 127(23):e663–828. doi: 10.1161/CIR.0b013e31828478ac. Epub 2013 Apr 29. No abstract available. Erratum in: Circulation. 2013 Jun 18;127(24):e863–4.
75. Knudsen CW, Omland T, Clopton P, Westheim A, Abraham WT, Storrow AB, et al. Diagnostic value of B-Type natriuretic peptide and chest radiographic findings in patients with acute dyspnea. Am J Med. 2004;116(6):363–8.
76. Cleland JG, Swedberg K, Cohen-Solal A, Cosin-Aguilar J, Dietz R, Follath F, et al. The Euro Heart Failure Survey of the EUROHEART survey programme. A survey on the quality of care among patients with heart failure in Europe. The Study Group on Diagnosis of the Working Group on Heart Failure of the European Society of Cardiology. The Medicines Evaluation Group Centre for Health Economics University of York. Eur J Heart Fail. 2000;2(2):123–32.
77. Publication Committee for the VMAC Investigators (Vasodilatation in the Management of Acute CHF). Intravenous nesiritide vs nitroglycerin for treatment of decompensated congestive heart failure: a randomized controlled trial. JAMA. 2002;287(12):1531–40.
78. Cuffe MS, Califf RM, Adams Jr KF, Benza R, Bourge R, Colucci WS, et al. Outcomes of a Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic Heart Failure (OPTIME-CHF) Investigators. Short-term intravenous milrinone for acute exacerbation of chronic heart failure: a randomized controlled trial. JAMA. 2002;287(12):1541–7.
79. McManus DD, Saczynski JS, Lessard D, Kinno M, Pidikiti R, Esa N, et al. Recent trends in the incidence, treatment, and prognosis of patients with heart failure and atrial fibrillation (the Worcester Heart Failure Study). Am J Cardiol. 2013;111(10):1460–5. doi:10.1016/j.amjcard.2013.01.298.
80. Mountantonakis SE, Grau-Sepulveda MV, Bhatt DL, Hernandez AF, Peterson ED, Fonarow GC. Presence of atrial fibrillation is independently associated with adverse outcomes in patients hospitalized with heart failure: an analysis of get with the guidelines-heart failure. Circ Heart Fail. 2012;5(2):191–201. doi:10.1161/CIRCHEARTFAILURE.111.965681 .Epub 2012 Feb 23
81. Wang NC, Maggioni AP, Konstam MA, Zannad F, Krasa HB, Burnett JC Jr,et al; Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study With Tolvaptan (EVEREST) Investigators. Clinical implications of QRS duration in patients hospitalized with worsening heart failure and reduced left ventricular ejection fraction. JAMA 2008;299(22):2656-2666. doi: 10.1001/jama.299.22.2656.
82. Chioncel O, Vinereanu D, Datcu M, Ionescu DD, Capalneanu R, Brukner I, et al. The Romanian Acute Heart Failure Syndromes (RO-AHFS) registry. Am Heart J. 2011 Jul;162(1):142–53.e1. doi: 10.1016/j.ahj.2011.03.033. Epub 2011 Jun 15.
83. Huvelle E, Fay R, Alla F, Cohen Solal A, Mebazaa A, Zannad F. Left bundle branch block and mortality in patients with acute heart failure syndrome: a substudy of the EFICA cohort. Eur J Heart Fail. 2010;12(2):156–63. doi:10.1093/eurjhf/hfp180 .Epub 2009 Dec 21
84. Petrie MC. It cannot be cardiac failure because the heart is not enlarged on the chest X-ray. Eur J Heart Fail. 2003;5(2):117–9.
85. Pistolesi M, Miniati M, Bonsignore M, Andreotti F, Di Ricco G, Marini C. Factors affecting regional pulmonary blood flow in chronic ischemic heart disease. J Thorac Imaging. 1988;3(3):65–72.

86. Ketai LH, Godwin JD. A new view of pulmonary edema and acute respiratory distress syndrome. J Thorac Imaging. 1998;13(3):147–71.
87. Connolly MA. Black, white, and shades of gray: common abnormalities in chest radiographs. AACN Clin Issues. 2001;12(2):259–69 ; quiz 330-2.
88. Chakko S, Woska D, Martinez H, de Marchena E, Futterman L, Kessler KM, Myerberg RJ. Clinical, radiographic, and hemodynamic correlations in chronic congestive heart failure: conflicting results may lead to inappropriate care. Am J Med. 1991;90(3):353–9.
89. Collins SP, Lindsell CJ, Storrow AB, Abraham WT; ADHERE Scientific Advisory Committee, Investigators and Study Group. Prevalence of negative chest radiography results in the emergency department patient with decompensated heart failure. Ann Emerg Med 2006;47(1): 13–8. Epub 2005 Jun 20.

Chapter 10
Acute Decompensated Heart Failure: Treatment Guidelines

Daniel Fishbein

Treatment of ADHF: Review of ACCF/AHA, ESC and HFSA Guidelines

Comprehensive guidelines for the management of ADHF have been published including: the American College of Cardiology Foundation/American Heart Association (ACCF/AHA) Guidelines for the Management of Heart Failure [1], the Heart Failure Society of America (HFSA) Comprehensive Practice Guidelines [2, 3], and the European Society of Cardiology (ESC) Task Force Guidelines [4].

There are three phases in the evaluation and management of patients who present with ADHF including [2, 5, 6]:

1. Initial assessment, monitoring, treatment and disposition. This phase generally occurs in the emergency department (ED).
2. Ongoing assessment and treatment. This phase generally occurs in a critical care or telemetry unit. Goals of treatment are to relieve congestion, initiate and/or optimize guideline determined medical therapy (GDMT), and further evaluate and address reversible factors that cause or worsen heart failure.
3. Discharge planning and post-discharge follow up.

D. Fishbein, MD
University of Washington Medical Center, Department of Medicine, Division of Cardiology, 1959 NE Pacific Street, #356422, Seattle, WA 98195, USA
e-mail: dfishbein@cardiology.washington.edu

H. Eisen (ed.), *Heart Failure*, DOI 10.1007/978-1-4471-4219-5_10

Initial Assessment and Treatment in the Emergency Department

A number of important issues need to be addressed as part of the initial assessment of a patient who presents to the ED with the primary symptom of dyspnea. These issues need to be addressed concurrently and often, treatment needs to be initiated in parallel with the ongoing diagnostic evaluation:

1. Is the patient's condition immediately life-threatening because of hypoxia, respiratory failure, hypotension, systemic hypoperfusion, bradyarrhythmia and/or tachyarrhythmia? Does the patient need mechanical ventilation, intravenous vasoactive medications, an intra-aortic balloon pump or other mechanical circulatory support, ventricular pacing, or cardioversion?
2. Is the patient having an acute coronary syndrome precipitating heart failure? Does the patient need to go emergently to the cardiac catheterization laboratory for percutaneous coronary intervention (PCI)?
3. Does the patient have heart failure? Is there an alternative cause of symptoms?
4. Are there precipitating factors that have caused or contributed to acute heart failure decompensation?
5. Relieve symptoms rapidly while avoiding harm. Improvement in symptoms generally requires relief of pulmonary congestion and improvement in elevated blood pressure without causing hypotension, arrhythmia, electrolyte abnormality, renal dysfunction, myocardial injury or respiratory compromise.
6. Does the patient need to be admitted to the hospital (CCU or telemetry floor), observed further in the ED, admitted to an observation unit, or discharged to home?

Initial Triage

Patients who present with acute dyspnea need to be assessed for the presence of pulmonary or hemodynamic instability that may require emergent intervention. Patients who present with tachypnea, hypoxia not readily corrected with nasal oxygen, respiratory distress or mental status changes may need emergent intervention with noninvasive ventilation or endotracheal intubation. While arterial blood gas determination is not routine in the assessment of most patients presenting with ADHF, it should be obtained in the patient with impending respiratory failure or severe lung disease. Endotracheal intubation and mechanical ventilation should be considered in patients with respiratory acidosis.

In EHFS II, ACS was the precipitating factor in 42 % of patients who presented with new onset heart failure and 23 % of patients who had preexisting heart failure. Patients with ACS generally present with precordial chest pain [7]. A 12-lead ECG is a critical part of the early evaluation of patients with suspected ADHF as the presence of ST segment elevation (or new LBBB) in the setting of an elevated

troponin is an indication for emergent coronary intervention as outlined in recent consensus documents [1, 8]. Patients may have ST segment depression and /or T wave inversion that, combined with clinical symptoms suggestive of ischemia and elevated troponin, are indicative of ACS [9]. ST-T wave changes alone may not be diagnostic of coronary ischemia or infarction and may be observed in other conditions including acute pericarditis, early repolarization patterns, LBBB, LV hypertrophy, and Brugada syndrome [10]. The ECG is helpful in identifying underlying heart rhythm abnormalities which may need urgent treatment (e.g. atrial fibrillation with rapid ventricular response, ventricular tachycardia, heart block).

Abnormal ECG findings are not helpful in discriminating HF from other causes of dyspnea (sensitivity 0.5, specificity 0.78 and positive likelihood ratio of 2.2). Atrial fibrillation, however, has a specificity of 0.93 and a positive likelihood ratio of 3.8 [11]. However, it is unlikely for patients with systolic dysfunction to have an entirely normal ECG. In a screening study of 534 patients with suspected heart failure, 96 patients had systolic dysfunction on echocardiography. Of these, 90 had major electrocardiographic abnormalities (atrial fibrillation, previous myocardial infarction, left ventricular hypertrophy, bundle branch block, or left axis deviation); none had a normal electrocardiogram. Of 438 patients with normal left ventricular systolic function, 169 had major electrocardiographic abnormalities [12].

Patients with STEMI, acute decompensation of chronic heart failure or acute heart failure due to myocardial inflammation may present with hypotension, evidence of compromised end-organ perfusion and pulmonary congestion. These patients commonly have sinus tachycardia, hypotension, a narrow pulse pressure, and evidence of pulmonary and systemic venous congestion. This subset of critically ill patients may need inotropic and/or vasopressor support, pulmonary artery catheterization to guide therapy and mechanical support with an IABP, Impella, TandemHeart, or extracorporeal life support (ECLS) [8].

Determination of either BNP or NT-proBNP is recommended in patients with dyspnea and signs and symptoms consistent with heart failure. The use of either biomarker is most helpful when there is an intermediate pretest probability of heart failure and the values are either very low or very high. Age, gender, renal function and obesity may affect natriuretic peptide levels. Levels should not be interpreted in isolation but rather, in the context of the broader clinical evaluation.

A BNP level < 100 pg/mL has a sensitivity, specificity, negative predictive and positive predictive value of 90 %, 76 %, 79 %, and 89 %, respectively [13]. BNP levels tend to increase with age. In patients less than 70 years of age, a BNP level >400 pg/mL has a sensitivity of 60 %, specificity of 95 %, positive predictive value of 86 %, negative predictive value of 81 % and diagnostic accuracy of 82 %. In patients ≥ 70 years of age, a BNP level >400 pg/mL has a sensitivity of 65 %, specificity of 83 %, positive predictive value of 86 %, negative predictive value of 60 % and diagnostic accuracy of 72 % [14]. Approximately 75 % of patients who present with acute dyspnea will have either low (<100 pg/mL) or high (>400–500 pg/mL) BNP levels. In general, in patients who present to the ED with dyspnea, if the BNP is <100 pg/ml, heart failure is unlikely to be the cause of dyspnea. If the BNP is >500 pg/ml, HF is likely with a positive predictive value of 90 %.

With BNP levels between 100–500 pg/ml, alternative causes of increased BNP need to be considered including stable chronic LV dysfunction, RV failure due to cor pulmonale, acute pulmonary embolism or renal insufficiency. Patients may present with HF and normal BNP levels in the following settings: flash pulmonary edema within 1–2 h of onset, HF upstream from the left ventricle, (e.g., acute papillary muscle rupture with acute mitral regurgitation), and obesity. In patients with a body mass index >35 kg/m^2, a BNP cutoff of 60 pg/mL has been recommended to rule out and 200 pg/mL to rule in HF as the cause of acute dyspnea. In general, BNP is elevated in the setting of chronic renal insufficiency. It may be reasonable to recalibrate the BNP cutoff to 200–225 pg/mL in patients with an estimated glomerular filtration rate of <60 mL/min to rule out heart failure. BNP levels are lower in obese people with and without heart failure. There seems to be a linear decrease in BNP level with increasing BMI [15, 16]. In general, in patients with chronic heart failure, changes of >50 % from baseline represent worsening heart failure. However, significant variation in levels can occur in the same patient and individual differences in NP do not necessarily represent an acute clinical event. There is a substantial grey zone in interpreting the results [17].

An NT-proBNP <300 pg/ml has a 99 % negative predictive value to exclude heart failure in patients who present with dyspnea. This is independent of age and BMI [18]. An NT-proBNP >900 pg/mL has a sensitivity of 90 %, specificity of 85 % and positive predictive value of 76 % to predict heart failure as the cause of dyspnea [19]. Age stratification of NT-proBNP using cut points of 450, 900, and 1800 pg/ml for age groups of <50, 50–75, and >75 years, respectively reduces false-negative findings in younger patients, reduces false-positive findings in older patients, and improves the overall positive predictive value without a change in overall sensitivity or specificity. These cut-points have a 90 % sensitivity and 84 % specificity for acute HF [20, 21] and are predictive of acute heart failure across a wide range of BMIs [22].

Initial Treatment

The HFSA and ESC guidelines recommend that oxygen should be administered by nasal cannula or face mask in patients with hypoxia but is not recommended in the absence of hypoxia. The HFSA and ESC guidelines recommend the use of non-invasive positive pressure ventilation for patients with severe dyspnea and clinical evidence of pulmonary edema [2, 4]. The ESC guidelines specifically recommend non-invasive ventilation in patients with dyspnea, evidence of pulmonary edema and a respiratory rate of >20 breaths/minute.

The ESC Guidelines recommend that IV morphine sulfate (MS) should be considered, especially in anxious, restless or distressed patients to relieve these symptoms and improve breathlessness. However, the HFSA guidelines recommend that

if used at all, MS should be used with caution given recent data demonstrating an association between MS use and adverse outcomes.

Treatment with an intravenous loop diuretic is consistently recommended in the ACCF/AHA, ESC and HFSA guidelines as first line treatment in the initial management of patients with ADHF and that diuretic therapy should be initiated in the ED without delay [1, 2, 4]. Although there are no randomized placebo-controlled clinical trials to establish the safety and efficacy of diuretics in ADHF, extensive observational experience has shown that diuretics relieve congestion and improve symptoms. The impact of diuretic therapy on mortality has not been adequately studied.

The HFSA Guidelines do not make specific recommendations about initial diuretic dose. The ACCF/AHA Guidelines recommend that in patients already receiving a loop diuretic, the initial diuretic dose should equal or exceed their chronic oral daily dose and be given either as intermittent intravenous boluses or continuous infusion [1]. The ESC Guidelines recommend that an initial dose of furosemide 20–40 mg IV (or 0.5–1.0 mg bumetanide IV or 10–20 mg of torsemide IV) be given on admission. In patients with evidence of volume overload, a higher dose of parenteral diuretic may be considered based on renal function and history of chronic oral diuretic use. Continuous infusion may also be considered after an initial starting bolus dose. ESC recommends that the total furosemide dose should remain <100 mg in the first 6 h and 240 mg during the first 24 h [5].

Indications for Hospitalization

Recommendations for hospitalization from the HFSA Guidelines are summarized in Table 10.1 [2]. A recently published consensus document from the Society for Academic Emergency Medicine/Heart Failure Society of America Acute Heart Failure Working Group has suggested that ED patients with ADHF can be divided into three groups based on risk profile, presence of co-morbidities, initial response to therapy in the ED and barriers to self-care [23]. Patients at high risk for mortality or serious adverse events (those with low blood pressure, hypoxia, renal insufficiency or myocardial ischemia/infarction) should be admitted to the CCU.

Identifying Precipitating Causes of Acute HF Decompensation

An essential task in the evaluation of a patient who presents with acute decompensated heart failure is to identify new or chronic issues/conditions that may cause, precipitate or contribute to heart failure decompensation. This should be done early in the evaluation so that appropriate therapies can be initiated, symptoms can be

Table 10.1 Recommendations for hospitalizing patients presenting with ADHF

Recommendation	Clinical circumstance
Hospitalization recommended	Evidence of severely decompensated HF, including: Hypotension Worsening renal function Altered mentation
	Dyspnea at rest
	Typically reflected by resting tachypnea; less commonly reflected by oxygen saturation <90 %
	Hemodynamically significant arrhythmia; including new onset of rapid atrial fibrillation
	Acute coronary syndromes
Hospitalization should be considered	Worsened congestion
	Even without dyspnea
	Signs and symptoms of pulmonary or systemic congestion; even in the absence of weight gain
	Major electrolyte disturbance
	Associated comorbid conditions:
	Pneumonia
	Pulmonary embolus
	Diabetic ketoacidosis
	Symptoms suggestive of transient ischemic accident or stroke
	Repeated ICD firings
	Previously undiagnosed HF with signs and symptoms of systemic or pulmonary congestion

Reprinted from Lindenfeld et al. [2]

alleviated more rapidly, reversible myocardial dysfunction can be treated and recurrent heart failure hospitalizations can be prevented. Table 10.2 summarizes conditions that can cause or contribute to the development of acute decompensated heart failure.

Co-morbid conditions are common and play a significant role in hospitalization for ADHF. In the OPTIMIZE-HF registry, one or more precipitating factors were identified in 61.3 % of patients admitted with ADHF. The most common precipitating factors included: pneumonia/respiratory process (15.3 %), ischemia/acute coronary syndrome (14.7 %), arrhythmia (13.5 %), and poorly controlled hypertension (10.7 %). Nonadherence to medications was identified in 8.9 % and nonadherence to diet was identified in 5.2 % [24].

Coronary Artery Disease

Coronary artery disease is present in approximately 50–70 % of patients with ADHF [7, 25–30]. Patients may present with ACS complicated by heart failure or ADHF with underlying CAD.

Table 10.2 Possible precipitating causes of heart failure decompensation

Coronary artery disease
Myocardial ischemia
ACS
Mechanical complications of AMI (VSD, MR)
Valvular disease
Mitral regurgitation: worsening chronic or acute
Progressive aortic stenosis
Worsening tricuspid insufficiency
Aortic insufficiency
Endocarditis
Aortic dissection
Progressive cardiac dysfunction
Progression of underlying cardiac dysfunction
Physical, emotional or environmental stress
Cardiac toxins – alcohol, cocaine, methamphetamines, chemotherapy
RV pacing
Persistent tachycardia
Frequent PVCs
Myocardial disease
Lymphocytic myocarditis
Giant cell myocarditis
Post-partum cardiomyopathy
Sarcoid
Uncontrolled high blood pressure
Dietary and medication adherence
Excessive salt and water intake
Medication nonadherence
Iatrogenic volume expansion
Arrhythmia
Atrial fibrillation
Atrial flutter
Other supraventricular arrhythmia
Recurrent ventricular tachycardia
Bradycardia-sinus node dysfunction, heart block, AF with slow ventricular response
Recent onset LBBB
Non-cardiac conditions
Systemic infection: sepsis, pneumonia, URI, UTI, viral infection (especially influenza)
Renal insufficiency
Thyroid disorders
Anemia
COPD/asthma
Sleep apnea
Pulmonary embolism

(continued)

Table 10.2 (continued)

AV shunts
Urinary outlet obstruction
Tamponade
Iron deficiency
CVA
Depression, dementia, and cognitive impairment
Recent addition of medications with negative inotropic effects:
Calcium channel blockers: especially the non-dihydropyridines verapamil and diltiazem
Class Ia, Ic and III antiarrhythmic medications:
Quinidine, procainamide, disopyramide, flecainide, sotalol, propafenone, dronedarone
β-adrenergic blocking agents
Non-cardiac medications that promote sodium retention:
Nonsteroidal anti-inflammatory drugs
COX-2 inhibitors
Corticosteroids
Thiazolidinediones
Pregabalin
Chemotherapy
Anthracyclines
Monoclonal antibodies – Trastuzumab and Bevacizumab
Taxanes – paclitaxel and docetaxel
Cyclophosphamide
Small tyrosine kinase inhibitors – Sunitinib, sorafenib, imatinib

ACS Complicated by Heart Failure

Approximately 10–20 % of patients with ACS have associated heart failure on presentation and another 10 % of ACS patients develop heart failure during hospitalization. Patients with ACS due to a STEMI typically have chest pain, diagnostic ECG changes and high levels of biomarkers consistent with substantial myocardial injury [29]. Patients with heart failure complicating an STEMI (either on presentation or developing later after hospitalization) have significantly increased in-hospital and post-discharge mortality compared to patients without heart failure [29–32]. Patients with ACS who develop heart failure after admission are at greater risk than patients with ACS who have heart failure on presentation [30, 32]. The severity of heart failure measured by the Killip classification is a powerful predictor of mortality in patients with heart failure complicating ACS. Patients with Killip class II or III are 4 times more likely to die during hospitalization compared with Killip class I patients while patients with Killip class IV (cardiogenic shock) are 10 times more likely [30, 32]. Patients with heart failure and unstable angina have also been found have a significant fourfold increase in mortality compared to similar patients without HF [31].

The Global Registry of Acute Coronary Events (GRACE) enrolled 16,166 patients with ACS. Patients who presented with HF complicating ACS had lower rates of catheterization and PCI and were less likely patients receive β-blockers and statins [31]. In the National Registry of Myocardial Infarction (NRMI), patients with HF complicating ACS were less likely to receive aspirin, heparin, intravenous nitroglycerine and β-blockers compared to patients with ACS without heart failure. In addition, patients with heart failure were less likely to undergo PCI or CABG compared with patients without heart failure on presentation (40 % vs 20 %) [32].

An analysis of the Can Rapid Risk Stratification of Unstable Angina Patients Suppress Outcomes with Early Implementation of the American College of Cardiology/American Heart Association (ACC/AHA) Guidelines (CRUSADE) initiative (2.8 % of patients had HF) demonstrated that patients with a non-STEMI with heart failure with preserved EF had a significantly higher mortality rate than patients without HF and preserved systolic function and a similar mortality to patients with no HF and systolic dysfunction. Patients with both HF and systolic dysfunction had the highest mortality (1.5 % vs 5.7 % vs 5.8 % vs 10.7 %). Cardiac catheterization and PCI rates were lower for patients without heart failure with systolic dysfunction and with HF with or without systolic dysfunction. Patients with HF received aspirin, clopidogrel, glycoprotein IIb/IIIa inhibitors, heparin, B-blockers and statins less frequently than patients with no HF and preserved systolic function [33].

There is broad consensus that patients with HF complicating ACS should undergo urgent coronary angiography and coronary intervention in the catheterization laboratory [1, 2, 9, 34, 35].

ADHF with Underlying CAD

It has been estimated that 50–70 % of patients with ADHF have concomitant coronary artery disease. Registry data suggest that CAD is associated with higher in-hospital and post-discharge mortality rates. In the OPTIMIZE – Registry, in-hospital mortality rates were 3.75 % vs 2.9 % and post-discharge 60–90 day mortality rates were 9.2 vs 6.9 % in patients with CAD vs no CAD [36].

In multicenter registries of patients admitted with ADHF, rates of diagnostic coronary angiography are relatively low overall: OPTIMIZE –HF 8.7 % [36]; ADHERE 10 % [25]; EHFS 16 % [27]; and EHFS II 36.5 % (EHFS II reported angiography within a year of hospitalization) [7]. In OPTIMIZE-HF, 18.6 % of patients presenting with de novo heart failure underwent coronary angiography [36]. Rates of coronary revascularization were relatively low: ADHERE 8.1 % PCI, 1.8 % CABG [25]; EHFS PCI 4 %, CABG 3 % [27]; EHFS II PCI 8.4 %, CABG 1.8 % [7]; OPTIMIZE-HF 1.3 % PCI, 1.0 % CABG [37].

In OPTIMIZE-HF, patients with CAD who did not undergo revascularization had a higher post-discharge mortality compared to patients without CAD (10.6 vs

6.9 %). Patients who did undergo revascularization during HF hospitalization had a similar post-discharge mortality compared to patients without CAD [36].

The data from the OPTIMIZE-HF registry was analyzed to determine if the performance of coronary angiography during the index HF hospitalization had an impact on care and post-discharge outcome [37]. 8.7 % of all patients underwent coronary angiography. 27.5 % of patients who underwent angiography also had in-hospital revascularization. Patients with CAD who underwent angiography were more likely to be treated with aspirin, statins, B-blockers, and angiotensin converting enzyme inhibitors at the time of discharge. In patients with CAD, the use of in-hospital coronary angiography was associated with a significantly lower mortality and rate of rehospitalization in the first 60–90 days after adjustment for multiple comorbidities (mortality HR 0.31; $p = 0.004$; death or rehospitalization HR 0.65; $p = 0.003$) when compared to patients with CAD who did not undergo coronary angiography. This data suggests that early coronary angiography and revascularization may be beneficial in patients admitted to the hospital with CAD and ADHF.

These results were registry based and may not account for unmeasured variables or selection biases. In the randomize Surgical Treatment for Ischemic Heart Failure (STICH) trial, there was no difference in death from any cause in patients with LVEF ≤ 35 % and coronary artery disease amenable to CABG randomized to medical therapy or medical therapy plus CABG on intention to treat analysis. However, when early crossovers were considered, "on-therapy" CABG was associated with a lower mortality at 5 years (25 % vs 42 %; HR 0.50; p=0.008). Myocardial viability or inducible myocardial ischemia did not identify patients with a differential survival benefit from CABG compared to medical therapy alone [38–40].

Practice guidelines provide recommendations on the use of coronary angiography in the evaluation of patients with chronic heart failure. However, they do not give specific recommendations about the timing of invasive evaluation of coronary anatomy and specifically do not provide recommendations about indications for coronary angiography in patients hospitalized for ADHF. Given the absence of definitive data concerning coronary angiography and revascularization in ADHF, decisions should be individualized based on patient preference, symptoms, clinical presentation, comorbidities, candidacy for revascularization and willingness to undergo revascularization [1, 2]. In general, coronary angiography is recommended for patients with heart failure and symptoms suggestive of angina to assess for the possibility of revascularization. Non-invasive imaging *or* coronary angiography is recommended for patients with new onset heart failure, no angina and unknown CAD status and patients with new or worsening heart failure without obvious cause, no angina and known CAD. Recommendations from the HFSA Guidelines for the evaluation for CAD in patients with ADHF are reviewed in Table 10.3 [2].

Uncontrolled Hypertension

Hypertension is an important precipitant of decompensated heart failure, especially among blacks, women and patients with HFpEF. In the OPTIMIZE-HF registry, poorly controlled hypertension was a precipitating factor in 10.7 % of patients [24]. In

Table 10.3 HFSA Guidelines for the evaluation for CAD in patients with ADHF

Ongoing assessment for risk factors for CAD is recommended in all patients with chronic HF regardless of LVEF. (Strength of Evidence = A)
It is recommended that the diagnostic approach for CAD be individualized based on patient preference and comorbidities, eligibility, symptoms suggestive of angina and willingness to undergo revascularization. (Strength of Evidence = C)
It is recommended that patients with HF and symptoms suggestive of angina undergo cardiac catheterization with coronary angiography to assess for potential revascularization. (Strength of Evidence = B)
It is recommended that, at the initial diagnosis of HF and any time symptoms worsen without obvious cause, patients with HF, no angina, and known CAD should undergo risk assessment that may include noninvasive stress imaging and/or coronary angiography to assess severity of coronary disease and the presence of ischemia. (Strength of Evidence = C)
It is recommended that patients with HF, no angina, and unknown CAD status who are at high risk for CAD should undergo noninvasive stress imaging and/or coronary angiography to assess severity of coronary disease and the presence of ischemia. (Strength of Evidence = C)
In patients with HF, no angina, and unknown CAD status who are at low risk for CAD noninvasive evaluation should be considered and coronary angiography may be considered. (Strength of Evidence = C)
Any of the following imaging tests should be considered to identify inducible ischemia or viable myocardium:
Exercise or pharmacologic stress myocardial perfusion imaging
Exercise or pharmacologic stress echocardiography
Cardiac magnetic resonance imaging (MRI)
Positron emission tomography scanning (PET) (Strength of Evidence = B)

Reprinted from Lindenfeld et al. [2]

the ADHERE Registry, almost 50 % of patients admitted with decompensated heart failure has an initial blood pressure of >140/90 mmHg [25]. Medical non-adherence with antihypertensive medications may result in an abrupt increase in blood pressure and precipitate worsening heart failure or acute pulmonary edema [1, 41].

Arrhythmia

Arrhythmia was a precipitating factor of heart failure decompensation in 13.5 % of patients enrolled in the OPTIMIZE-HF registry [24]. Atrial fibrillation (AF) is present in approximately 30–40 % of patients hospitalized with ADHF [7, 27, 35, 42–45]. New onset or newly diagnosed AF has been reported to occur in approximately 20 % percent of patients admitted with ADHF [35, 44, 45]. AF is associated with the loss of coordinated atrial contraction. In patients with heart failure and especially in patients with HFpEF, this may be associated with significantly decreased left ventricular filling, increased PCWP and decreased cardiac output. In AF with rapid ventricular response, ventricular filling is further compromised and myocardial ischemia and/or pulmonary edema may be precipitated [46, 47].

Atrial flutter, other supraventricular tachyarrhythmias and ventricular tachycardia may also precipitate acute heart failure. Frequent premature ventricular contractions (PVCs) may be associated with a distinct cardiomyopathy (PVC-related

cardiomyopathy) or worsening heart failure and LV dysfunction in the setting of a preexisting cardiomyopathy. In general, a PVC burden of approximately 20–24 % of all QRS complexes on a 24 h Holter monitor identifies a patient with LV systolic dysfunction who may improve with PVC ablation [48–51].

Medication and Dietary Non-adherence

Excessive sodium and fluid intake may contribute to heart failure decompensation. In the OPTIMIZE-HF Registry, non-adherence to diet was identified as a precipitating factor in 5.2 % of patients hospitalized for ADHF. Non-adherence to medication was a precipitating factor in 8.9 % of patients [24]. Non-adherence with diet or HF medication has been reported to be an even more common precipitating factor in some single-center studies [52, 53]. Factors that have been associated with medical non-adherence include more advanced NYHA functional class, minority ethnicity, lower financial status, and lack of perceived social support. Patient perception of barriers to medication adherence may also be fundamental to poor adherence. Frequently reported barriers include: forgetting to take medication, cost, too many pills taken per day, too frequent medication schedule and the belief that skipping one dose of medication will not have an adverse impact on the patient's condition [54, 55].

Patients with heart failure commonly have excessive and bothersome thirst mediated by activation of central arterial volume receptors and increased levels of angiotensin II both of which stimulate thirst centers in the brain. This leads to excessive sodium and water intake [56–59]. This is a particularly difficult issue in patients with severe heart failure who are not able to be treated with an ACE inhibitor or ARB at reasonable or target dose. In addition, older patients commonly have chemosensory deficits that decrease salt detection and sensitivity and increase salt affinity and intake. Salt affinity may be modifiable toward normal after >2 months of sodium restriction [60]. Patients may also be unaware of the salt content of foods they are consuming or may feel that they do not need to limit sodium intake. A careful review of the patient's history of dietary intake of sodium and free water (including "hidden" sources of free water such as fruit) is an important part of the assessment of patients admitted with ADHF.

Pneumonia or Other Pulmonary Processes

Pneumonia and other acute respiratory processes were the most common precipitating factor (15.3 %) identified in patients hospitalized for ADHF in the OPTIMIZE-HF registry [24]. Pulmonary infections may alter pulmonary function, cause hypoxia, and increase metabolic demands and are poorly tolerated by patients with heart failure. Pulmonary congestion in a patient with chronic obstructive pulmonary disease can compromise already marginal pulmonary function. Patients with heart failure are hypercoagulable and pulmonary embolus

may be a cause of HF decompensation [61–64]. Sleep disordered breathing is very common in patients with heart failure. It may worsen heart failure by causing hypoxia, increasing sympathetic nervous system activation and causing or worsening systemic hypertension. Sleep disordered breathing has also been associated with left ventricular remodeling, endothelial dysfunction with progression of coronary artery disease, left ventricular hypertrophy and atrial fibrillation [65–67].

Infection

Systemic bacterial or viral infection (pneumonia, urinary tract infection, influenza) are common precipitants of worsening heart failure. Infections increase metabolic demands. In addition, sepsis can cause reversible myocardial dysfunction likely mediated by release of pro-inflammatory cytokines [68, 69].

Thyroid Disease

Hypothyroidism and hyperthyroidism can cause or worsen heart failure. All patients seen for ADHF should have thyroid function studies obtained on admission. Approximately 20 % of patients admitted with ADHF are treated for thyroid disease and should have their therapy reevaluated during hospitalization [70, 71]. Amiodarone-induced hyperthyroidism (AIT) can cause severe worsening of heart failure with or without new or worsening arrhythmias and can be difficult to treat. The clinical presentation of AIT is variable and is often similar to other forms of thyrotoxicosis. However, AIT often occurs in elderly patients and may be "apathetic" with atypical symptoms such as reduced appetite and depression and absence of hyperactivity, tremor, nervousness and heat intolerance [72].

Medications

A number of non-cardiac medications can precipitate worsening heart failure. Nonsteroidal anti-inflammatory drugs and COX-2 inhibitors inhibit the physiologic production of vasodilatory and natriuretic prostanoids in the kidney and promote sodium and water retention, worsen renal function, inhibit the effect of ACE inhibitors, contribute to diuretic resistance and are associated with a significantly increased risk of hospitalization for heart failure [73].

The thiazolidinediones (TZD), (pioglitazone and rosiglitazone) used to treat diabetes, have been associated with the development of lower extremity edema and new or worsening heart failure [74]. These side effects are primarily due to fluid retention caused by TZD stimulation of the peroxisome proliferator-activated receptor-gamma (PPARγ). PPARγ-mediated activation of the collecting duct epithelium's sodium channel (ENaC) and stimulation of sodium transporters

in the proximal tubule contribute to salt and water retention [75, 76]. In addition, TZDs reduce systemic vascular resistance and may cause fluid extravasation by exposing the capillaries of the lower extremities to higher perfusion pressures. TZDs also increase the concentration of vascular endothelial growth factor which is a potent inducer of vascular permeability which may predispose patients to edema [77].

Insulin can also cause sodium retention mediated by stimulation of a broad range of sodium transporters in the proximal tubule, loop of Henle and distal tubule [74]. Pregabalin, which is frequently used to treat diabetic peripheral neuropathic pain, has also been reported to precipitate heart failure decompensation [78].

Cardiotoxicity is a common complication of many conventional and targeted biological anti-cancer medications [79–83]. Cocaine, excessive alcohol intake, and methamphetamine are associated with worsening heart failure [84–89].

A number of cardiac medications have negative inotropic properties and can worsen heart failure. Recent initiation or uptitration of β-blockers has been associated with worsening heart failure, especially in patients with severe ventricular dysfunction and those recently treated with inotropic agents. Calcium channel blockers (CCBs), especially the non-dihydropyridine CCBs, have been associated with worsening heart failure. A large number of antiarrhythmic agents may also precipitate worsening heart failure including quinidine, procainamide, disopyramide, flecainide, sotalol, propanone, and dronedarone.

Right Ventricular (RV) Pacing

Right ventricular pacing can lead to abnormal electrical and mechanical activation patterns (referred to as ventricular "dyssynchrony") which lead to adverse effects on left ventricular performance and hemodynamics, subsequent adverse effects on cardiac structure and function, and clinical heart failure.

Patients with a single lead pacemaker or ICD may develop gradually progressive sinus bradycardia in response to beta blocker or amiodarone therapy and present with worsening heart failure in the setting of recent onset ventricular pacing. A similar scenario may be seen in patients who develop atrial fibrillation with a slow ventricular response in the setting of beta blockade or amiodarone therapy. These patients may improve by pacemaker reprogramming that minimizes RV pacing or an upgrade to a device that provides biventricular pacing [90, 91].

Renal Dysfunction

Renal dysfunction is common in patients with ADHF. In the ADHERE registry, chronic renal insufficiency was reported in 30 % of patients and 21 % had a creatinine >2.0 mg/dL [25]. In OPTIMIZE-HF, the mean creatinine was 1.8 mg/dL [92].

Elevated BUN and creatinine may be manifestations of renal hypoperfusion in the setting of low cardiac output, high filling pressures and/or neurohormonal activation. In HF, renal cortical blood flow is especially decreased and tubulointerstitial damage may develop due to decreased local renal perfusion and increased venous congestion. Albuminuria can occur in heart failure and is a manifestation of both a loss of glomerular integrity and tubular damage. A high albumin load may also contribute to tubular damage [93]. In addition, patients with heart failure commonly have risk factors for both cardiac and renal disease including diabetes and hypertension that may contribute to renal insufficiency independent of hemodynamic derangements from heart failure. A gradual or acute reduction in renal function will decrease renal clearance of sodium and water, worsen diuretic resistance, contribute to inadequate blood pressure control, contribute to hyperkalemia, and worsen anemia all of which will contribute to worsening HF.

Benign prostatic hypertrophy is common in men over the age of 50 years and may contribute to urinary obstruction, impaired renal function and worsening heart failure in men with ADHF. The prevalence of histologically diagnosed prostatic hyperplasia increases from 40 to 50 percent in men age 51 to 60 years, to over 80 percent in men older than age 80 years [94]. A population based study from Olmstead County, Minnesota found that moderate to severe lower urinary tract obstructive symptoms were present in 13 % of men 40–49 years and 28 % of those older than 70 years [95]. An evaluation for urinary obstruction can easily performed using bladder scanning. We have found that routine bladder scanning of men hospitalized with ADHF who have an elevated creatinine or diuretic resistance is helpful in identifying lower urinary tract obstruction. Relief of urinary obstruction with placement of a urinary catheter commonly results in improvements in renal function, diuretic resistance, pulmonary and systemic venous congestion and heart failure symptoms..

Ongoing Assessment and Treatment

The goals of treatment for patients admitted with ADHF from the HFSA guidelines are summarized in Table 10.4 [2].

Most patients have a significant improvement within 1–6 h after diuretic administration [96]. However, when diuresis is inadequate to relieve symptoms, the ACCF/AHA, HFSA, and ESC guidelines recommend giving a higher dose of diuretic or adding a second thiazide or thiazide-like diuretic (hydrochlorothiazide, chlorothiazide or metolazone). The HFSA and ESC guidelines also recommend considering use of a continuous infusion of a loop diuretic. The ACCF/AHA guidelines note that low-dose dopamine added to loop diuretic therapy may be considered to improve diuresis and preserve renal function.

The ACCF/AHA, HFSA, and ESC guidelines suggest that veno-venous ultrafiltration may be considered in volume overloaded patients to treat congestive symptoms and relieve volume overload. The ACCF/AHA guidelines suggest that UF may

Table 10.4 HFSA treatment goals for patients admitted for ADHF

HFSA treatment goals for patients admitted for ADHF [2]
Improve symptoms, especially congestion and low-output symptoms Restore normal oxygenation
Optimize volume status
Identify etiology
Identify and address precipitating factors
Optimize chronic oral therapy
Minimize side effects
Identify patients who might benefit from revascularization
Identify patients who might benefit from device therapy
Identify risk of thromboembolism and need for anticoagulant therapy
Educate patients concerning medications and self-management of HF
Consider and, where possible, initiate a disease management program

Reprinted from Lindenfeld et al. [2]
HFSA Heart Failure Society of America

be appropriate "for patients with refractory congestion not responding to medical therapy". The HFSA guidelines state that UF "may be considered in lieu of diuretics".

The ACCF/ACC, HFSA, and ESC guidelines emphasize the importance of careful monitoring of vital signs, signs and symptoms of congestion, urine output, electrolytes and renal function after initiation of diuretic therapy. Excessive diuresis may result in hypotension and a reduction in cardiac output. During loop diuretic-induced natriuresis, intravascular volume is generally maintained by vascular "refilling' or re-equilibration as interstitial fluid moves from the interstitial space to the intravascular space. The rate of refilling varies among patients. During brisk diuresis, it is possible for the rate of diuresis to exceed the rate of refilling. This may result in low intravascular volume, inadequate cardiac filling, and hypotension despite persistent volume overload. Patients with HPpEF are at greater risk of diuretic-induced hypotension – these patients tend to be less volume overloaded and have a steep diastolic filling curve so that moderate reductions in intravascular volume may result in significant reductions in cardiac filling and cardiac output. Patients with infiltrative or restrictive cardiomyopathy may have diuretic induced hypotension in the setting of continued volume overload as elevated ventricular filling pressures are needed to maintain normal cardiac output [2, 97]. Diuresis that results in a decrease in ventricular filling pressures makes patients more sensitive to the hypotensive effects of other vasodilators used in the routine treatment of heart failure.

The ACCF/AHA and HFSA guidelines recommend that in the absence of symptomatic hypotension, intravenous nitroglycerine, nitroprusside or nesiritide may be considered as an addition to diuretic therapy for relief of dyspnea in patients with ADHF. Blood pressure should be monitored frequently and the vasodilator should be stopped or dose decreased if symptomatic hypotension occurs. The ESC Guidelines recommend NTG or nitroprusside in patients with pulmonary

congestion/edema provided SBP >110 mmHg to reduce pulmonary capillary wedge pressure. Caution is advised when using nitroprusside in patients with acute myocardial infarction.

The ACCF/AHA and HFSA guidelines suggest that the use of the intravenous inotropes dobutamine, milrinone, and dopamine (ACCF/AHA only) be limited to patients with LV dilation, LV systolic dysfunction and evidence of low cardiac output or end-organ dysfunction. Commonly, these patients will have low blood pressure and evidence of hypoperfusion manifest by cold clammy skin, cool distal extremities, decreased urine output and altered mentation. These agents may also be appropriate in patients who have evidence of elevated filling pressures and an inadequate response to diuretics and parenteral vasodilators or who have worsening renal function in response to diuretic therapy [2, 98]. The guidelines emphasize that there is no evidence to support the routine use of inotropic therapy in patients with acute decompensated heart failure. Patients treated with an inotrope should have frequent blood pressure monitoring and continuous cardiac rhythm monitoring as treatment with these agents has been associated with hypotension and an increased risk of atrial and ventricular arrhythmias. In the ESC guidelines, inotropic agents are not recommended unless the patient is hypotensive (systolic blood pressure of <85 mmHg) and has evidence of hypoperfusion.

The ACCF/AHA guidelines recommend that guideline determined medical therapy (GDMT) including ACEI or ARB, β-blocker and MRA be continued in patients with HFrEF hospitalized with ADHF in the absence of hemodynamic instability, worsening renal function or hypokalemia. In addition, the ACCF/AHA guidelines recommend that medications on admission be reassessed during the ADHF hospitalization and that GDMT be initiated in patients who have HFrEF who are not receiving appropriate GDMT. The HFSA guidelines recommend that "near optimal" pharmacologic therapy, including ACEI and β-blocker, be achieved during the heart failure hospitalization. The ESC guidelines recommend that ACEI or ARB, β-blocker, and MRA be initiated and up-titrated as appropriate in patients with HFrEF and that digoxin may provide symptom benefit and reduce the risk of HF hospitalization in patients with severe systolic HF.

The HFSA guidelines recommend fluid restriction of <2 L/day in patients with ADHF with moderate hyponatremia (serum sodium <130 mEq/L). Stricter fluid restriction may be considered in patients with more severe hyponatremia (serum sodium <125 mEq/L). The ACCF/AHA guidelines recommend fluid restriction and optimization of medications that modulate the RAAS and decrease thirst in patients hospitalized for ADHF who have hyponatremia. These guidelines also recommend consideration of a vasopressin antagonist in patients hospitalized with ADHF who have persistent severe hyponatremia and volume overload (hypervolemic hyponatremia) who are at risk for or are having cognitive symptoms despite water restriction and optimization of GDMT.

The ACCF/AHA and ECS guidelines do not recommend the routine use of invasive hemodynamic monitoring with pulmonary artery catheterization in patients hospitalized for ADHF. PA catheterization should be considered in a patient: who is refractory to pharmacologic therapy; who has persistent clinically significant

hypotension; who has significantly worsening renal function in response to therapy; or whose volume status and cardiac filling pressures are uncertain.

The ACCF/AHA, ECS and HFSA guidelines all recommend that patients hospitalized with ADHF who are not already anticoagulated receive venous thromboembolism (VTE) prophylaxis with an anticoagulant medication provided there are no contraindications to anticoagulation and in whom the risk-benefit ratio is favorable (ACCF/AHA). The HFSA guidelines recommend VTE prophylaxis with a mechanical device (intermittent pneumatic compression devices or graded compression stockings) in patients hospitalized with ADHF who have a contraindication to anticoagulation.

References

1. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey Jr DE, Drazner MH, et al. American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. Circulation. 2013;128(16):e240–327. doi:10.1161/CIR.0b013e31829e8776. Epub 2013 Jun 5.
2. Lindenfeld J, Albert NM, Boehmer JP, Collins SP, Ezekowitz JA, Givertz MM, et al. Heart Failure Society of America, HFSA 2010 Comprehensive Heart Failure Practice Guideline. Section 12: Evaluation and Management of Patients with Acute Decompensated Heart Failure. J Card Fail. 16(6):e131–56. doi:10.1016/j.cardfail.2010.04.004.
3. Givertz MM, Teerlink JR, Albert NM, Westlake Canary CA, Collins SP, Colvin-Adams M, et al. Acute decompensated heart failure: update on new and emerging evidence and directions for future research. J Card Fail. 2013;19(6):371–89. doi:10.1016/j.cardfail.2013.04.002.
4. McMurray JJ, Adamopoulos S, Anker SD, Auricchio A, Böhm M, Dickstein K, et al; Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology, Bax JJ, Baumgartner H, Ceconi C, Dean V, Deaton C, et al; ESC Committee for Practice Guidelines. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. Eur J Heart Fail. 2012;14(8):803–69. doi: 10.1093/eurjhf/hfs105. No abstract available. Erratum in: Eur J Heart Fail. 2013;15(3):361.
5. Dickstein K, Cohen-Solal A, Filippatos G, JJ MM, Ponikowski P, PA P-W, et al. ESC Committee for Practice Guidelines (CPG). ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2008: the Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2008 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association of the ESC (HFA) and endorsed by the European Society of Intensive Care Medicine (ESICM). Eur Heart J. 2008;29(19):2388–442. doi:10.1093/eurheartj/ehn309. Epub 2008 Sep 17.
6. Weintraub NL, Collins SP, Pang PS, Levy PD, Anderson AS, Arslanian-Engoren C, et al; American Heart Association Council on Clinical Cardiology and Council on Cardiopulmonary, Critical Care, Perioperative and Resuscitation. Acute heart failure syndromes: emergency department presentation, treatment, and disposition: current approaches and future aims: a scientific statement from the American Heart Association. Circulation. 2010;122(19):1975–96. doi: 10.1161/CIR.0b013e3181f9a223. Epub 2010 Oct 11.

7. Nieminen MS, Brutsaert D, Dickstein K, Drexler H, Follath F, Harjola VP, et al. EuroHeart Survey Investigators; Heart Failure Association, European Society of Cardiology. EuroHeart Failure Survey II (EHFS II): a survey on hospitalized acute heart failure patients: description of population. Eur Heart J. 2006;27(22):2725–36. Epub 2006 Sep 25.
8. O'Gara PT, Kushner FG, Ascheim DD, Casey DE Jr, Chung MK, et al. American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation. 2013;127(4):e362–425. doi: 10.1161/CIR.0b013e3182742cf6. Epub 2012 Dec 17. No abstract available. Erratum in: Circulation. 2013 Dec 24;128(25):e481.
9. Anderson JL, Adams CD, Antman EM, Bridges CR, Califf RM, Casey DE Jr, et al. American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. 2012 ACCF/AHA focused update incorporated into the ACCF/AHA 2007 guidelines for the management of patients with unstable angina/non-ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation. 2013;127(23):e663–828. doi: 10.1161/CIR.0b013e31828478ac. Epub 2013 Apr 29. No abstract available. Erratum in: Circulation. 2013 Jun 18;127(24):e863–4.
10. Thygesen K, Alpert JS, White HD. Joint ESC/ACCF/AHA/WHF Task Force for the Redefinition of Myocardial Infarction, Jaffe AS, Apple FS, Galvani M, Katus HA, Newby LK, Ravkilde J, et al. Universal definition of myocardial infarction. Circulation. 2007;116(22):2634–53. Epub 2007 Oct 19.
11. Wang CS, FitzGerald JM, Schulzer M, Mak E, Ayas NT. Does this dyspneic patient in the emergency department have congestive heart failure? JAMA. 2005;294(15):1944–56.
12. Davie AP, Francis CM, Love MP, Caruana L, Starkey IR, Shaw TR, et al. Value of the electrocardiogram in identifying heart failure due to left ventricular systolic dysfunction. BMJ. 1996;312(7025):222.
13. Maisel AS, Krishnaswamy P, Nowak RM, McCord J, Hollander JE, Duc P, et al. Breathing Not Properly Multinational Study Investigators. Rapid measurement of B-type natriuretic peptide in the emergency diagnosis of heart failure. N Engl J Med. 2002;347(3):161–7.
14. Maisel AS, Clopton P, Krishnaswamy P, Nowak RM, McCord J, Hollander JE, et al. BNP Multinational Study Investigators. Impact of age, race, and sex on the ability of B-type natriuretic peptide to aid in the emergency diagnosis of heart failure: results from the Breathing Not Properly (BNP) multinational study. Am Heart J. 2004;147(6):1078–84.
15. Wang TJ, Larson MG, Levy D, Benjamin EJ, Leip EP, Wilson PW, Vasan RS. Impact of obesity on plasma natriuretic peptide levels. Circulation. 2004;109(5):594–600.
16. Peacock WF, Mueller C, Disomma S, Maisel A. Emergency department perspectives on B-type natriuretic peptide utility. Congest Heart Fail 2008;14(4 Suppl 1):17-20. Review.
17. Maisel A, Mueller C, Adams Jr K, Anker SD, Aspromonte N, Cleland JG, et al. State of the art: using natriuretic peptide levels in clinical practice. Eur J Heart Fail. 2008;10(9):824–39. doi:10.1016/j.ejheart.2008.07.014. Epub 2008 Aug 29.
18. Bayes-Genis A, Lloyd-Jones DM, van Kimmenade RR, Lainchbury JG, Richards AM, Ordoñez-Llanos J, et al. Effect of body mass index on diagnostic and prognostic usefulness of amino-terminal pro-brain natriuretic peptide in patients with acute dyspnea. Arch Intern Med. 2007;167(4):400–7.
19. Januzzi Jr JL, Camargo CA, Anwaruddin S, Baggish AL, Chen AA, Krauser DG, et al. The N-terminal Pro-BNP investigation of dyspnea in the emergency department (PRIDE) study. Am J Cardiol. 2005;95(8):948–54.
20. Januzzi Jr JL, Chen-Tournoux AA, Moe G. Amino-terminal pro-B-type natriuretic peptide testing for the diagnosis or exclusion of heart failure in patients with acute symptoms. Am J Cardiol. 2008;101(3A):29–38. doi:10.1016/j.amjcard.2007.11.017.
21. Collins SP, Lindsell CJ, Storrow AB, Abraham WT. ADHERE Scientific Advisory Committee, Investigators and Study Group. Prevalence of negative chest radiography results

in the emergency department patient with decompensated heart failure. Ann Emerg Med. 2006;47(1):13–8. Epub 2005 Jun 20.
22. Januzzi JL, van Kimmenade R, Lainchbury J, Bayes-Genis A, Ordonez-Llanos J, Santalo-Bel M, et al. NT-proBNP testing for diagnosis and short-term prognosis in acute destabilized heart failure: an international pooled analysis of 1256 patients: the International Collaborative of NT-proBNP Study. Eur Heart J. 2006;27(3):330–7. Epub 2005 Nov 17.
23. Collins S, Storrow AB, Albert NM, Butler J, Ezekowitz J, Felker GM, et al. SAEM/HFSA Acute Heart Failure Working Group. Early management of patients with acute heart failure: state of the art and future directions. A consensus document from the society for academic emergency medicine/heart failure society of America acute heart failure working group. J Card Fail. 2015;21(1):27–43. doi: 10.1016/j.cardfail.2014.07.003. Epub 2014 Jul 18.
24. Fonarow GC, Abraham WT, Albert NM, Stough WG, Gheorghiade M, Greenberg BH, et al. OPTIMIZE-HF Investigators and Hospitals. Factors identified as precipitating hospital admissions for heart failure and clinical outcomes: findings from OPTIMIZE-HF. Arch Intern Med. 2008;168(8):847–54. doi:10.1001/archinte.168.8.847.
25. Adams KF, Fonarow GC, Emerman CL, LeJemtel TH, Costanzo MR, Abraham WT, et al. ADHERE Scientific Advisory Committee and Investigators. Characteristics and outcomes of patients hospitalized for heart failure in the United States: rationale, design, and preliminary observations from the first 100,000 cases in the Acute Decompensated Heart Failure National Registry (ADHERE). Am Heart J. 2005;149(2):209–16.
26. Fonarow GC, Heywood JT, Heidenreich PA, Lopatin M, Yancy CW. ADHERE Scientific Advisory Committee and Investigators. Temporal trends in clinical characteristics, treatments, and outcomes for heart failure hospitalizations, 2002 to 2004: findings from Acute Decompensated Heart Failure National Registry (ADHERE). Am Heart J. 2007;153(6):1021–8.
27. Cleland JG, Swedberg K, Follath F, Komajda M, Cohen-Solal A, Aguilar JC, et al. Study Group on Diagnosis of the Working Group on Heart Failure of the European Society of Cardiology. The EuroHeart Failure survey programme-- a survey on the quality of care among patients with heart failure in Europe. Part 1: patient characteristics and diagnosis. Eur Heart J. 2003;24(5):442–63.
28. Fonarow GC, Abraham WT, Albert NM, Stough WG, Gheorghiade M, Greenberg BH, et al. OPTIMIZE-HF Investigators and Hospitals. Age- and gender-related differences in quality of care and outcomes of patients hospitalized with heart failure (from OPTIMIZE-HF). Am J Cardiol. 2009;104(1):107–15. doi:10.1016/j.amjcard.2009.02.057.
29. Gheorghiade M, Sopko G, De Luca L, Velazquez EJ, Parker JD, Binkley PF, et al. Navigating the crossroads of coronary artery disease and heart failure. Circulation. 2006;114(11):1202–13.
30. Flaherty JD, Bax JJ, De Luca L, Rossi JS, Davidson CJ, Filippatos G, et al. Acute Heart Failure Syndromes International Working Group. Acute heart failure syndromes in patients with coronary artery disease early assessment and treatment. J Am Coll Cardiol. 2009;53(3):254–63. doi: 10.1016/j.jacc.2008.08.072.
31. Steg PG, Dabbous OH, Feldman LJ, Cohen-Solal A, Aumont MC, López-Sendón J, Global Registry of Acute Coronary Events Investigators, et al. Determinants and prognostic impact of heart failure complicating acute coronary syndromes: observations from the Global Registry of Acute Coronary Events (GRACE). Circulation. 2004;109(4):494–9. Epub 2004 Jan 26.
32. Wu AH, Parsons L, Every NR, Bates ER. Second National Registry of Myocardial Infarction. Hospital outcomes in patients presenting with congestive heart failure complicating acute myocardial infarction: a report from the Second National Registry of Myocardial Infarction (NRMI-2). J Am Coll Cardiol. 2002;40(8):1389–94.
33. Spencer FA, Meyer TE, Gore JM, Goldberg RJ. Heterogeneity in the management and outcomes of patients with acute myocardial infarction complicated by heart failure: the National Registry of Myocardial Infarction. Circulation. 2002;105(22):2605–10.

34. Cuffe MS, Califf RM, Adams KF Jr, Benza R, Bourge R, Colucci WS, et al. Outcomes of a Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic Heart Failure (OPTIME-CHF) Investigators. Short-term intravenous milrinone for acute exacerbation of chronic heart failure: a randomized controlled trial. JAMA. 2002;287(12):1541–7.
35. McManus DD, Saczynski JS, Lessard D, Kinno M, Pidikiti R, Esa N, et al. Recent trends in the incidence, treatment, and prognosis of patients with heart failure and atrial fibrillation (the Worcester Heart Failure Study). Am J Cardiol. 2013;111(10):1460–5. doi:10.1016/j.amjcard.2013.01.298.
36. Rossi JS, Flaherty JD, Fonarow GC, Nunez E, Gattis Stough W, Abraham WT, et al. Influence of coronary artery disease and coronary revascularization status on outcomes in patients with acute heart failure syndromes: a report from OPTIMIZE-HF (Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure). Eur J Heart Fail. 2008;10(12):1215–23. doi:10.1016/j.ejheart.2008.09.009. Epub 2008 Nov 8. Now #62.
37. Flaherty JD, Rossi JS, Fonarow GC, Nunez E, Stough WG, Abraham WT, et al. Influence of coronary angiography on the utilization of therapies in patients with acute heart failure syndromes: findings from Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure (OPTIMIZE-HF). Am Heart J. 2009n;157(6):1018–25. doi:10.1016/j.ahj.2009.03.011. Epub 2009 Apr 23.
38. Velazquez EJ, Lee KL, Deja MA, Jain A, Sopko G, Marchenko A, STICH Investigators, et al. Coronary-artery bypass surgery in patients with left ventricular dysfunction. N Engl J Med. 2011;364(17):1607–16. doi:10.1056/NEJMoa1100356. Epub 2011 Apr 4.
39. Bonow RO, Maurer G, Lee KL, Holly TA, Binkley PF, Desvigne-Nickens P, STICH Trial Investigators, et al. Myocardial viability and survival in ischemic left ventricular dysfunction. N Engl J Med. 2011;364(17):1617–25. doi:10.1056/NEJMoa1100358. Epub 2011 Apr 4.
40. Panza JA, Holly TA, Asch FM, She L, Pellikka PA, Velazquez EJ. Inducible myocardial ischemia and outcomes in patients with coronary artery disease and left ventricular dysfunction. J Am Coll Cardiol. 2013;61(18):1860–70. doi:10.1016/j.jacc.2013.02.014. Epub 2013 Mar 7.
41. Gandhi SK, Powers JC, Nomeir AM, Fowle K, Kitzman DW, Rankin KM, Little WC. The pathogenesis of acute pulmonary edema associated with hypertension. N Engl J Med. 2001;344(1):17–22.
42. Fonarow GC, Stough WG, Abraham WT, Albert NM, Gheorghiade M, Greenberg BH, OPTIMIZE-HF Investigators and Hospitals. et al. Characteristics, treatments, and outcomes of patients with preserved systolic function hospitalized for heart failure: a report from the OPTIMIZE-HF Registry. J Am Coll Cardiol. 2007;50(8):768–777. PubMed
43. Tavazzi L, Maggioni AP, Lucci D, Cacciatore G, Ansalone G, Oliva F, Porcu M, Italian survey on Acute Heart Failure Investigators. Nationwide survey on acute heart failure in cardiology ward services in Italy. Eur Heart J. 2006;27(10):1207–15. Epub 2006 Apr 7. PMID:16603579[PubMed – indexed for MEDLINE 1.
44. Mountantonakis SE, Grau-Sepulveda MV, Bhatt DL, Hernandez AF, Peterson ED, Fonarow GC. Presence of atrial fibrillation is independently associated with adverse outcomes in patients hospitalized with heart failure: an analysis of get with the guidelines-heart failure. Circ Heart Fail. 2012;5(2):191–201. doi:10.1161/CIRCHEARTFAILURE.111.965681. Epub 2012 Feb 23.
45. Ambrosy AP, Fonarow GC, Butler J, Chioncel O, Greene SJ, Vaduganathan M, et al. The global health and economic burden of hospitalizations for heart failure: lessons learned from hospitalized heart failure registries. J Am Coll Cardiol. 2014;63(12):1123–33. doi:10.1016/j.jacc.2013.11.053. Epub 2014 Feb 5.
46. Rosca M Lancellotti P, Popescu BA, LA Piérard. Left atrial function: pathophysiology, echocardiographic assessment, and clinical applications. Heart. 2011;97(23):1982–9. doi: 10.1136/heartjnl-2011-300069.
47. Melenovsky V, Hwang SJ, Redfield MM, Zakeri R, Lin G, Borlaug BA. Left atrial remodeling and function in advanced heart failure with preserved or reduced ejection fraction. Circ Heart

Fail. 2015;8(2):295–303. doi:10.1161/CIRCHEARTFAILURE.114.001667. Epub 2015 Jan 15.
48. Eugenio PL. Frequent premature ventricular contractions: an electrical link to cardiomyopathy. Cardiol Rev. 2015;2 Epub ahead of print.
49. El Kadri M, Yokokawa M, Labounty T, Mueller G, Crawford T, Good E, et al. Effect of ablation of frequent premature ventricular complexes on left ventricular function in patients with nonischemic cardiomyopathy. Heart Rhythm. 2015;12(4):706–13. doi:10.1016/j.hrthm.2014.12.017. Epub 2014 Dec 16.
50. Kumar S, Stevenson WG, John RM. Catheter ablation for premature ventricular contractions and ventricular tachycardia in patients with heart failure. Curr Cardiol Rep. 2014;16(9):522. doi:10.1007/s11886-014-0522-3.
51. Baman TS, Lange DC, Ilg KJ, Gupta SK, Liu TY, Alguire C, et al. Relationship between burden of premature ventricular complexes and left ventricular function. Heart Rhythm. 2010;7(7):865–9. doi:10.1016/j.hrthm.2010.03.036. Epub 2010 Mar 27.
52. Michalsen A, König G, Thimme W. Preventable causative factors leading to hospital admission with decompensated heart failure. Heart. 1998;80(5):437–41.
53. Diaz A, Ciocchini C, Esperatti M, Becerra A, Mainardi S, Farah A. Precipitating factors leading to decompensation of chronic heart failure in the elderly patient in South-American community hospital. J Geriatr Cardiol. 2011;8(1):12–4. doi:10.3724/SP.J.1263.2011.00012.
54. Wu JR, Moser DK, Chung ML, Lennie TA. Predictors of medication adherence using a multidimensional adherence model in patients with heart failure. J Card Fail. 2008;14(7):603–14. doi:10.1016/j.cardfail.2008.02.011. Epub 2008 May 27.
55. Mathes T, Jaschinski T, Pieper D. Adherence influencing factors – a systematic review of systematic reviews. Arch Public Health. 2014;72(1):37. doi:10.1186/2049-3258-72-37. eCollection 2014.
56. Waldréus N, Hahn RG, Jaarsma T. Thirst in heart failure: a systematic literature review. Eur J Heart Fail. 2013;15(2):141–9. doi:10.1093/eurjhf/hfs174. Epub 2012 Nov 23.
57. Coble JP, Grobe JL, Johnson AK, Sigmund CD. Mechanisms of brain renin angiotensin system-induced drinking and blood pressure: importance of the subfornical organ. Am J Phys Regul Integr Comp Phys. 2015;308(4):R238–49. doi:10.1152/ajpregu.00486.2014. Epub 2014 Dec 17.
58. Menani JV, De Luca Jr LA, Johnson AK. Role of the lateral parabrachial nucleus in the control of sodium appetite. Am J Phys Regul Integr Comp Phys. 2014;306(4):R201–10. doi:10.1152/ajpregu.00251.2012. Epub 2014 Jan 8.
59. Bourque CW. Central mechanisms of osmosensation and systemic osmoregulation. Nat Rev Neurosci. 2008;9(7):519–31. doi:10.1038/nrn2400. Epub 2008 May 29.
60. Wessler JD, Hummel SL, Maurer MS. Dietary interventions for heart failure in older adults: re-emergence of the hedonic shift. Prog Cardiovasc Dis. 2014;57(2):160–7. doi:10.1016/j.pcad.2014.03.007. Epub 2014 Mar 12.
61. Cugno M, Mari D, Meroni PL, Gronda E, Vicari F, Frigerio M, et al. Haemostatic and inflammatory biomarkers in advanced chronic heart failure: role of oral anticoagulants and successful heart transplantation. Br J Haematol. 2004;126(1):85–92.
62. Lip GY, Gibbs CR. Does heart failure confer a hypercoagulable state? Virchow's triad revisited. J Am Coll Cardiol. 1999;33(5):1424–6.
63. de Peuter OR, Kok WE, Torp-Pedersen C, Büller HR, Kamphuisen PW. Systolic heart failure: a prothrombotic state. Semin Thromb Hemost. 2009;35(5):497–504. doi:10.1055/s-0029-1234145. Epub 2009 Sep 8.
64. Stein PD, Sostman HD, Hull RD, Goodman LR, Leeper Jr KV, Gottschalk A, et al. Diagnosis of pulmonary embolism in the coronary care unit. Am J Cardiol. 2009;103(6):881–6. doi:10.1016/j.amjcard.2008.11.040. Epub 2009 Jan 24.
65. Costanzo MR, Khayat R, Ponikowski P, Augostini R, Stellbrink C, Mianulli M, Abraham WT. Mechanisms and clinical consequences of untreated central sleep apnea in heart failure. J Am Coll Cardiol. 2015;65(1):72–84. doi:10.1016/j.jacc.2014.10.025.

66. Valdivia-Arenas MA, Powers M, Khayat RN. Sleep-disordered breathing in patients with decompensated heart failure. Heart Fail Rev. 2009;14(3):183–93. doi:10.1007/s10741-008-9103-0. Epub 2008 Aug 29.
67. Khayat R, Jarjoura D, Porter K, Sow A, Wannemacher J, Dohar R, et al. Sleep disordered breathing and post-discharge mortality in patients with acute heart failure. Eur Heart J. 2015; 36:1463–9.
68. Zanotti-Cavazzoni SL, Hollenberg SM. Cardiac dysfunction in severe sepsis and septic shock. Curr Opin Crit Care. 2009;15(5):392–7. doi:10.1097/MCC.0b013e3283307a4e.
69. Flynn A, Chokkalingam Mani B, Mather PJ. Sepsis-induced cardiomyopathy: a review of pathophysiologic mechanisms. Heart Fail Rev. 2010;15(6):605–11. doi:10.1007/s10741-010-9176-4.
70. Klein I, Danzi S. Thyroid disease and the heart. Circulation. 2007;116(15):1725–35.
71. Cooper DS, Biondi B. Subclinical thyroid disease. Lancet. 2012;379(9821):1142–54. doi:10.1016/S0140-6736(11)60276-6. Epub 2012 Jan 23.
72. Bogazzi F, Tomisti L, Bartalena L, Aghini-Lombardi F, Martino E. Amiodarone and the thyroid: a 2012 update. J Endocrinol Investig. 2012;35(3):340–8. doi:10.3275/8298. Epub 2012 Mar 19.
73. Bhala N, Emberson J, Merhi A, Abramson S, Arber N, et al. Coxib and traditional NSAID Trialists' (CNT) Collaboration. Vascular and upper gastrointestinal effects of non-steroidal anti-inflammatory drugs: meta-analyses of individual participant data from randomised trials. Lancet. 2013;382(9894) doi:10.1016/S0140–6736(13)60900–9. Epub 2013 May 30.
74. Gilbert RE, Krum H. Heart failure in diabetes: effects of anti-hyperglycaemic drug therapy. Lancet. 2015;385(9982):2107–17. doi:10.1016/S0140-6736(14)61402-1.
75. Guan Y, Hao C, Cha DR, Rao R, Lu W, Kohan DE, et al. Thiazolidinediones expand body fluid volume through PPARgamma stimulation of ENaC-mediated renal salt absorption. Nat Med. 2005;11(8):861–6. Epub 2005 Jul 10.
76. Seki G, Endo Y, Suzuki M, Yamada H, Horita S, Fujita T. Role of renal proximal tubule transport in thiazolidinedione-induced volume expansion. World J Nephrol. 2012;1(5):146–50. doi:10.5527/wjn.v1.i5.146.
77. Emoto M, Fukuda N, Nakamori Y, Taguchi A, Okuya S, Oka Y, Tanizawa Y. Plasma concentrations of vascular endothelial growth factor are associated with peripheral oedema in patients treated with thiazolidinedione. Diabetologia. 2006;49(9):2217–8. Epub 2006 Jul 1.
78. Murphy N, Mockler M, Ryder M, Ledwidge M, McDonald K. Decompensation of chronic heart failure associated with pregabalin in patients with neuropathic pain. J Card Fail. 2007;13(3):227–9.
79. Curigliano G, Mayer EL, Burstein HJ, Winer EP, Goldhirsch A. Cardiac toxicity from systemic cancer therapy: a comprehensive review. Prog Cardiovasc Dis. 2010;53(2):94–104. doi:10.1016/j.pcad.2010.05.006.
80. Berardi R, Caramanti M, Savini A, Chiorrini S, Pierantoni C, Onofri A, et al. State of the art for cardiotoxicity due to chemotherapy and to targeted therapies: a literature review. Crit Rev Oncol Hematol. 2013;88(1):75–86. doi:10.1016/j.critrevonc.2013.02.007. Epub 2013 Mar 21.
81. Albini A, Pennesi G, Donatelli F, Cammarota R, De Flora S, Noonan DM. Cardiotoxicity of anticancer drugs: the need for cardio-oncology and cardio-oncological prevention. J Natl Cancer Inst. 2010;102(1):14–25. doi:10.1093/jnci/djp440. Epub 2009 Dec 10.
82. Bhave M, Akhter N, Rosen ST. Cardiovascular toxicity of biologic agents for cancer therapy. Oncology (Williston Park). 2014;28(6):482–90.
83. Accordino MK, Neugut AI, Hershman DL. Cardiac effects of anticancer therapy in the elderly. J Clin Oncol. 2014;32(24):2654–61. doi:10.1200/JCO.2013.55.0459. Epub 2014 Jul 28.
84. Iacovoni A, De Maria R, Gavazzi A. Alcoholic cardiomyopathy. J Cardiovasc Med (Hagerstown). 2010;11(12):884–92. doi:10.2459/JCM.0b013e32833833a3.
85. Awtry EH, Philippides GJ. Alcoholic and cocaine-associated cardiomyopathies. Prog Cardiovasc Dis. 2010;52(4):289–99. doi:10.1016/j.pcad.2009.11.004.

86. Maraj S, Figueredo VM, Lynn MD. Cocaine and the heart. Clin Cardiol. 2010;33(5):264–9. doi:10.1002/clc.20746.
87. Phillips K, Luk A, Soor GS, Abraham JR, Leong S, Butany J. Cocaine cardiotoxicity: a review of the pathophysiology, pathology, and treatment options. Am J Cardiovasc Drugs. 2009;9(3):177–96. doi:10.2165/00129784-200909030-00005.
88. Figueredo VM. Chemical cardiomyopathies: the negative effects of medications and nonprescribed drugs on the heart. Am J Med. 2011;124(6):480–8. doi:10.1016/j.amjmed.2010.11.031.
89. Won S, Hong RA, Shohet RV, Seto TB, Parikh NI. Methamphetamine-associated cardiomyopathy. Clin Cardiol. 2013;36(12):737–42. doi:10.1002/clc.22195. Epub 2013 Aug 27.
90. Tops LF, Schalij MJ, Bax JJ. The effects of right ventricular apical pacing on ventricular function and dyssynchrony implications for therapy. J Am Coll Cardiol. 2009;54(9):764–76. doi:10.1016/j.jacc.2009.06.006.
91. Akerström F, Pachón M, Puchol A, Jiménez-López J, Segovia D, Rodríguez-Padial L, Arias MA. Chronic right ventricular apical pacing: adverse effects and current therapeutic strategies to minimize them. Int J Cardiol. 2014;173(3):351–60. doi:10.1016/j.ijcard.2014.03.079. Epub 2014 Mar 20.
92. Gheorghiade M, Abraham WT, Albert NM, Greenberg BH, O'Connor CM, She L, et al. OPTIMIZE-HF Investigators and Coordinators. Systolic blood pressure at admission, clinical characteristics, and outcomes in patients hospitalized with acute heart failure. JAMA. 2006;296(18):2217–26.
93. Damman K, Voors AA, Navis G, van Veldhuisen DJ, Hillege HL. The cardiorenal syndrome in heart failure. Prog Cardiovasc Dis. 2011;54(2):144–53. doi:10.1016/j.pcad.2011.01.003.
94. Berry SJ, Coffey DS, Walsh PC, Ewing LL. The development of human benign prostatic hyperplasia with age. J Urol. 1984;132(3):474–9.
95. Chute CG, Panser LA, Girman CJ, Oesterling JE, Guess HA, Jacobsen SJ, Lieber MM. The prevalence of prostatism: a population-based survey of urinary symptoms. J Urol. 1993;150(1):85–9.
96. Mebazaa A, Pang PS, Tavares M, Collins SP, Storrow AB, Laribi S, et al. The impact of early standard therapy on dyspnoea in patients with acute heart failure: the URGENT-dyspnoea study. Eur Heart J. 2010;31(7):832–41. doi:10.1093/eurheartj/ehp458. Epub 2009 Nov 11.
97. Stevenson LW, Tillisch JH. Maintenance of cardiac output with normal filling pressures in patients with dilated heart failure. Circulation. 1986;74(6):1303–8.
98. Hunt SA, Abraham WT, Chin MH, Feldman AM, Francis GS, Ganiats TG, et al. 2009 focused update incorporated into the ACC/AHA 2005 Guidelines for the Diagnosis and Management of Heart Failure in Adults: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines: developed in collaboration with the International Society for Heart and Lung Transplantation. Circulation. 2009;119(14):e391–479. doi: 10.1161/CIRCULATIONAHA.109.192065. Epub 2009 Mar 26.

Chapter 11
Acute Decompensated Heart Failure: Treatment – Specific Therapies

Daniel Fishbein

There have been few prospective randomized clinical trials conducted to guide treatment of patients with ADHF. Many of the guideline recommendations are based on broad clinical experience, registry data, meta-analyses, and a limited number of prospective, randomized clinical trials.

Oxygen

Routine administration of oxygen is recommended in patients with hypoxia (ESC, ACC/AHA, and HFSA guidelines). While there are no randomized trials of oxygen in ADHF, improvement in systemic and myocardial oxygenation would be expected to improve symptoms and clinical status of the patient with ADHF. Supplemental oxygen is recommended for patients with acute myocardial infarction complicated by heart failure. In some patients, oxygen may lower elevated pulmonary vascular resistance and improve right heart failure. However, routine administration of oxygen in the presence of normal oxygen saturations on room air is not recommended. In patients with a history of chronic obstructive pulmonary disease, high concentrations of oxygen can result in respiratory depression and worsening hypercapnia. High concentrations of inhaled oxygen have been shown to decrease cardiac output and increase systemic vascular resistance in patients with stable mild-moderate heart failure and LV systolic dysfunction [1].

D. Fishbein, MD
Division of Cardiology, Department of Medicine, University of Washington Medical Center, 1959 NE Pacific Street, #356422, Seattle, WA 98195, USA
e-mail: dfish@uw.edu

H. Eisen (ed.), *Heart Failure*, DOI 10.1007/978-1-4471-4219-5_11

Morphine

Morphine has been used in patients with ADHF for decades. Proposed mechanisms of benefit include reduction in dyspnea and anxiety, a resulting decrease in sympathetic tone with a reduction in afterload, and venodilation with a reduction in preload [2]. Venodilation seems to be mediated by histamine release and not by opiate receptors [3]. There is some controversy about whether morphine reduces left sided filling pressures in ADHF [4]. Morphine causes nausea and reduces respiratory drive. Despite long-standing practice, there is little prospective data to support the use of morphine in ADHF. Several studies have suggested an increase in adverse events in patients with ADHF treated with morphine [5, 6]. An analysis from the ADHERE registry found that treatment with intravenous morphine was a predictor of in-hospital adverse events [7]. Patients who received morphine were more likely to require mechanical ventilation (15.4 % vs 2.8 %), had a longer median hospitalization (5.6 days vs 4.2 days), more ICU admissions (38.7 % vs 14.4 %), and had a greater in-hospital mortality (13.0 % vs 2.4 %) (all $p < 0.001$). After risk adjustment and exclusion of ventilated patients, morphine remained an independent predictor of mortality with a HR of 4.84 ($p < 0.001$). Despite risk adjustment, some of this data may be confounded by the likelihood that patients who received morphine were sicker. The HFSA Guidelines recommend caution "that if used at all, [morphine] should be used with caution, especially in patients with abnormal mental status or impaired respiratory drive" [8].

Noninvasive Ventilation (NIV)

Patients with severe decompensated heart failure may present with acute respiratory distress and severe hypoxia related to extravasation of fluid into the alveoli, dilution of surfactant, decrease in oxygen uptake, alveolar collapse, intrapulmonary shunting and VQ mismatch. Positive pressure ventilation decreases work of breathing, improves oxygenation, improves lung compliance by recruiting previously collapsed alveoli, reduces respiratory distress, reduces afterload and improves cardiac output [9]. Patients with ADHF and acute cardiogenic pulmonary edema may be supported with noninvasive methods of ventilation (NIV) also known as noninvasive positive pressure ventilation (NPPV).

There are two common methods of delivering NIV. Continuous positive airway pressure (CPAP) maintains the same positive pressure throughout the respiratory cycle. Noninvasive intermittent positive pressure ventilation (NIPPV), also referred to as bi-level noninvasive pressure support ventilation (NIPSV), increases airway pressure more during inspiration than expiration.

Several meta-analyses of predominantly small single-center randomized trials that compared NIV with standard therapy in patients with acute cardiogenic pulmonary edema found that NIV significantly reduced mortality and the need for

intubation/mechanical ventilation. The level of evidence was greater for CPAP than NIPPV [10, 11]. In an analysis of three studies comparing CPAP with NIPPV in acute cardiogenic pulmonary edema, estimates of the incidence of new myocardial infarction were increased in the NIPPV group (relative risk 1.99; p = 0.03) [11]. This finding was driven by the results from a small study of 27 patients with acute pulmonary edema randomized to CPAP or NIPPV [12].

The Three Interventions in Cardiogenic Pulmonary Oedema (3CPO) trial randomized 1069 patients with acute cardiogenic pulmonary edema to standard oxygen therapy, CPAP, or NIPPV. There was no difference in 7-day mortality between patients receiving standard oxygen therapy and those receiving NIV. There was no difference in the combined end point of death or intubation at 7 days between the patients randomized to CPAP or NIPPV. NIV was associated with greater mean improvements at 1 h after initiation of therapy in patient-reported dyspnea, heart rate, acidosis, and hypercapnea. Patients receiving standard oxygen therapy and those receiving NIV had similar rates of endo tracheal intubation, admission to the critical care unit, and myocardial infarction. Patients receiving CPAP and those receiving NIPPV also had similar rates of these outcomes. There were no differences in the rates of myocardial infarction between the three groups. There was no difference in the rate of myocardial infarction when standard oxygen therapy was compared with NIV and when CPAP was compared with NIPPV [13]. One of the criticisms of the 3CPO Trial was the lower than expected rate of intubation (2.8 %) and the lower than expected 7-day mortality (9.8 %) in the control group. There was a 15.3 % crossover rate between standard therapy and NIV. The lower event rates decreased the power of the study to show a difference between standard oxygen therapy and NIV. It is possible that the population studied was not sick enough to show a benefit from NIV and that those patients with more severe compromise in the control group crossed over to NIV support [14].

Two subsequent meta-analyses that included patients in the 3CPO Trial found that NIV reduced morality and endotracheal intubation when compared with standard therapy in patients with acute cardiogenic pulmonary edema [14, 15]. The Cochran analysis suggested that CPAP should be considered the first option in the selection of NIV in light of more robust evidence of safety and effectiveness when compared with NIPPV.

A recent meta-analysis of randomized studies compared out-of-hospital NIV with "standard" therapy for treatment of adults with severe respiratory distress. NIV used by emergency medical services for treatment of patients in respiratory distress reduced in-hospital mortality (RR = 0.58) and the need for endotracheal intubation (RR = 0.37) when compared with standard therapy. Four of seven studies in the analysis included only patients with suspected acute cardiogenic pulmonary edema. An additional two studies included patients with cardiogenic pulmonary edema and other causes of respiratory distress [16].

The HFSA Practice Guidelines recommend that the "use of non-invasive positive pressure ventilation may be considered for severely dyspneic patients with clinical evidence of pulmonary edema" (Strength of Evidence A). The ESC guidelines suggest that NIV may be used as adjunctive therapy to relieve symptoms in patients

with pulmonary edema and severe respiratory distress or patients who fail to improve with pharmacologic therapy.

Contraindications to NIV include: immediate need for intubation; inability to cooperate because of anxiety, decreased level of consciousness or severe cognitive impairment; inability to tolerate the mask; and vomiting. Adverse effects include: worsening of severe right heart failure; hypercapnia; anxiety; claustrophobia; pneumothorax; and aspiration. Caution should be exercised in patients with cardiogenic shock, COPD, or severe right heart failure [17]. Endotracheal intubation and mechanical ventilation should be reserved for patients with: respiratory failure leading to hypercapnia and respiratory acidosis; hypoxia that cannot be corrected with oxygen by nasal cannula, mask or NIV; physical exhaustion; diminished consciousness; and/or inability to maintain or protect their airway [18].

Diuretic Therapy

Diuretics differ in their site and mechanism of action and in their impact on sodium and water excretion. Diuretics are classified by their site of action in the nephron (loop diuretics), chemical structure (thiazides), mode of action (MRAs, carbonic anhydrase inhibitors), and/or specific physiologic effects (potassium sparing diuretics). Figure 11.1 outlines the site of action in the nephron of each class of diuretic [19].

Loop Diuretics (LD)

Pharmacokinetics/Pharmacology

LDs are first line therapy in the treatment of patients with ADHF. Of all diuretic classes, LDs have the most immediate onset of action when given intravenously and the greatest impact on sodium and water excretion. Furosemide, bumetanide, and torsemide are sulfonamide loop diuretics that reversibly bind to and reversibly inhibit the Na^+: K^+:$2Cl^-$ co-transporter on the apical membrane of epithelial cells in the thick ascending limb of the loop of Henle. LDs inhibit sodium transport at this site in the nephron. Loop diuretics can increase sodium excretion by as much as 20–25 % of filtered sodium and augment excretion of both sodium and water. Inhibition of the co-transporter also inhibits reabsorption of calcium and magnesium. The increased sodium delivered to the distal convoluted tubule significantly increases the excretion of urinary potassium via the sodium potassium co-transporter. This effect is amplified by elevated levels of aldosterone typically seen in patients with ADHF. Loop diuretics indirectly decrease the reabsorption of water in the collecting ducts by decreasing the concentration of sodium in the medullary interstitium resulting in a decrease in the driving force for water reabsorption in the

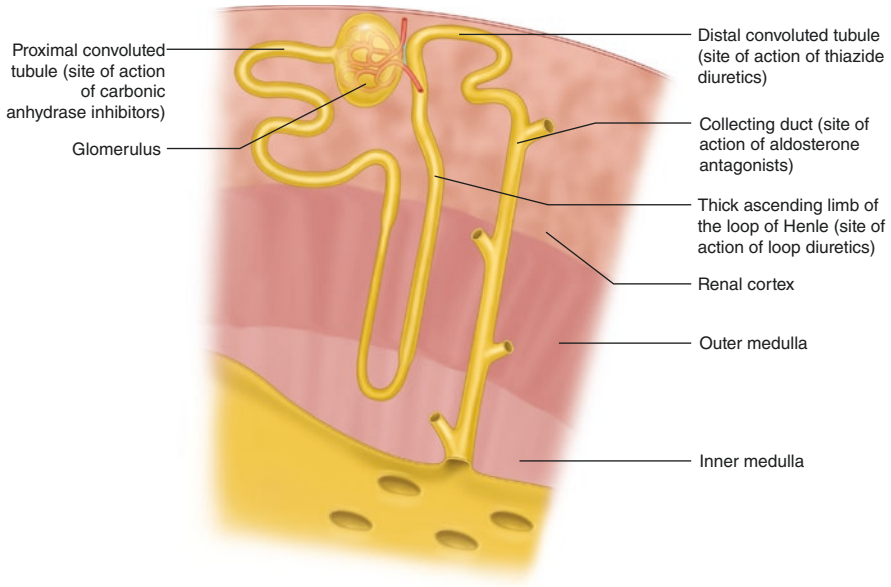


Fig. 11.1 Schematic diagram of the nephron demonstrating the site of action of diuretics [19]

collecting duct. Urine produced in response to LDs is mildly hypotonic when compared with plasma [19–26].

Ethacrynic acid is a non-sulfonamide loop diuretic that inhibits reabsorption of sodium and chloride in the ascending loop of Henle and distal renal tubule by interfering with the chloride-binding co-transport system, causing increased excretion of water, sodium, chloride, magnesium, and calcium. Ethacrynic is a less effective diuretic than the other three loop diuretics, is probably more ototoxic at high doses, and is cumbersome to administer intravenously because of its relative insolubility. Its use is limited to patients who have an allergy to sulfonamide LDs [27].

An adequate intraluminal concentration of diuretic is needed for LDs to be effective. Because LDs are extensively bound to plasma proteins, delivery to the loop of Henley by glomerular filtration is limited. LDs are secreted into the intraluminal space of the nephron by the organic acid transport system in the proximal tubule. Intraluminal concentration is dependent on dose, bioavailability, adequate renal blood flow and adequate proximal tubule secretory function. Secretion into the proximal tubule may be impaired in heart failure by a decrease in renal plasma flow. In addition, in renal insufficiency, the accumulation of organic anions (e.g., blood urea nitrogen) competes with LDs for the receptor sites of the organic anion transporter. Higher doses are required to overcome this competitive inhibition and to obtain therapeutic urinary concentrations in patients with heart failure and renal impairment [20, 25].

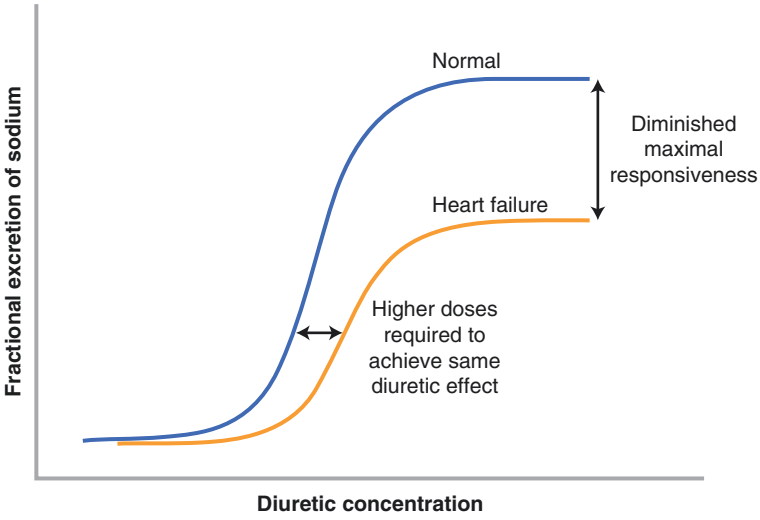


Fig. 11.2 Schematic of doseresponse curve of loop diuretics in heart failure patients compared with normal controls [23]

Loop diuretics have an "S" shaped dose-response curve characterized by a threshold concentration below which no diuresis occurs (the minimal effective concentration), a steep increase in dose response, and a concentration ceiling above which no additional diuretic effect is seen. Diuretic effect is dependent on achieving an adequate or "threshold" intraluminal concentration of diuretic in the thick ascending limb of the loop of Henle. In heart failure, the dose response curve is shifted downward and to the right so that a higher concentration of LD is needed to induce a diuresis and the peak response is decreased (see Fig. 11.2) [23].

The dose response curve has a number of clinical implications. First, there is a threshold concentration of LD that needs to be achieved at the active site to elicit any diuretic response. Diuretic doses that achieve intraluminal concentrations below threshold are ineffective so that it is important to demonstrate a response to a specific dose of LD rather than give an inadequate dose more frequently. Because of individual differences in diuretic sensitivity and pharmacokinetics, the dose that achieves threshold concentrations differs among patients. Second, the diuretic ceiling limits the maximal effect of increasing diuretic dose. A ceiling dose of diuretic can be identified in individual patients (the lowest dose of LD that elicits a maximal response). If additional diuresis is needed, the dosing frequency should be increased rather than increasing the LD dose above the ceiling dose [19, 25].

When a bolus of LD is administered, there is generally a diuretic response within 30 minutes that peaks in 1 hour provided that the intraluminal concentration of diuretic is above the threshold concentration in the loop of Henle. When the intraluminal concentration of LD declines below the threshold concentration, urinary excretion of sodium stops and compensatory sodium retention occurs (post-

diuretic salt retention or "rebound") until another diuretic dose is administered and threshold concentration is again achieved. It takes four half-lives for LDs to reach steady state so that administration at a frequency of longer than 4 half-lives will allow for a period of "post-diuretic sodium retention" [23]. Diuretic rebound is directly related to sodium and water excretion and can be prevented by replacement of excreted sodium with normal saline. If dietary intake is not limited, diuretic-induced net sodium excretion may be nullified by post-diuretic salt retention. This phenomenon suggests that in patients hospitalized with ADHF, sodium intake should be restricted and LDs should be given at least 2–3 times/day or administered as a continuous infusion [19, 21, 26, 28].

Two forms of diuretic tolerance have been described. Acute tolerance develops within the first several days of LD therapy and refers to a progressive time-dependent decline in sodium excretion in response to the same dose of LD. This form of early tolerance has been referred to as the "breaking phenomenon". A number of studies have demonstrated decreases in mean blood pressure and eGFR and increases in renin, angiotensin II, aldosterone and plasma norepinephrine levels after a single dose of IV furosemide. The pathophysiology of early tolerance is likely multi-factorial with contributions from: a decrease in renal blood flow mediated by hypotension, increased angiotensin II and sympathetic activation; increases in renin, angiotensin II and aldosterone levels; an increase in sodium reabsorption in the proximal tubule mediated by angiotensin II; and an increase in distal sodium absorption mediated by aldosterone [25, 26, 29]. The release of adenosine by the macula densa/juxtaglomerular apparatus in response to a LD-induced increase in sodium chloride concentration in the distal loop of Henley may contribute to early tolerance by reducing renal blood flow and GFR [30–32]. In addition, vasopressin-induced upregulation of the Na^+: K^+:$2Cl^-$ co-transporter may also contribute to tolerance [33].

A second type of LD tolerance occurs with chronic administration of LD. With LD administration, the nephron distal to the loop of Henle is flooded with solute. This causes diuretic-induced hypertrophy of the distal convoluted tubule and functional changes in the distal nephron that result in increased sodium reabsorption in the distal nephron. This attenuates loop diuretic-induced sodium and water excretion [20, 23].

Furosemide, bumetanide, and torsemide all act by reversibly inhibiting the Na^+:K^+: $2Cl^-$ co-transporter in the ascending limb of the loop of Henle. They differ primarily in oral bioavailability, dose, metabolism, relative potency and duration of action. Furosemide is the most commonly used diuretic in patients with ADHF. In the ADHERE Registry, 84 % of patients received IV furosemide, 7 % received IV bumetanide and 2 % received IV torsemide [34]. All of the loop diuretics (including ethacrynic acid) are extensively bound to plasma proteins, have limited glomerular filtration and are secreted into the intraluminal space of the nephron by the organic acid transport system in the proximal tubule. Furosemide has the most variable bioavailability ranging from 40–70 % of the oral dose. The bioavailability of bumetanide and torsemide are 80–100 % of the oral dose. Furosemide is metabolized and excreted by the kidney. Bumetanide

Table 11.1 Pharmacokinetics of the loop diuretics [24]

Property	Furosemide	Bumetanide	Torsemide
Relative IV potency, mg	40	1	20
Bioavailability, %	10–100 (average, 50)	80–100	80–100
Oral to intravenous conversion	2:1	1:1	1:1
Initial outpatient total daily oral dose, mg	20–40	0.5–1	5–10
Maintenance outpatient total daily oral dose, mg	40–240	1–5	10–200
Onset, min			
Oral	30–60	30–60	30–60
Intravenous	5	2–3	10
Peak serum concentration after oral administration, h	1	1–2	1
Affected by food	Yes	Yes	No
Metabolism	50 % renal conjugation	50 % hepatic	80 % hepatic
Half-life, h			
Normal	1.5–2	1	3–4
Renal dysfunction	2.8	1.6	4–5
Hepatic dysfunction	2.5	2.3	8
Heart failure	2.7	1.3	6
Average duration of effect, h	6–8	4–6	6–8
Approximate cost of oral 30-day supply (community pharmacy), $	4	4	19–23

Reprinted from Felker and Mentz [23], with permission from Elsevier

and torsemide are primarily metabolized by the liver. The onset of diuretic effect when given intravenously is 5 min for furosemide, 2–3 min for bumetanide and 10 min for torsemide. The onset of diuretic effect when given orally is 30–60 min for all three LDs. Furosemide has a half-life of 1.5–2 h, bumetanide 0.8 (range 0.3–1.5) h and torsemide 3.5 h. The duration of action of furosemide is 6–8 h; bumetanide 4–6 h and torsemide 12 h (range 6–16). Furosemide and bumetanide are available for oral and intravenous administration while torsemide is currently available only for oral administration in the United States. The relative potency of LDs given intravenously is furosemide 40 mg: bumetanide 1 mg: torsemide 20 mg. IV to PO conversion is 1:2 for furosemide and 1:1 for bumetanide and torsemide [35–38]. Table 11.1 summarizes the pharmacokinetics of the sulfonamide loop diuretics [24, 39]

Ethacrynic acid has a bioavailability of 100 % of the oral dose, is significantly protein bound and is secreted into the proximal tubule via the organic acid transporter. It has a half-life of approximately 1 h, duration of action of 4–6 h, and potency relative to IV furosemide of 0.7 [24].

Hemodynamic Effects

Loop diuretics should be given intravenously in ADHF as the bioavailability of furosemide is highly variable and the absorption of all loop diuretics may be impeded by bowel edema or intestinal hypoperfusion [40]. Loop diuretics have a number of benefits in volume-overloaded patients with ADHF. Intravenous administration of an effective dose of loop diuretic generally results in a diuretic effect that peaks within an hour of administration [19, 23, 24, 38]. Diuretic induced excretion of sodium and water affects a reduction in right- and left-sided filling pressures with a decrease in pulmonary and systemic venous congestion and a decrease in left ventricular dilation. In patients with LV systolic dysfunction and volume overload, the left ventricle is operating on the flat part of the LV performance curve where stroke volume is relatively independent of LV filling pressures. Diuretic induced reductions in LV filling pressure generally do not cause hypotension or a reduction in stroke volume or cardiac index [41]. Diuretic-related reduction in left and right sided ventricular filling pressures is associated with an improvement in stroke volume and cardiac output related to: a decrease in functional mitral and tricuspid regurgitation; a decrease in right ventricular volume with relief of ventricular-interdependent LV compression; improved endocardial blood flow; and a reduction in LV wall tension resulting in a decrease in myocardial oxygen consumption. The reduction in wall tension may be particularly important in patients with coronary artery disease. The associated reduction in secondary mitral regurgitation and left ventricular wall tension results in an improvement in cardiac output and overall myocardial performance [42–45]**.**

Loop diuretics also have hemodynamic effects independent of their diuretic effects. Several studies have suggested that administration of an intravenous loop diuretic results in an early reduction in pulmonary capillary wedge pressure that may be independent of diuretic effect [46–48]. This effect is likely due to dose-dependent direct venodilation mediated by the release of vasodilatory prostaglandins [49, 50]. These findings may explain why LDs can produce clinically significant reductions in left- and right-sided filling pressures and improvement in symptoms in as little as 15 min after administration [47]**.**

In contrast, in some patients, IV loop diuretics may cause an early increase in systemic vascular resistance and systolic blood pressure. This effect is not mediated by a direct vascular effect but rather, by neurohormonal activation of the sympathetic nervous system and RAAS [42, 43, 50]. In a study of the hemodynamic and neurohormonal responses to IV furosemide in 15 patients with severe chronic heart failure, mean arterial pressure, heart rate, systemic vascular resistance, and left ventricular filling pressure increased and stroke volume index decreased 20 min after the administration of intravenous furosemide. These changes were associated with increases in plasma norepinephrine, plasma renin activity and plasma arginine vasopressin. At 2 h, patients had diuresed and had a reduction in filling pressures to below baseline. Neurohormone levels returned toward baseline [51]. In another

study, neurohormonal activation was followed in 34 patients admitted with acute decompensation of chronic HFrEF. Patients were treated with hemodynamically guided therapy with diuretics and sodium nitroprusside titrated to reduce filling pressures and lower systemic vascular resistance. Patients were then transitioned to oral therapy. Neurohormone levels were obtained at baseline, during parenteral treatment (mean 1.4 days) and after transition to oral therapy (mean 3.4 days). Filling pressures (PCWP 31 to 18 mmHg; RA 15 to 8 mmHg) and cardiac index (1.7 to 2.6 L/min/m^2) improved during treatment with parenteral medications. Plasma norepinephrine levels did not change during parenteral therapy but decreased after transition to oral medication. Plasma aldosterone and plasma renin activity increased during parenteral therapy. Aldosterone levels returned to baseline and plasma renin activity remained elevated after transition to oral medication. Plasma endothelin levels decreased during parenteral therapy and remained lower after transition to oral medication [52]. These observations support the early use of a vasodilator added to a diuretic to attenuate the effects of LD-induced neurohormonal activation.

LD Dose and Mode of Administration

There has been little prospective evidence to guide diuretic use in ADHF. It has been hypothesized that the continuous infusion of a loop diuretic should avoid the periods of ineffective diuretic concentration in the loop of Henle seen with intermittent bolus therapy and should result in greater diuresis. It has also been suggested that continuous infusion should be associated with fewer electrolyte abnormalities, preservation of renal function and a shorter length of stay. A Cochran review published in 2005 compared intermittent bolus administration with continuous intravenous infusion of loop diuretics in eight studies of a total of 254 patients. The studies were small (8–107 patients) and heterogeneous. There were significant differences among the studies with respect to diuretic dose, method of administration, follow-up period and clinical outcomes reported [53]. The authors concluded that the data were insufficient to assess the merits of the two methods of LD administration.

The Diuretic Optimization Strategies in Acute Heart Failure (DOSE) trial was a multicenter, randomized, controlled, double-blind trial that assessed the effect of diuretic dose and mode of administration in patients admitted with ADHF [54]. 308 patients hospitalized for ADHF with a history of chronic heart failure treated with an oral loop diuretic at a daily dose of furosemide of 80–240 mg/day or equivalent for at least one month prior to hospitalization were enrolled in the study. Using a 2×2 factorial design, patients were randomized in a 1:1:1:1 ratio to receive furosemide administered intravenously by means of either a bolus every 12 h or continuous infusion and with either a low dose (equivalent to the patient's previous oral dose) or a high dose (2.5 times the previous oral dose). Dose adjustments could be made at 48 h. There were two co-primary end-points: patients' global assessment of symptoms, quantified as the area under the curve on a visual-analogue scale over

the course of 72 h (the efficacy end-point); and the change in the serum creatinine level from baseline to 72 h (the safety end-point). There was no significant difference in the patients' global assessment of symptoms or mean change in creatinine between the bolus and continuous infusion groups. Patients in the bolus therapy group were more likely to require an increase in furosemide dose at 48 h. There was a non-significant trend toward greater improvement in symptoms assessed by the visual analogue scale in the high dose group compared to the low dose group (P = 0.06). The high dose strategy was associated with greater relief of dyspnea (P = 0.04), greater fluid (p = 0.001) and weight (p = 0.01) loss and fewer adverse events (p = 0.033). Patients in the high dose group were less likely to require an increase in furosemide dose and more likely to be changed to oral therapy at the 48-h reevaluation. There were more cases of ventricular tachycardia and myocardial infarction with bolus than with continuous infusion and with the low-dose strategy than with the high-dose strategy. A higher proportion of patients in the high dose group met the pre-specified secondary safety end-point of an increase in serum creatinine of more than 0.3 mg per deciliter at any time during the 72 h after randomization. Although prior studies have suggested that an increase in creatinine during hospitalization for ADHF is associated with worse long-term outcome [55, 56], there was no evidence of worse clinical outcome in the high dose group at 60 days. This is consistent with other reports that found that a transient increase in creatinine during hospitalization may not be associated with poorer outcomes after discharge [57, 58].

Two recent meta-analyses that included the results from the DOSE Trial compared the efficacy of continuous infusion versus IV bolus of loop diuretics in patients hospitalized with ADHF. One meta-analysis included ten randomized controlled trials with a total of 518 patients in the analysis. Continuous infusion of diuretics was associated with a significantly greater weight loss compared with bolus injection but no significant differences in urine output, the incidence of electrolyte abnormality, change in creatinine level, hospital length of stay, the incidence of ototoxicity, cardiac mortality, or all-cause mortality [59]. The second meta-analysis included 7 cross-over and 8 parallel-arm randomized trials in adults with a total of 844 patients in the analysis. 8/15 studies included patients with ADHF, 3 included ICU patients, 2 included cardiac surgery patients and 2 included patients with chronic kidney disease. A non-significant net increase in daily urine output was seen with continuous infusion diuretic therapy. When the 8 studies that included an initial loading dose were analyzed, continuous loop diuretic infusion was associated with a significant net increase in daily urine output of 294 ml/day and a significant net negative weight loss of 0.78 kg when compared with intermittent infusion [60].

The optimal dose of LD is uncertain and needs to be individualized based on age, prior diuretic use, severity of heart failure, the presence of impaired systemic perfusion, creatinine and estimated glomerular filtration rate calculated using either the Cockroft-Gault (CG) or the Modified Diet in Renal Disease (MDRD) equations. Diuretics should be given at a dose and frequency sufficient to relieve symptoms and signs of congestion and normalize volume status without causing

excessively rapid reduction in intravascular volume or clinically significant electrolyte abnormalities [8].

The ACCF/ACC guidelines recommend that in patients already receiving a loop diuretic, the initial diuretic dose should equal or exceed their chronic oral daily dose and be given either as intermittent intravenous boluses or continuous infusion [28]. The ESC guidelines recommend that an initial dose of furosemide 20–40 mg IV (or 0.5–1.0 mg bumetanide or 10–20 mg of torsemide) be given on admission; in patients with evidence of volume overload, the dose of parenteral diuretic may be higher based on renal function and a history of chronic oral diuretic use [18]. Continuous infusion may also be considered after an initial starting bolus dose. The ESC recommends that the total furosemide dose should remain <100 mg in the first 6 h and <240 mg during the first 24 h. Diuretic dosing guidelines from the ASCEND-HF trial based on creatinine clearance and the chronicity of heart failure are summarized in Table 11.2 [61]. The recommended doses of LDs given by continuous infusion are summarized in Table 11.3 [23, 62].

Table 11.2 Standardizing care for acute decompensated heart failure in a large megatrial: The approach for the Acute Studies of Clinical Effectiveness of Nesiritide in Subjects with Decompensated Heart Failure (ASCEND-HF) [61]

Creatinine clearance[a]	Patient	Initial IV dose[b]	Maintenance dose
>60 ml/(min 1.73m^2)	New-onset HF or no maintenance diuretic therapy	Furosemide 20–40 mg 2–3 times daily	Lowest diuretic dose that allows for clinical stability is the ideal dose
	Established HF or chronic oral diuretic therapy	Furosemide bolus equivalent to oral dose	
<60 mL/(min 1.73m^2)	New-onset HF or no maintenance diuretic therapy	Furosemide 20–80 mg 2–3 times daily	
	Established HF or chronic oral diuretic therapy	Furosemide bolus equivalent to oral dose	

Reprinted from Ezekowitz et al. [61], with permission from Elsevier
[a]Creatinine clearance is calculated from the Cockroft-Gault or Modified Diet in Renal Disease formula
[b]Intravenous continuous furosemide at doses of 5 to 20 mg/h is also an option See text for details

Table 11.3 Continuous infusion with as needed uptitration [23]

IV loading dose (mg)		Infusion rate (mg/h)		
Creatinine clearance	All GFRs	<25	25–75	>75
Furosemide	40	20, then 40	10, then 20	10
Bumetanide	1	1, then 2	0.5, then 1	0.5
Torsemide	20	10, then 20	5, then 10	5

Reprinted with permission from Brater [22], with permission from Elsevier
Note: Before increasing to a higher infusion rate, a repeat loading dose should be administered

Response to Therapy

There is conflicting data concerning the rapidity of response to parenteral diuretics in patients with ADHF. There is a general understanding that most patients have a rapid and significant improvement in dyspnea after administration of a parenteral diuretic although not all studies confirm this [8, 63]. In the Value of Endothelin Receptor Inhibition With Tezosentan in Acute Heart Failure (VERITAS) trial, patients admitted to the hospital with acute heart failure, dyspnea, tachypnea and evidence of volume overload or LV systolic dysfunction were treated with standard heart failure therapy which consisted mostly of parenteral diuretics and randomized to an infusion of tezosentan, an intravenous short-acting endothelin receptor antagonist, or placebo. The primary end-point was the change in dyspnea over the first 24 h measured at 3, 6 and 24 h using a visual analog scale. There were rapid and significant improvements in dyspnea in the placebo and tezosentan groups at 3, 6, and 24 h. Interestingly, these changes were associated with small changes in hemodynamic parameters. In the placebo group, baseline PCWP was 25.6 mmHg and decreased by 1.5, 1.9, and 2.9 mmHg at 3, 6, and 24 h, respectively. Baseline RAP was 15.9 mmHg and changed by 0.8, −0.2 and 0.7 mmHg at 3, 6, and 24 h respectively. Baseline cardiac index was 2.01 L/min/m^2 and increased by 0.18, 0.18 and 0.15 L/min/m^2 at 3, 6, and 24 h, respectively. Baseline systemic vascular resistance was 1813 dyne-sec/cm^5 and changed by −157, −54 and 136 dyne-sec/cm^5 at 3, 6, and 24 h [64].

In the Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study with Tolvaptan (EVEREST) trial, patients with chronic heart failure and systolic dysfunction who were hospitalized for worsening HF received standard therapy for acute heart failure and were randomized to receive tolvaptan, an oral non-peptide selective V_2-receptor antagonist or placebo. Approximately 2/3 of the placebo patients reported mild, moderate or marked improvement in dyspnea but only one third of patients reported moderate or marked improvement in dyspnea at day 1 of the study. Physician assessment of signs and symptoms of heart failure on day 1 noted improvement in dyspnea in 47.1 % of patients, orthopnea in 59.2 %; JVD in 43.8 %; rales in 43.7 % and edema in 52.6 % [65].

The rate of dyspnea relief was reviewed in a post hoc analysis of data from the Placebo-controlled Randomized study of the selective A1 adenosine receptor antagonist rolofylline for patients hospitalized with acute heart failure and volume Overload to assess Treatment Effect on Congestion and renal funcTion (PROTECT) clinical trial pilot study. In PROTECT, patients with acute heart failure and mild to moderate renal impairment defined as an eGFR of 20–80 mL/min using the Cockcroft-Gault equation with dyspnea at rest or with minimal activity, signs and symptoms of volume overload and an elevated BNP or NT-pro-BNP were randomized within 24 h of presentation to treatment with placebo or one of three doses of rolofylline, a selective A1 adenosine receptor antagonist. Dyspnea relief was defined as a moderate to marked improvement in dyspnea using a seven-point Likert scale and occurred in the placebo group in 49 %, 64 %, 78 %, and 75 % of patients at 24 h, 48 h, day 7 and day 14, respectively. Improvement at 24 and 48 h was associated

with greater improvement in patient-reported general wellbeing, and greater decreases from baseline in edema, rales, jugular venous distention and orthopnea. Patients with relief of dyspnea did not have a greater decrease in weight compared to patients without relief of dyspnea [66].

The frequency of early dyspnea relief was assessed in the Preliminary study of RELAX in Acute Heart Failure (Pre-RELAX-AHF) study. Patients in Pre-RELAX-HF had acute heart failure, evidence of volume overload, a systolic blood pressure of >125 mmHg, and impaired renal function with an eGFR of 30–75 ml/min/1.73 m^2 calculated using the simplified Modification of Diet in Renal Disease (sMDRD) equation. Patients were randomized to placebo or one of four doses of relaxin, a naturally occurring peptide vasodilator. Early dyspnea relief was defined as moderate or marked improvement in dyspnea assessed by the Likert scale at 6, 12, and 24 h after the start of study medication. Moderate or marked improvement in dyspnea at 6, 12 and 24 h was observed in only 23 % of patients in the placebo group. 70 % of all patients had moderate or marked improvement in dyspnea at 14 days. Improvement in dyspnea was correlated with improvements in general well-being measured by a visual analogue scale, orthopnea, dyspnea on exertion, edema, and rales but not with improvements in JVP or weight. Early dyspnea relief was predicted by a higher initial systolic blood pressure and respiratory rate [67].

The Ularitide Global Evaluation in Acute Decompensated Heart Failure (URGENT) Dyspnoea study was an international, multi-center, observational cohort study of 524 acute heart failure patients managed conventionally and enrolled within 1 h of first hospital medical evaluation [68]. The primary outcome was patient assessed dyspnea at 6 h measured by a 5-point Likert scale. Dyspnea improvement was reported in 76 % of patients after 6 h of standard therapy.

LD Side Effects

Excessive Diuresis

Excessive diuresis may result in hypotension and a reduction in cardiac output. During LD-induced natriuresis, intravascular volume is generally maintained by vascular “refilling” or equilibration as interstitial fluid moves into the intravascular space. The rate of refilling varies among patients. During brisk diuresis, it is possible for the rate of volume loss to exceed the rate of refilling. This may result in low intravascular volume, inadequate cardiac filling, and hypotension despite persistent volume overload.

Patients with HPpEF are at greater risk of diuretic-induced hypotension. These patients tend to be less volume overloaded and have a steep diastolic filling curve so that moderate reductions in intravascular volume may result in significant reductions in cardiac filling and cardiac output. Patients with infiltrative or restrictive cardiomyopathy may have diuretic-induced hypotension in the setting of continued volume overload as elevated ventricular filling pressures are needed to maintain

normal cardiac output [41]. Diuresis that results in a decrease in ventricular filling pressures may makes patients more sensitive to the hypotensive effects of other vasodilators used in the routine treatment of heart failure.

Electrolyte Abnormalities

LDs cause urinary losses of potassium due to augmented distal tubular secretion of potassium in response to increased distal tubular sodium reabsorption (creating a lumen negative gradient that favors potassium secretion) and secondary hyperaldosteronism. Electrolytes need to be monitored frequently, especially early during the period when diuresis is most significant. Hypokalemia should be treated promptly with either oral or intravenous potassium supplementation. Electrolytes should be monitored at least daily during hospitalization and more frequently if potassium supplementation is needed. Patients also need to be monitored for the development of hyperkalemia which may develop later during hospitalization as a result of less daily diuresis, fixed dosing of potassium supplementation, the initiation or uptitration of angiotensin converting enzyme inhibitors (ACEI), angiotensin receptor blockers (ARBs), and/or mineralocorticoid receptor blockers (MRAs), and the development of renal insufficiency.

LDs also cause hypomagnesemia. 70 % of filtered magnesium is reabsorbed in the thick ascending limb of the loop of Henle. Inhibition of the Na^+: K^+:$2Cl^-$ cotransporter decreases the lumen positive charge in this segment and reduces the driving force for paracellular magnesium reabsorption. Hypomagnesemia can be associated with arrhythmia and can exacerbate diuretic-induced hypokalemia. Monitoring magnesium levels is indicated in patients admitted with ADHF.

Hypersensitivity Reactions

Furosemide, bumetanide and torsemide are sulfonamides and can cause hypersensitivity reactions which are usually manifest as rash or, rarely, acute interstitial nephritis. All three medications have chemical similarities to sulfonamide antibiotics, sulfonylureas, carbonic anhydrase inhibitors, and thiazide diuretics. There is little evidence that sensitivity to a sulfonamide antibiotic predicts sensitivity to a loop diuretic beyond the finding that patients who have a reaction to one medication are at increased risk of reactions to medications in general [69–72]. Despite this data, the United Stated Food and Drug Administration approved product information for bumetanide and torsemide caution: “Patients allergic to sulfonamides may show hypersensitivity to Bumex” [73] and “Torsemide Tablets are contraindicated in patients with known hypersensitivity to torsemide or to sulfonylureas” [74].

Ethacrynic acid is a loop diuretic without a sulfhydryl group. It can be used safely in patients with hypersensitivity to furosemide, bumetanide or torsemide. The major limitation to using ethacrynic acid is that it is significantly less effective than the other LDs in facilitating sodium excretion.

Ototoxicity

Furosemide can cause dose-related ototoxicity with tinnitus and/or clinical or subclinical hearing loss [75–78]. Permanent hearing loss can occur but is unusual. Ototoxicity of LDs is related to the blood level of the drug. Rapid infusion or use of large parenteral doses, especially in the setting of renal insufficiency, increases the risk of toxicity. Reducing the infusion rate or changing to oral administration reduces the risk of ototoxicity. It is recommended that infusion rates of furosemide should not exceed 4 mg/min in adults [79]. The risk of ototoxicity is also increased in the setting of hypoproteinemia, or concomitant use of other ototoxic drugs such as aminoglycosides or ethacrynic acid. Hearing impairment may be associated with high dose intravenous bumetanide although bumetanide is probably less ototoxic than furosemide. Ototoxicity is less common with torsemide than with furosemide or bumetanide. Ethacrynic acid can also cause ototoxicity. The mechanism differs from that of furosemide. Hearing loss from ethacrynic acid is more commonly irreversible [75].

Muscle Pain: Bumetanide

Diffuse muscle pain is a limiting side effect of high dose intravenous bumetanide. Pain can be severe and is reversible with reduction in dose or discontinuation of the medication. Muscle pain is not associated with elevations in skeletal muscle enzymes. Dosing of torsemide is not limited by muscle pain.

Other Diuretic Classes

Carbonic Anhydrase Inhibitors

The zinc metalloenzyme carbonic anhydrase plays a key role in $NaHCO_3^-$ resorption and acid secretion in the proximal tubule and, to a lesser extent, in the collecting duct. Acetazolamide is the prototype of a group of carbonic acid inhibitors and the only one used in clinical practice. Acetazolamide inhibits the absorption of $NaHCO_3^-$ in the proximal tubule. In the absence of another diuretic that inhibits sodium reabsorption in the distal nephron, treatment with acetazolamide does not cause a significant diuresis. It does however, cause significant excretion of $HCO3^-$, an increase in urinary pH, significant excretion of potassium and metabolic acidosis [80]. Acetazolamide has been shown to cause a marked natriuresis when added to either hydrochlorothiazide or furosemide in patients resistant to either diuretic and who have a low fractional excretion of sodium [81]. However, its use is limited by the development of metabolic acidosis. In clinical practice, acetazolamide is only used in ADHF in the setting of marked diuretic-induced normokalemic, hypochloremic metabolic acidosis [82].

Thiazide and Thiazide-Like Diuretics

Benzothiadiazides were the first drugs to inhibit the Na^+-Cl^- cotransporter in the distal convoluted tubule. This class of medication came to be known as thiazide diuretics (hydrochlorothiazide, chlorothiazide). Subsequently, drugs that were pharmacologically similar to thiazides and inhibited the Na^+-Cl^-cotransporter were termed thiazide – like diuretics (metolazone, chlorthalidone) [27]. Thiazide diuretics inhibit the Na^+-Cl^- cotransporter in the distal convoluted tubule and promote Na^+ and Cl^- excretion. Thiazides are only moderately effective diuretics – they block the reabsorption of 5–10 % of filtered sodium compared with LDs which block 25 % of filtered sodium. Thiazides are ineffective as monotherapy in the treatment of more than mild heart failure and are not used as single agents in the treatment of ADHF. However, thiazide diuretics are very useful when added to LDs in treating patients with ADHF who remain volume overloaded despite appropriate treatment with adequately dosed LD (see below). Side effects from thiazide diuretics include hypokalemia, hyponatremia (unrelated to arginine vasopressin release), metabolic alkalosis, hypomagnesemia, hypercalcemia and hyperuricemia [23, 25, 83].

Potassium Sparing Diuretics

Triamterene and amiloride have the same mechanism of action and are the only drugs in this class. Spironolactone and eplerenone also decrease the excretion of potassium but are more appropriately classified as mineralocorticoid receptor antagonists (see below). Triamterene and amiloride block epithelial Na^+ channels (amiloride-sensitive Na+ channels or ENaC) in the luminal membrane of principal cells in the late distal tubule and collecting duct. The effect of ENaC blockade on lumen negative voltage decreases potassium (and H^+, Ca^{2+} and Mg^{2+}) excretion and increases serum potassium concentration. Na^+ excretion is minimally increased (2 % of filtered load of sodium). The major side effect of this class of medication is the risk of hyperkalemia. As a result, these medications are contraindicated in in patients with hyperkalemia or patients with conditions that put them at risk of hyperkalemia including renal insufficiency, treatment with ACEI or ARB, treatment with potassium supplements, or treatment with MRAs. In light of their modest natriuretic effects and risk of hyperkalemia, triamterene and amiloride have little use in the treatment of patients with ADHF [25, 27].

Mineralocorticoid Receptor Antagonists (MRAs)

Aldosterone is a steroid hormone with mineralocorticoid effects that is primarily produced in the renal cortex. Aldosterone plays a major role in the control of sodium and potassium homeostasis by increasing sodium and water resorption and increasing K^+ and H^+ excretion. Aldosterone binds to cytosolic mineralocorticoid receptors (MRs) with high aldosterone affinity in epithelial cells in the late distal convoluted

tubule and collecting duct. MRs are members of the superfamily of receptors for steroid hormones, thyroid hormones, vitamin D and retinoids. When aldosterone binds to MR, the MR-aldosterone complex translocates to the nucleus and binds to specific DNA sequences that regulate the expression of multiple gene products. Transepithelial NaCl transport is enhanced. The resulting increase in lumen-negative transepithelial voltage increases the driving force for K^+ and H^+ secretion into the tubular lumen. The genomic effects of aldosterone take several hours to begin to take effect. Aldosterone also has non-genomic effects that are fast acting (occur within minutes) and are probably mediated by binding to plasma membrane MRs. These effects have not been well characterized but probably include an increase in blood pressure that is independent of sodium retention [27, 84, 85].

The MRAs spironolactone and eplerenone competitively inhibit the binding of aldosterone to the MR. The effects on urinary excretion of sodium are similar to those of the renal epithelial Na^+ channel inhibitors. However, unlike the effects of Na^+ channel inhibitors, the clinical effects of MRAs are dependent on endogenous aldosterone levels. Aldosterone levels are increased in heart failure despite treatment with ACEI or ARB and are increased further after administration of loop diuretics [86]. The higher the aldosterone level, the greater the impact of MRAs on urinary excretion. In the Randomized Aldactone Evaluation Study (RALES), spironolactone 25 mg daily did not increase urinary sodium excretion [87]. However, there is literature suggesting that higher doses (50–100 mg daily) of spironolactone significantly increase urinary excretion of sodium when added to standard therapy in patients with ADHF [88, 89].

MR antagonists are the only diuretics that do not require access to the tubular lumen to induce a diuresis. Spironolactone is absorbed partially (~65 %), is metabolized extensively by the liver, undergoes enterohepatic recirculation, is highly protein bound, and has a short half-life of ~1.6 h. The half-life is prolonged to 9 h in patients with cirrhosis. Eplerenone has good oral availability, is eliminated primarily by metabolism by CYP3A4 to inactive metabolites, and has a half-life of ~5 h.

MRAs are generally not used as diuretics in ADHF. They may be used to attenuate potassium losses from LD therapy. They should be initiated or continued during ADHF hospitalization as guideline directed medical therapy for their long-term benefit in patients with HFrEF (see below) [90].

The major side effect of MRAs is life-threatening hyperkalemia. Because spironolactone has affinity for other steroid receptors (progesterone and androgen receptors), it may cause gynecomastia, impotence, decreased libido, hirsutism, and menstrual irregularities. Eplerenone has very low affinity for androgen and progesterone receptors and generally does not cause these side effects.

Monitoring Response to Diuretic Therapy

A primary goal in the treatment of patients with ADHF is to relieve symptoms associated with pulmonary and systemic venous congestion without causing excessively rapid diuresis resulting in hypotension, renal insufficiency or electrolyte

abnormalities. Patients with ADHF need to be carefully monitored for: persistent or worsening signs and symptoms of heart failure; respiratory compromise; adequacy of diuresis; oxygenation; adequate end-organ perfusion; hypotension; worsening renal function; and electrolyte abnormalities. The ACCF/AHA Guidelines recommend that patients should be followed with careful measurement of fluid intake and output, vital signs, daily weight, careful clinical assessment of signs and symptoms of congestion and systemic perfusion, and daily electrolytes and creatinine [28].

Routine use of a Foley catheter is not recommended for monitoring urine output. There should be a high index of suspicion for bladder outlet obstruction particularly in older men. Determining a post-void urine residual volume should be considered in middle age and older men and all patients with renal insufficiency or diuretic resistance. Placement of a catheter is recommended when close monitoring of urine output is needed or if bladder outlet obstruction may be contributing to renal insufficiency and diuretic resistance. Recommendations for patient monitoring are summarized in Table 11.4 [8, 28].

One of the primary goals of care in a patient hospitalized with ADHF is sustained decongestion. The ACCF/AHA Guidelines recommend that patients receive intravenous diuretics until congestion resolves at which time, oral diuretics should be initiated with a goal of maintaining volume status. Generally, patients are transitioned to oral diuretics by using the total daily dose of IV diuretic to calculate the initial total daily dose of oral diuretic. The conversion of IV to oral diuretic dose is 1:1 for bumetanide and torsemide and 1:2 for furosemide. The calculated total daily dose of oral diuretic should be divided in half and given twice daily. Patients should be observed for at least 24 h after transition to oral diuretics to ensure that volume status, serum potassium and renal function remain stable. Patients with a history of diuretic resistance or persistent congestion may not tolerate the transition to oral diuretics because of recurrent or worsening volume overload. Conversely, patients may become more responsive to diuretics as volume overload improves and guideline directed medical therapy is initiated or uptitrated. These patients may develop low blood pressure, orthostatic symptoms, hypokalemia, hyperkalemia and/or worsening renal function. Because of these possibilities, oral diuretics need to be carefully titrated after the transition from IV diuretics using signs and symptoms of congestion and volume depletion, careful monitoring of daily weight and fluid intake and output, and changes in electrolytes and renal function.

Determining whether a patient continues to be volume overloaded can be challenging. In the OPTIMIZE-HF Registry, 50 % of patients lost less than ≤2 kg and 25 % of patients lost no weight during heart failure hospitalization. At *discharge*, one quarter had lower extremity edema, 15 % had rales, and half had persistent symptoms. This data suggests that a significant proportion of patients hospitalized for ADHF remain congested at discharge [91]. In a post-hoc analysis of the placebo group in the EVEREST trial, a modified composite congestion score (CCS) was calculated by summing individual scores for orthopnea, JVD and pedal edema that were graded daily on a 0–3 scale of clinician-investigator determined severity (total possible score 0–9) [92]. The median CCS score decreased from a mean of 4 at baseline to 1 at discharge. At discharge, nearly three quarters of study participants had a CCS of 0–1 and less than 10 % of patients had a CCS > 3. Each CCS point >0

Table 11.4 Patient monitoring during treatment for ADHF [8]

Monitoring recommendations for patients hospitalized with ADHF		
Frequency	Value	Specifies
At least daily	Weight	Determine after voiding in the morning Account for possible increased food intake due to improved appetite
At least daily	Fluid intake and output	
More than daily	Vital signs	Orthostatic blood pressure if indicated Oxygen saturation daily until stable
At least daily	Signs	Edema Ascites Pulmonary rales Hepatomegaly Increased JVP Hepatojuglar reflux Liver tenderness
At least daily	Symptoms	Orthopnea PND or cough Nocturnal cough Dyspnea Fatigue, lightheadedness
At least daily	Electrolytes	Potassium Sodium
At least daily	Renal function	BUN Serum Creatinine[a]

Reprinted from Heart Failure Society of America et al. [8], pp. e1–e194, © 2010, with permission from Elsevier

[a]See background section for addictional recommendations on laboratory evaluations

was associated with a hazard ratio of 1.34 and 1.16 for mortality at 30 days and for the study period, respectively (median follow up was 9.9 months). Patients with a CCS of 0 at discharge experienced a heart failure rehospitalization rate of 26.2 % and all-cause mortality rate of 19.1 % during the follow-up period. Patients with CCS scores of 1 or 3–9 at discharge had HF rehospitalization rates of 34.9 % and 34.7 %, respectively and an all-cause mortality rates of 24.8 % and 42.8 %, respectively.

Some patients, especially those with HFpEF, have no or little history of weight gain prior to hospitalization and may have an improvement in symptoms with improvement in blood pressure and little diuresis. However, it is notable that in the OPTIMIZE-HF registry, patients with HFpEF had a similar distribution of weight loss, symptom improvement, and frequency of edema and rales at discharge compared with patients with HFrEF [91].

The data concerning the relationship between weight loss, net fluid loss, dyspnea relief and clinical outcomes in patients hospitalized for ADHF is conflicting. In the EVEREST trial, there was a correlation between weight loss and patient assessed dyspnea relief [93]. The Ultrafiltration versus Intravenous Diuretics for Patients

Hospitalized for Acute Decompensated Congestive Heart Failure (UNLOAD) trial compared ultrafiltration (UF) with IV diuretic therapy in patients with ADHF. In the patients randomized to UF, there was a greater reduction in body weight, greater fluid loss and a reduction in rehospitalization and unscheduled clinic visits, but no difference in dyspnea score when compared with the IV diuretic arm [94]. In the ESCAPE trial, there was no association between weight loss and clinical events (days alive out of the hospital in the first 6 months; death; death or rehospitalization; and death, rehospitalization, or cardiac transplantation) although patients with the greatest weight loss had a significantly decreased orthopnea score [95]. In the PROTECT Trial, there was a strong association with weight loss, early dyspnea relief and reduced early post-discharge mortality [96]. In the Pre-RELAX-AHF study, there was an association between sustained relief of dyspnea at 5 days and reduced 30-day mortality [67]. Data from the Diuretic Optimization Strategy Evaluation in Acute Heart Failure (DOSE-AHF) trial found that weight loss, fluid loss and NT-proBNP reduction at 72 h did not correlate with dyspnea relief but did correlate with improved outcomes at 60 days. Improvement in dyspnea was associated with a small improvement in clinical outcomes [97].

These data challenge the idea that weight loss is a sufficient surrogate marker for adequate decongestion and suggest that careful evaluation of symptoms, physical findings, laboratory measures, weight change and net fluid balance need to be considered when assessing volume status and diuretic dosing [28, 97]. The diagnostic value of clinical markers of congestion from a scientific statement from the Acute Heart Failure Committee of the Heart Failure Association of the European Society of Cardiology is summarized in Table 11.5 [98].

Hemoconcentration (HC)

Several studies have suggested that hemoconcentration (an increase in low hemoglobin or a relative increase in the cellular elements in blood) is a surrogate marker for intravascular volume status and may be a useful indicator of adequate decongestion in patients hospitalized for ADHF [99, 100]. A post-hoc analysis from the ESCAPE trial assessed the impact of hemoconcentration on outcome [58]. Three hundred thirty-six of 433 randomized patients who had paired baseline and pre-discharge hematocrit, albumin or total protein values were included in the analysis. Baseline to discharge differences in the laboratory values that fell within the top tertile of the group were defined as indicators of hemoconcentration. Patients with ≥ 2 paired laboratory values in the top tertile were considered to have evidence of hemoconcentration. The group of patients with evidence of HC received higher doses of diuretics, lost more weight and fluid and had greater reductions in filling pressures. HC was strongly associated with worsening renal function whereas changes in RA and PCWP were not associated with worsening renal function. HC was strongly associated with a lower 180-day mortality rate that persisted after adjustment for baseline differences in risk (HR 0.16; $P = 0.001$).

Table 11.5 Diagnostic value of clinical markers of congestion [98]

Sign or symptom	Sensitivity	Specificity	PPV	NPV
Dyspnoea on exertion	66	52	45	27
Orthopnoea	66	47	61	37
Oedema	46	73	79	46
Resting JVD	70	79	85	62
S3	73	42	66	44
Chest X-ray				
Cardiomegaly	97	10	61	—
Redistribution	60	68	75	52
Interstitial oedema	60	73	78	53
Pleural effusion	43	79	76	47

Reprinted from Mihai [98], with permission from John Wiley and Sons
JVD jugular venous distension, *S3* third heart sound, *PPV* positive predictive value, *NPV* negative predictive value. All numbers are expressed as percentages

A post hoc analysis of 1969 patients enrolled in the PROTECT study assessed the relationship between the change in hematocrit during heart failure hospitalization and outcome [101]. Anemia at baseline was defined, according to the World Health Organization (WHO) criteria, as a baseline hemoglobin level of <13 g/dl for men and <12 g/dl for women and was present in 50.3 % of patients. Hemoconcentration was defined as an increase in hemoglobin levels between baseline and day 7 and was seen in 69.1 % of patients. HC was associated with better renal function at baseline, more weight loss and greater deterioration in renal function. The total dose of diuretics was *lower* in the patients with HC. Greater weight loss and better baseline renal function were associated with a more rapid increase in hemoglobin concentration. The absolute change in hemoglobin was an independent predictor of outcome. There was a 34 % reduction in all-cause mortality at 180 days for each gram/dl increase in hemoglobin between baseline and day 7.

A retrospective analysis of 1684 patients assigned to the placebo arm in the EVEREST trial found that 26 % of patients had evidence of hemoconcentration defined as a ≥ 3 % absolute increase in hematocrit between baseline and discharge or day 7 [102]. Patients with greater increases in hematocrit tended to have better baseline renal function. HC was associated with a greater risk of in-hospital worsening of renal function, which generally returned to baseline at 4 weeks after discharge. Patients with HC were less likely to have clinical congestion at discharge, and experienced greater in-hospital decreases in body weight and natriuretic peptide levels. After adjustment for baseline clinical risk factors, every 5 % absolute increase in in-hospital hematocrit change was associated with a 19 % reduction in all-cause mortality following discharge over an average follow up 9.9 months. HCT change was also associated with a significantly decreased risk of cardiovascular mortality or HF hospitalization at ≤100 days following randomization (HR 0.73). In the Korean Heart Failure (KorHF) Registry, HC (defined as an increase in hemoglobin levels between admission and discharge) occurred in 43 % of patients and was

found to be an independent negative predictor of the combined primary end-point of all-cause mortality and HF hospitalization after adjusting for other HF risk factors (HR = 0.671; P < 0.001) [103].

There may be a difference in the prognostic value of hemoconcentration based on when it occurs during the HF hospitalization. In a single center study of 845 patients hospitalized for ADHF, hemoconcentration (defined as an increase in both hemoglobin and hematocrit) occurred in 422 patients. HC was defined as "early" or "late" based on whether the maximal increase in hemoglobin and hematocrit occurred in the first or second half of the hospitalization. Early and late patients had similar baseline characteristics, cumulative in-hospital diuretic administration, and degree of worsening renal function. Late patients had higher average daily loop diuretic doses, greater weight loss, later transition to oral diuretics, and shorter length of stay. Late HC was associated with a significant survival advantage over a median follow-up of 3.4 years compared with early HC (HR: 0.73, p = 0.026) and no HC (HR: 0.74; p = 0.0090). Early HC was not associated with a survival advantage [104].

This data suggests that more complete decongestion is associated with a better post-discharge prognosis and that HC may be a reasonable surrogate for assessing the adequacy of decongestion during an admission for decompensated heart failure. However, the data supporting the use of HC to guide therapy have significant limitations. A prospective randomized study comparing HC with usual clinical care as a therapeutic strategy to guide treatment has not been performed. It is possible that patients with HC are healthier and more diuretic responsive. Most of the data comes from studies of patients with HFrEF. Because HC has been variably defined, it is unclear what degree of change in hemoglobin, hematocrit or both is clinically significant [99]. Also, in some patients, the absence of hemoconcentration may not reflect residual volume overload but instead, occult blood loss, poor nutritional status, medications, or the effects of serial phlebotomy. Therefore, the data do not support the routine intensification of diuretic therapy in patients who do not demonstrate an increase in hemoglobin or hematocrit [105].

Natriuretic-Peptide (NP) Guided Therapy

NP levels are important markers of risk that add prognostic information in ambulatory patients with chronic HF and in hospitalized patients with ADHF [8, 106, 107]. In addition, the pre-discharge NP and change in NP from admission to discharge provide additional independent information that helps identify patients at risk for hospitalization or death after discharge [108–110].

However, it is not clear if serial NP measurements are useful in guiding therapy in patients hospitalized with acute heart failure. The Rapid Emergency Department Heart Failure Outpatients Trial (REDHOT II) was a multicenter, prospective randomized controlled study of 447 patients hospitalized with acute heart failure randomized to serial BNP testing at 3, 6, 9, and 12 h, then daily versus standard care. No difference was found between the two groups with respect to length of stay,

in-hospital mortality, 30-day mortality, or readmission rate [111]. The HFSA and ACCF/AHA guidelines do not recommend the use serial NP testing to guide therapy in patients hospitalized with acute heart failure [8, 28].

Pulmonary Artery Catheterization (PAC)

Invasive hemodynamic monitoring (IHM) with a pulmonary artery catheter (PAC) has been used in small non-randomized studies to guide diuretic and vasodilator therapy to achieve pre-specified near normal filling pressures in patients with severe refractory heart failure. This approach resulted in sustained improvements in hemodynamics, severity of mitral regurgitation, exercise tolerance and symptoms [45, 112, 113].

The Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization (ESCAPE) trial evaluated whether the routine use of a PAC was safe and improved clinical outcomes in patients with ADHF [114]. Four hundred forty-three patients with severe symptomatic heart failure at 26 sites were randomized to receive therapy guided by clinical assessment and PAC or clinical assessment alone. The target patient was sufficiently ill with advanced heart failure to make the use of the PAC reasonable, but also sufficiently stable to make crossover to PAC for urgent management unlikely. Patients who were felt to require a PAC for management of heart failure were not included in the study but were included in a PAC registry. The goal of treatment in both groups was resolution of clinical signs and symptoms of congestion, particularly jugular venous pressure elevation, edema, and orthopnea. Additional goals in the PAC group included achieving a pulmonary capillary wedge pressure of 15 mm Hg and a right atrial pressure of 8 mm Hg. Medications were not specified, but inotrope use was explicitly discouraged. The patient population was a particularly ill group as reflected by an average LVEF 19 %, urea nitrogen 35 mg/dL, creatinine1.5 mg/dL, RAP 14 mmHg, PCWP 25 mmHg, and cardiac index 1.9 l/min/m^2.

Treatment in both groups led to substantial reductions in symptoms, JVP and edema. The use of a PAC did not significantly affect the primary end-point of number of days alive and out of the hospital during the first six months. There was no difference between groups with respect to number of days hospitalized, mortality at 180 days, or in-hospital plus 30-day mortality. Exercise and quality of life endpoints improved in both groups with a trend toward greater improvement in the PAC group. The Minnesota Living with Heart Failure questionnaire improved in both groups with greater improvement in the PAC group at 1 but not 6 months. The time trade-off tool showed great improvement for the PAC group compared with the clinical assessment group at all time points suggesting a greater improvement in quality of life. There was a consistent trend of greater improvement in clinical status in patients in whom therapy had been adjusted using PAC. There were no deaths related to PAC use. Adverse events specifically attributable to PACs occurred in 9/215 (4.2 %) patients and included: PAC-related infection (4 patients), bleeding (2 patients), catheter knotting (2 patients), pulmonary infarction/hemorrhage (2 patients) and ventricular tachycardia (1 patient).

The neutral findings from ESCAPE are consistent with recent meta-analysis data concerning the use of PACs in more diverse populations of patients in the critical care setting [115, 116]. These findings cannot be extrapolated to all patients in the critical care setting as patients enrolled in ESCAPE and other randomized studies were not felt to require invasive hemodynamic monitoring - that is, physicians had clinical equipoise about the need for a PAC.

Complications associated with the use of PACs include hematoma, pneumothorax, infection, pulmonary infarction, pulmonary hemorrhage, hemothorax, arterial puncture, catheter knotting, heart block in the setting of LBBB, and ventricular tachycardia. In the UK multicenter randomized Pulmonary Artery Catheters in Management of Patients in Intensive Care (PAC-Man) trial, the incidence of complications directly attributable to PAC insertion was significantly higher (10 %) than in the ESCAPE trail (4.2 %). However, the patients enrolled in the PAC-Man trial were significantly sicker than those in ESCAPE: 65 % had multi-system organ failure; only 11 % had decompensated heart failure; and the in-hospital mortality rate was 66 % in the control group [117].

The HFSA, ACCF/AHA, and ESC guidelines do not recommend the routine use of invasive hemodynamic monitoring in ADHF but do outline indications for PAC in carefully selected patients [8, 28, 118]. IHM should be considered in patients whose volume status and filling pressures are uncertain. In addition, placement of a PA catheter should be strongly considered in patients who are hypotensive, in cardiogenic shock, are unresponsive to initial medical therapy, or who develop clinically significant hypotension and/or significant worsening of renal function during initial treatment for ADHF. IHM will help identify patients who have hypotension because of low filling pressures, can guide the use of higher dose diuretic therapy and/or parenteral vasodilator therapy in patients with marginal blood pressure and persistent pulmonary congestion, and can indicate the need for inotropic therapy in patients with end-organ dysfunction, hypotension or worsening renal failure. IHM is indicated in patients with persistent severe symptoms despite adjustment of recommended therapies. In addition, invasive measurement of hemodynamics is indicated in patients being considered for heart transplantation to determine PA pressures, pulmonary vascular resistance, and transpulmonary gradient and in patients being considered for a long-term left ventricular assist device to better assess right ventricular performance [8, 119].

Diuretic Resistance

An impaired response to loop diuretics is seen in some patients with ADHF and is referred to as diuretic resistance (DR). Estimating an accurate incidence of diuretic resistance among patients with ADHF is hindered by the absence of a uniformly accepted definition. Probably the most commonly cited definition is “failure to decongest despite adequate and escalating doses of diuretics” [120]. Other definitions include measures of sodium excretion or volume loss related to the amount of

furosemide administered [20]. A practical definition may be: persistent volume overload despite administration of 160 to 320 mg of furosemide or LD equivalent given intravenously over a 24-h period [83]. DR is more common in patients with diabetes, atherosclerotic disease, lower eGFR, high BUN and/or low systolic BP and is associated with greater risk of death and heart failure rehospitalization [121, 122].

DR results from the interplay between the pathophysiology of sodium retention in heart failure and the renal and neurohormonal responses to diuretic therapy. As described above, the diuretic response curve in heart failure is shifted downward and to the right so that the intraluminal threshold for diuresis is increased and the maximal effect or "ceiling" is reduced. DR represents a further shift downward and to the right of the response curve. The pathophysiology of DR is multifactorial. Potential causes include: changes in cardiac and renal hemodynamics (see below); decreased delivery of LDs to the proximal tubule as a result of decreased renal blood flow or decreased secretion of LDs into the proximal tubule due competition with organic acids (e.g. BUN) for binding sites on the organic acid transport system; the "breaking phenomenon" (see above); activation of the RAAS and sympathetic nervous system resulting in decreased renal blood flow; and an increase in the absorption of sodium at tubular sites not blocked by LDs including the proximal tubule (mediated by increases in angiotensin II) and the distal tubule and proximal collecting duct (mediated by increases in aldosterone) despite optimal doses of neurohormonal antagonists [86, 123]. Chronically, hypertrophy and hyperfunction of the tubular cells in the nephron distal to the loop of Henle occurs which results in enhanced sodium retention [25, 26].

Venous Congestion

There is increasing evidence that elevated central venous pressure and elevated intra-abdominal pressure (IAP) contribute to diuretic resistance and worsening renal function in patients with ADHF. This has been appreciated since 1950 [124]. A retrospective review of 2557 patients who underwent right heart catheterization at a single academic medical center found that elevated CVP was the only hemodynamic parameter that was associated with low eGFR on multivariate analysis [125]. In another study, 51 patients with heart failure underwent pulmonary artery catheterization. GFR and renal blood flow were assessed by (125)I-Iothalamate and (131) I-Hippuran clearances, respectively. High right atrial pressure had little impact on GFR in patients with normal or high renal blood flow but was associated with a significant reduction in GFR in patients with low renal blood flow [126]. In a study of 145 consecutive patients admitted with ADHF treated with intensive medical therapy guided by hemodynamic monitoring using a pulmonary artery catheter, elevated CVP on admission (and after intensive medical therapy) was the only hemodynamic measure that was associated with worsening renal function defined as increase in serum creatinine of $\geq$0.3 mg/dL. There was an incremental risk of worsening renal function with increasing CVP; 75 % of patients with baseline CVP > 24 mmHg developed worsening renal function during hospitalization [127].

Mullens measured intraabdominal pressure (IAP) serially using a transvesicle technique [128, 129] in 40 patients admitted for treatment of ADHF. 60 % of patients had increased intraabdominal pressure (>7 mmHg) and 10 % had intra-abdominal hypertension (≥12 mmHg). Increased IAP was associated with worse renal function at baseline. Intensive medical therapy resulted in improved hemodynamics and lower IAP. There was a strong correlation noted between reduction in IAP and improvement in renal function in patients with elevated IAP at baseline [130]. In a small group of patients hospitalized for ADHF who had increased IAP and ascites who developed progressive elevation in serum creatinine in response to intravenous loop diuretics, mechanical fluid removal by paracentesis decreased IAP and improved renal function [131].

These data suggest that high right atrial pressure and elevated intraabdominal pressure contribute to renal dysfunction and diuretic resistance in patients with ADHF. Elevated IAP may compress the renal veins, the ureters or the renal parenchyma and probably impacts intra-glomerular hemodynamics. Glomerular filtration pressure can be calculated by subtracting proximal tubular pressure (which can be estimated by IAP) from mean blood pressure. The renal filtration gradient, which strongly correlates with GFR, is calculated by subtracting proximal tubular pressure from glomerular filtration pressure (mean blood pressure – 2 IAP). As IAP increases, especially in patients with relatively low mean arterial pressure, GFR significantly decreases [130].

Cardiorenal Syndrome (CRS)

Combined disorders of cardiac and renal function are classified as cardiorenal syndromes. CRS Type 1 is defined by the development of acute kidney injury occurring in the setting of an acute cardiac illness, most commonly ADHF. It occurs in approximately 25–30 % of patients hospitalized for ADHF. The most commonly used criteria to identify patients with CRS Type 1 are an increase in serum creatinine >0.3 mg/dL or a reduction in eGFR of 20–25 %. Risk factors for developing CRS include prior heart failure, male gender, diabetes, admission creatinine ≥1.5 mg/dL, and hypertension [132, 133]. The clinical syndrome is characterized by a rise in serum creatinine (generally within the first 3 days of hospitalization), oliguria and diuretic resistance with or without worsening HF symptoms. While alterations in renal hemodynamics including renal hypoperfusion, low systemic blood pressure and elevated venous congestion play a role in diuretic resistance and renal insufficiency in ADHF, changes in renal hemodynamics alone do not account for this syndrome. In an analysis from the ESCAPE trial, no correlation was found between any baseline hemodynamic parameter or change in hemodynamic parameter and the development of worsening renal function during heart failure hospitalization [134]. In an analysis of hemodynamic data from patients enrolled in the Vasodilation in Management of Acute Congestive Heart Failure (VMAC) trial who had undergone right heart catheterization, no correlation was found between worsening renal function and baseline right atrial pressure (RAP) or change in RAP. Smaller net fluid loss

in the first 24 h was strongly associated with an increased risk of developing worsening renal function [135]. Emerging evidence suggests that the pathophysiology of CRS Type I is multifactorial, involves complex heart and renal crosstalk and is mediated by hemodynamic changes, neurohormonal activation, inflammation, immune cell signaling, hypothalamic-pituitary stress reaction, systemic endotoxin exposure from the abdominal viscera, and oxidative stress resulting in bidirectional organ injury. This pathophysiology is incompletely understood and definitive approaches to treatment have not been established [32, 122, 136–138].

Diuretic Resistance-Treatment Strategies

A number of treatment strategies have been found to be useful in patients with diuretic resistance. Diuretics should be given intravenously to avoid issues of decreased or delayed absorption because of intestinal edema. Escalating doses of IV diuretics should be administered to insure that the patient is diuretic resistant and not undertreated. Diuretics should be dosed at least 2–3 times a day or given as a continuous infusion to insure that the time of sub-threshold diuretic concentration in the loop of Henle is kept at a minimum. Data from several studies suggest that continuous infusion of loop diuretics improves diuresis and renal function when compared to bolus therapy [139, 140]. These results were not confirmed in the DOSE trial.

Combined Diuretic Therapy (CDT)

The addition of an oral or intravenous thiazide diuretic has been shown to be helpful in patients with diuretic resistance. Thiazide diuretics are weak natriuretic agents that block only 5–10 % of filtered sodium when used as monotherapy. They are ineffective as single agents in the treatment of patients with moderate to severe heart failure. However, in the setting of LD therapy, sodium delivery to the distal tubule increases significantly. Hypertrophy and hyperfunction of the distal nephron contribute to diuretic resistance. Blocking sodium uptake using TD has been shown to increase diuresis significantly. The combination of diuretics that act at different sites in the nephron has been termed “sequential nephron blockade”. Generally, it is appropriate to consider adding a TD when adequate diuresis has not been achieved despite an intravenous dose of furosemide of 180–360 mg daily (or other LD equivalent). There is little evidence to suggest that one TD is superior to another when used in combination with an intravenous LD. It has been suggested that metolazone is superior to other TDs in patients with renal insufficiency but other TDs have been shown to be effective in this patient population. Traditionally, TDs have been given 30 min before LD administration. However, this dosing regimen has not been studied - most studies of CDT looked at the effect of giving an LD and TD at the same time [20, 83, 141, 142].

The most serious complication of CDT is hypokalemia which can be profound. Hyponatremia is common. Hypomagnesemia can occur and may make hypokalemia worse. Occasionally, CDT results in a marked diuresis which may result in hypotension. Electrolytes, renal function, urine output and vital signs need to be followed closely.

Ultrafiltration (UF)

Ultrafiltration (UF) is the process of extracorporeal removal of plasma water from whole blood using a semipermeable membrane that allows for the removal of fluid in response to a transmembrane pressure gradient generated either by arterial pressure (in the case of arterial-venous ultrafiltration) or by an extracorporeal pump (in the case of veno-venous ultrafiltration). Blood is removed from and then returned to the circulation after passing through a UF filter. The fluid removed is isotonic with plasma. In the past, the use of UF was limited by machines that required high flow rates, large extracorporeal blood volumes and the use of large bore intravenous catheters. With contemporary UF devices (Aquadex System 100), veno-venous ultrafiltration can be performed using a double lumen venous catheter placed centrally or peripherally that can accommodate 10–40 ml/min of blood flow. Therapeutic anticoagulation using continuous infusion heparin is recommended to avoid clotting the UF filter. UF can be performed at the bedside without the need for specialized personnel. The total extracorporeal blood volume is 33 cc. Pump blood flow can be adjusted to between 10–40 ml/min. Fluid removal can range from 10–500 ml/h [23, 143, 144].

UF removes fluid from the intravascular space. The reduction in blood volume results in a decrease in intraluminal hydrostatic pressure that promotes movement of fluid from the interstitial to the intravascular space. This preserves intravascular volume and maintains adequate intra-cardiac filling pressures, cardiac output and systemic blood pressure. Ultrafiltration can safely remove fluid in patients with volume overload provided that the rate of fluid removal does not exceed the rate at which extravascular fluid is reabsorbed into the intravascular space (the plasma refill rate or PRR). The PRR is proportional to the trans-capillary pressure gradient (the net difference between intraluminal and interstitial oncotic and hydrostatic pressure gradients) and the permeability of the capillary membrane. The plasma refill rate is approximately 15 ml/min but is variable among patients and changes in the same patient in response to heart failure treatment [23, 143, 144].

UF has been shown in patients with refractory heart failure to lower right atrial and pulmonary capillary wedge pressure and increase cardiac output and stroke volume without changing mean arterial pressure, heart rate or plasma volume [145]. One study compared UF with continuous infusion of furosemide with a goal of achieving a 50 % reduction in RA pressure in 16 patients with ADHF. The UF and furosemide patients had a similar reduction in RA and PCW pressures immediately after treatment. Both groups had elevation in plasma renin activity, norepinephrine

and aldosterone levels immediately after treatment. At day 4, the UF group demonstrated a sustained reduction in filling pressures while the furosemide group had a return of filling pressures to baseline. In addition, by day 2, plasma renal activity, plasma norepinephrine levels, and aldosterone levels decreased to below baseline in the UF group but remained elevated in the furosemide group. These differences in filling pressures and neurohormone levels were sustained for three months [146]. These observations led to the hypothesis that ultrafiltration may be superior to IV diuretic therapy in avoiding diuretic-induced neurohormonal activation.

The Relief for Acutely Fluid-Overloaded Patients with Decompensated Congestive Heart Failure (RAPID-CHF) trial was a small multicenter study that compared a single 8-h session of UF with usual care to usual care alone in 40 patients hospitalized for ADHF who had evidence of significant volume overload on physical exam. The primary end-point was weight loss 24 h after the time of enrollment. Ultrafiltration was successfully performed in 18 of the 20 patients assigned to UF group. Fluid removal after 24 h was 4650 ml in the UF group and 2838 ml in the usual care groups ($p = 0.001$). Weight loss after 24 h, the primary end-point, was 2.5 kg in the UF group and 1.86 kg in the usual care group ($p = 0.240$). UF was well tolerated. Dyspnea and CHF symptoms were significantly improved in the UF group compared to usual care at 48 h. There were greater improvements in global CHF and dyspnea assessments in the UF group compared with the usual care group at 48 h. There was no difference in the median length of stay between the study groups [147].

The Ultrafiltration versus Intravenous Diuretics for Patients Hospitalized for Acute Decompensated Congestive Heart Failure (UNLOAD) trial tested the hypothesis that veno-venous ultrafiltration is superior to intravenous diuretics in patients hospitalized with ADHF [94]. 200 patients hospitalized with ADHF who had evidence of volume overload were randomized within 24 h of admission to parenteral diuretics or ultrafiltration without concomitant diuretic therapy. The duration and rate (up to 500 ml/h) of fluid removal were decided by the treating physician. The minimum daily intravenous diuretic dose had to be at least twice the before-hospitalization daily oral dose. The primary efficacy end-points were weight loss and patients' dyspnea assessment 48 h after randomization. The primary safety end-points were: changes in serum blood urea nitrogen, creatinine, and electrolytes assessed at entry and at intervals up to 90 days after enrollment; and episodes of hypotension within 48 h of randomization.

Weight loss at 48 h was greater in the ultrafiltration group (5.0 kg vs 3.1 kg; $p = 0.001$). Dyspnea score improved to a similar degree in the two treatment arms. Changes in serum creatinine were similar in the two groups. Serum potassium <3.5 mEq/L was more common in the diuretic group than in the ultrafiltration group (12 % vs 1 %, $P = 0.018$). There was no difference in the length of index hospitalization. Fewer patients in the ultrafiltration group required vasoactive drugs at 48 h. At 90 days, the ultrafiltration group had fewer patients rehospitalized for HF (18 % vs 32 %; $p = 0.037$). New York Heart Association functional class, Minnesota Living with Heart Failure scores, 6 -minute walk distance, Global Assessment scores and

B-type natriuretic peptide levels were similarly improved in both groups at discharge and at 30 and 90 days.

The Cardiorenal Rescue Study in Acute Decompensated Heart Failure (CARRESS-HF) compared veno-venous ultrafiltration to diuretic-based stepped pharmacologic therapy in patients hospitalized for ADHF who had worsening renal function and persistent congestion [148]. Patients could be considered for inclusion in the trial if they were hospitalized for ADHF, had worsened renal function defined as an increase in serum creatinine of at least 0.3 mg/dL within 12 weeks before or 10 days after the index admission for heart failure and had evidence of persistent congestion (defined by at least two of the following: at least 2+ peripheral edema, jugular venous pressure greater than 10 cm of water, or pulmonary edema or pleural effusions on chest radiography). There was no exclusion criterion based on ejection fraction. Patients with a serum creatinine level >3.5 mg/dL at the time of admission and those receiving intravenous vasodilators or inotropic agents were excluded from the study. Patients were randomized in a 1:1 ratio to ultrafiltration using the Aquadex System 100 with fluid removal at a rate of 200 ml per hour without concomitant diuretic therapy or stepped pharmacologic therapy targeted to achieve a daily urine output of 3–5 l and that could include bolus furosemide, continuous infusion furosemide, a thiazide diuretic, metolazone, dopamine or dobutamine at 2 mcg/kg/min, and nitroglycerine or nesiritide. The primary end point was the bivariate change from baseline in the serum creatinine level and body weight, assessed 96 h after random assignment. Patients were followed for 60 days.

UF was found inferior to pharmacologic therapy due to an increase in creatinine in the ultrafiltration group (+0.23 vs −0.04; p = 0.003). There was no difference between treatment groups with respect to change in weight. A higher percentage of patients in the ultrafiltration group than in the pharmacologic-therapy group had a serious adverse event (72 % vs. 57 %, P = 0.03) predominantly related to bleeding complications, renal failure and infection. There was no difference in the estimated 60-day mortality rate or the composite rate of death or hospitalization for heart failure. At 96 h and at day 7 or hospital discharge, there were no significant between group differences in scores on the dyspnea and global well-being visual-analogue scales. Clinical decongestion at 96 h (defined as JVP < 8 cm of water, no more than trace peripheral edema, and the absence of orthopnea) occurred in 9 % of patients with pharmacologic therapy and 10 % of patients with ultrafiltration.

Ultrafiltration has not been established as first line therapy to treat volume overload in ADHF in light of cost, the need for veno-venous access, provider experience, the need for specially trained nursing support, and the lack of benefit in randomized trials comparing UF to standard therapy. The ACCF/AHA and HFSA guidelines suggest that UF may be considered for patients with obvious volume overload in lieu of diuretics or for patients with refractory congestion not responding to medical therapy [8, 28]. Providers should be aware that initiating UF in patients with significant or progressive renal insufficiency, diuretic resistance, and refractory volume overload may cause worsening renal function and the need for chronic renal replacement therapy.

Parenteral Vasodilators

Vasodilators have a role in the management of patients with ADHF, especially in patients with hypertension on presentation, in patients without hypotension and with systolic dysfunction who have severe symptomatic volume overload and in patients who do not respond promptly to diuretic therapy alone in the absence of hypotension. Three parenteral vasodilators are appropriate in the treatment of ADHF: nitroglycerine, sodium nitroprusside and nesiritide. Vasodilators decrease preload and afterload to varying degrees, increase stroke volume, and decrease functional mitral regurgitation. Guidelines from the ACCF/AHA and HFSA endorse the use of nitroglycerine, nitroprusside, or nesiritide as additions to diuretic therapy for relief of congestive symptoms in the absence of hypotension [8, 28]. The use of IV nitroglycerine in the absence of hypotension is also endorsed by guidelines from the ESC and the American College of Emergency Physicians [118, 149]. The 2012 ESC guidelines suggest that: "an IV infusion of a nitrate should be considered in patients with pulmonary congestion/edema and a systolic blood pressure of > 110 mmHg, who do not have severe mitral or aortic stenosis, to reduce pulmonary capillary wedge pressure and systemic vascular resistance. Nitrates may also relieve dyspnea and congestion. Symptoms and blood pressure should be monitored frequently during administration of IV nitrates" [118]. The HFSA Guidelines suggest that intravenous vasodilators (nitroprusside, nitroglycerin, or nesiritide) may be considered in patients with ADHF who have persistent severe HF despite aggressive treatment with diuretics and standard oral therapies. It should be noted that only 18 % of patients enrolled in the ADHERE registry received IV vasodilators and <1 % of patients receive nitroprusside [150].

Nitroglycerin, nitroprusside and nesiritide all act by activating soluble guanylate cyclase in smooth muscle cells. The resulting increase in intracellular cyclic guanosine monophosphate (cGMP) results in vasodilation. The physiologic effect may be predominantly venodilation (NTG) or so called "balanced" arterial and venous dilation (SNP, nesiritide, and higher dose NTG). Most studies of vasodilator therapy in ADHF have looked at short-term hemodynamic end-points. These studies suggest that vasodilator therapy is associated with an improvement in hemodynamic parameters with a reduction in right atrial and pulmonary capillary wedge pressures, a reduction in the severity of mitral regurgitation and an increase in cardiac output. Reasonable goals for the use of vasodilator therapy include: more rapid relief of dyspnea; control of blood pressure in the patient presenting with ADHF and hypertension; improvement of symptoms in patients with an inadequate response to diuretic therapy; treatment of myocardial ischemia (with NTG); and improvement in hemodynamics while transitioning to oral heart failure medication [45, 61, 151–156].

Hypotension is the most important limitation of using vasodilators in heart failure. Vasodilators should be avoided in patients with a systolic blood pressure of <90–110 mmHg or mean blood pressures of less than 65 mmHg. Blood pressure should be monitored frequently and the vasodilator should be discontinued if

hypotension develops. Vasodilator therapy may be reinitiated at a lower dose once hypotension resolves. Because volume depleted patients are at significant risk of developing hypotension with vasodilator therapy, it is important to establish that the patient is volume overloaded prior to starting any of these medications. Vasodilators should be used with caution in patients with HFpEF as these patients are more preload sensitive. Vasodilators should also be used with caution, if at all, in patients with significant aortic or mitral stenosis [8, 118, 157].

Organic Nitrates/Nitroglycerine

Nitroglycerine and other organic nitrates are pro-drugs that are converted to nitric oxide and other NO-containing compounds. NO stimulates the enzyme guanylate cyclase which in turn increases the production of cyclic guanosine monophosphate (cGMP) in the vascular wall. Increases in cGMP reduce cytosolic calcium levels by decreasing the release of calcium from the cytoplasmic reticulum and by reducing calcium influx from the extracellular space. In addition, NO-mediated increases in intracellular cGMP activate protein kinase G (PKG) which also plays an important role in mediating nitrate-mediated vasorelaxation. These changes lead to smooth muscle relaxation and venous and arterial vasodilation [153–158]. Endothelial release of prostacyclin may also contribute to the vascular effects [159]. The exact mechanism of the process of biotransformation from nitroglycerine to NO is incompletely understood. Some studies suggest that NTG is hydrolyzed by hepatic glutathione–organic nitrate reductase. Other data suggest that mitochondrial aldehyde dehydrogenase (ALDH-2) mediates NTG biotransformation [160].

Organic nitrates can be administered sublingually, orally, by inhalation, transdermally, or intravenously. At low dose (30–40 μg/min), intravenous NTG predominantly causes venodilation. At higher doses, NTG also causes arterial and coronary vasodilation [158]. The onset of the hemodynamic effects of NTG is immediate. The offset is also rapid. NTG has an elimination half-life of 3 minutes. Nitrates are cleared by extraction in the vasculature, hydrolysis in the blood, and metabolism by glutathione-nitrate reductase in the liver. Glass bottles and non-polyvinyl chloride plastic tubing must be used to avoid absorption onto plastic surfaces. The drug is generally initiated at an infusion rate of 10 mcg/min and increased in increments of 5–10 μg/min every 3–5 minutes titrated to relief of symptoms of angina or dyspnea, reduction in PCWP, change in systolic blood pressure, or drug related side effects [17]. The maximum dose is between 200–500 mcg/min [153, 161].

The hemodynamic effects of a therapeutic dose of NTG in patients with heart failure due to systolic dysfunction include reductions in right- and left-sided filling pressures, pulmonary and systemic vascular resistance, and systolic blood pressure. Cardiac output generally improves due to a reduction in systemic vascular resistance and the severity of mitral regurgitation [152, 153, 161]. In some patients, there may also be an improvement in myocardial ischemia related to NTG-mediated dilation of epicardial coronary arteries and reductions in preload and afterload.

There is evidence that the vasodilator response and hemodynamic effects of organic nitrates are attenuated in patients with heart failure. This is referred to as "nitrate resistance". Up to 50 % of patients with heart failure do not have a significant reduction in PCWP with conventional doses of nitrate (e.g. isosorbide dinitrate 40 mg orally) [162–165]. Nitrate resistance can be overcome with increasing doses of nitrate but approximately 20 % of patients do not have a hemodynamic response to NTG regardless of dose [165, 166]. Nitrate resistance appears to be more common in patients with high right atrial pressure and/or significant edema. Proposed mechanisms for nitrate resistance include: an increase in sodium and water in the vascular wall; mechanical compression of arterioles by excessive interstitial fluid [164]; sulfhydryl group deficiency [167]; and neurohormonal activation leading to vasoconstriction with attenuation of the vasodilatory effects of nitrates [161]. Patients who do not have hemodynamic or clinical benefit at doses of IV NTG of greater than 200 mcg/min should be considered non-responders and are not expected to have clinical benefit from further dose escalation.

In addition, there is substantial evidence that treatment of ADHF with nitroglycerine is limited by the development of early tolerance that results in a marked attenuation of the initial hemodynamic response and occurs in as little as 12–24 h after NTG initiation [161, 168, 169]. Early tolerance occurs in about half of patients and cannot be predicted by baseline hemodynamic measurements, the magnitude of the initial change in hemodynamics in response to NTG or baseline or treatment plasma levels of epinephrine, norepinephrine or renin [170]. A number of mechanisms have been proposed to explain nitrate tolerance including: early volume expansion after NTG initiation; neurohormonal activation in response to NTG administration (RAAS, sympathetic nervous system, arginine vasopressin, endothelin); sulfhydryl group depletion; nitrate-mediated increases in vascular superoxide/peroxynitrite production; impairment of nitrate biotransformation; and abnormalities of nitric oxide signal transduction including desensitization of soluble guanylate cyclase and increased phosphodiesterase activity [161, 168–170]. Data suggests that volume expansion, neurohormonal activation and sulfhydryl depletion are less likely to play an important role in the development of nitrate tolerance [161, 165, 171–174].

A number of strategies have been proposed to avoid nitrate tolerance. Sulfhydryl group repletion has been proposed for the prevention of tolerance [168]. This has not been supported by studies of concomitant treatment with the sulfhydryl group donor N-acetylcysteine or the sulfhydryl-containing ACE inhibitor captopril [171, 173, 175]. Hydralazine has been shown to prevent the development of NTG tolerance in both experimental models and patients with congestive heart failure [176–178]. It has been suggested that hydralazine prevents tolerance by preventing NTG-induced increases in vascular superoxide/peroxynitrite production or by scavenging vascular superoxide/peroxynitrite. The African American Heart Failure Trial (A-HeFT) demonstrated an improvement in survival and a decrease in hospitalization in patients with chronic HFrEF with hydralazine and isosorbide dinitrate added to standard heart failure therapy compared with chronic heart failure therapy alone [179]. The use of hydralazine and ISDN has not been investigated in patients with

ADHF. The strategy of a >12-h nitrate free interval used to prevent tolerance in patients with chronic stable angina or chronic heart failure is not practical in the treatment of ADHF.

Randomized Clinical Trials of Nitrates in ADHF

A prospective randomized trial studied the benefit of furosemide and isosorbide dinitrate in 104 patients who presented to mobile emergency units with pulmonary edema and oxygen saturations of less than 90 % [180]. All patients were treated with oxygen, morphine sulfate 3 mg bolus and furosemide 40 mg IV and then randomized to high dose isosorbide dinitrate (3 mg bolus administered intravenously every 5 min) or high dose furosemide (80 mg IV every 15 min and isosorbide dinitrate infusion at 1 mg/h (16 mcg/min) increased by 1 mg/h every 10 min. Treatment was continued in both groups until oxygen saturation increased to at least 96 % or mean arterial blood pressure decreased by at least 30 % or to lower than 90 mm Hg. The main end-points were death, need for mechanical ventilation, and myocardial infarction. The group that received high dose nitrates had significantly fewer myocardial infarctions (17 % vs 37 %; $p = 0.047$) and less need for mechanical ventilation (13 % vs 40 %; $p = 0.0041$). In addition, there were significantly greater improvements in heart rate, respiratory rate and oxygenation in the high dose nitrate group. Limitations of the study were that it was not blinded, it was conducted in an ambulatory out of hospital setting, and that a significant number of patients who were screened for enrollment did not meet the inclusion criteria and were excluded from randomization.

The Vasodilation in the Management of Acute Congestive Heart Failure (VMAC) Trial was a complex, randomized, multicenter, double blind, double-dummy, controlled trial of 489 patients with ADHF [181]. The study included patients with preserved and depressed systolic function and patients with and without coronary artery disease. 246 patients underwent right heart catheterization at the discretion of the investigator (the catheterized stratum). Patients were randomized to receive intravenous NTG, intravenous nesiritide or placebo added to standard therapy for the first 3 h followed by nesiritide or NTG added to standard therapy for 24 h (the patients in the initial placebo group were again randomized to nesiritide or NTG at 3 h.) Nesiritide was administered as a 2 mcg/kg bolus followed by a fixed-dose infusion of 0.01 mcg/kg/min infusion. The dose could be increased every 3 h up to 0.03 mcg/kg/min. The NTG dose was not dictated by protocol but was determined by the investigator and could be changed throughout the study period at the discretion of the investigator. The primary end-points of the trial were change in PCWP at 3 h in the catheterized stratum and patient self-evaluation of dyspnea at 3 h in the catheterized and non-catheterized strata. Secondary end-points included comparisons of hemodynamic and clinical effects between nesiritide and NTG groups at 24 h. At 3 h, the mean dose of NTG was 42 mcg/min in the catheterized patients and 29 mcg/min in the non-catheterized patients. At 24 h, the mean dose of NTG in the

catheterized patients increased to 55 mcg/min, but did not change in the non-catheterized patients. Only 23/273 patients in the nesiritide arm had an increase in nesiritide dose. At 3 h, there was a greater reduction in PCWP in the nesiritide group compared to both the placebo ($P < 0.001$) and NTG groups ($P = 0.03$). PCWP decreased by 5.8 mmHg in the nesiritide group; 3.8 mmHg in the NTG group; and 2 mmHg in the placebo group. The difference in PCWP between NTG and placebo was not significant. At 3 h, there was greater improvement in dyspnea when nesiritide was compared to placebo but not to NTG. There was no difference in dyspnea or global clinical assessment between NTG and placebo. At 24 h, there was a greater reduction in PCWP in the nesiritide group compared with the NTG group (−8.2 vs −6.3 mmHg; $p < 0.05$) but no difference in dyspnea and only a modest difference in improvement in global clinical status favoring nesiritide.

The most important limitation in the use of NTG is dose-related hypotension. Hypotension can develop in volume depleted patients or in patients in whom cardiac output is critically dependent on preload (e.g., aortic stenosis, restrictive cardiomyopathy, RV infarction). Sublingual nitroglycerin may rarely produce bradycardia and hypotension, probably due to activation of the Bezold-Jarisch reflex. Side effects of NTG include headache and abdominal pain. Serious side effects are unusual. NTG use is contraindicated in patients who have recently taken one of the phosphodiesterase type 5 (PDE5) inhibitors (sildenafil, vardenafil, tadalafil, avanafil) used to treat erectile dysfunction or pulmonary hypertension because of the risk sustained hypotension. Approximately 20 % of patients with heart failure are resistant to the hemodynamic effects of any dose of NTG [8, 182, 183].

The preferred dose and route of administration of nitrates have not been established. A common approach is to give nitrates at progressive dose increments with a goal of reducing mean blood pressure by 10 mmHg while maintaining systolic blood pressure >90 mmHg. Invasive hemodynamic monitoring is not needed. IV administration is preferred by most HF specialists. Starting nitroglycerin at 10–20 mcg/min and increasing dose up to physiologic effect up to a maximum of 200 mcg/min or isosorbide dinitrate 1–10 mg/h are common dosing regimens [61]. NTG should not be abruptly withdrawn in patients with ADHF as this may precipitate reflex vasoconstriction with acute decompensation.

Sodium Nitroprusside

Nitroprusside (SNP) is a powerful “balanced” nitrovasodilator affecting both arterial and venous vasodilation. It is a water-soluble sodium salt comprised of Fe^{2+} complexed with nitric oxide (NO) and five cyanide anions. It functions as a prodrug in that it reacts with sulfhydryl groups on erythrocytes, albumin and other proteins to form nitrosothiol and ultimately NO in the vasculature. The mechanism of release of NO is not entirely clear. NO activates the guanylyl cyclase–cyclic GMP–PKG pathway which, in turn, results in vascular smooth muscle

relaxation and venous and arterial vasodilation. Dilation of arterial résistance vessels reduces LV afterload. The venodilator effect increases venous capacitance and decreases preload. Infusion results in a reduction in RA pressure, PCWP, systemic vascular resistance and pulmonary vascular resistance, an increase in stroke volume and cardiac output, reduction in secondary mitral regurgitation and little change in heart rate. In general, in patients with severe heart failure, nitroprusside increases cardiac output and renal blood flow, and improves GFR and diuretic effectiveness. However, excessive reduction in systemic blood pressure may prevent an increase or result in a decrease in renal blood flow. Nitroprusside generally reduces systolic and diastolic ventricular wall stress and lowers myocardial oxygen consumption [153, 184–186].

Nitroprusside is an unstable molecule that decomposes when exposed to light. The medication must be protected from light to prevent degradation and subsequent rapid cyanide release on administration. The drug is administered as a continuous infusion. The onset of effect is within 30 s of the start of an infusion with peak hemodynamic effect seen within 2 min. The hemodynamic effects resolve within 2 min of stopping the infusion [153, 184–186].

The major side effect of SNP is hypotension which can be rapidly reversed by lowering the dose or discontinuing the medication. Nitroprusside-related hypotension may be harmful in patients with myocardial infarction or ischemia. Nitroprusside may cause coronary steal in patients with coronary artery disease by dilating nonobstructed coronary arteries directing blood away from maximally dilated coronary beds downstream from a flow limiting stenosis. Unlike organic nitrates, tachyphylaxis to SNP does not occur. Some patients may have rebound elevation of systemic vascular resistance and blood pressure with clinical deterioration after abrupt discontinuation [187]. Therefore, gradual weaning after initiation of oral vasodilator therapy is recommended. Nitroprusside can worsen arterial hypoxemia in patients with chronic obstructive pulmonary disease or pneumonia due to worsening ventilation-perfusion mismatching resulting from nitroprusside-induced reversal of hypoxic pulmonary vasoconstriction with pulmonary arteriolar dilation in in nonventilated areas. Methemoglobinemia is an unusual complication of treatment with SNP and is due to oxidation of hemoglobin by nitric oxide.

Toxicity from SNP may result from conversion of nitroprusside to cyanide and thiocyanate. Nitroprusside metabolism results in the release of cyanide anions in vivo. Cyanide is generally rapidly metabolized by hepatic rhodanase to thiocyanate which is eliminated in the urine. The elimination half-life for thiocyanate is 3 days in patients with normal renal function but can be much longer in patients with renal insufficiency. Cyanide can also bind to tissue cytochrome oxidase. Accumulation of cyanide leads to severe lactic acidosis and symptoms of restlessness, agitation, and sinus tachycardia. Patients are at risk of cyanide toxicity when SNP is infused at rates >5 mcg/kg/min or administered in the setting of significant hepatic dysfunction. Cyanide toxicity is better correlated with serum rather than whole blood cyanide concentrations. Elevated lactate concentration is an excellent surrogate marker for cyanide toxicity. Cyanide toxicity can be treated by administration of thiosulfate or hydroxycobalamin. These medications are equally effective and have no significant adverse effects [188].

The risk of thiocyanate toxicity increases in patients receiving SNP at rates >3 mcg/kg/min for ≥72 h and in patients with renal insufficiency. Signs and symptoms of thiocyanate toxicity include anorexia, nausea, fatigue, disorientation, and toxic psychosis. Thiocyanate can be removed readily by hemodialysis while cyanide cannot [185]. Thiocyanate and cyanide toxicity are rare in patients receiving ≤ 3 mcg/kg/min for ≤72 h.

There are a limited number of clinical trials that demonstrate efficacy of SNP in ADHF. A small single center trial of SNP in patients with refractory heart failure demonstrated a consistent reduction in PCWP from a mean of 32.2 to 17.2 mmHg, increase in cardiac output from 2.98 to 5.2 l/min, reduction in mean blood pressure of 15 mmHg, and doubling of forward LVEF and stroke volume with similar responses in patients with and without an ischemic etiology of heart failure [189]. A single center open label randomized controlled trial compared SNP to furosemide in 50 patients with a PCWP >20 mmHg within 24 h of an acute myocardial infarction [190]. Within 1 h, there were greater decreases in PCWP (−9 vs. −4 mmHg) and systemic vascular resistance (−21 % vs +10 %), and greater increases in cardiac index (+16 % vs. −7 %) in the SNP group compared with the furosemide group, respectively.

A multi-center randomized placebo-controlled study compared a 48-h infusion of SNP to placebo in 812 men with presumed acute myocardial infarction and a left ventricular filling pressure ≥12 mmHg [191]. The mortality rates at 21 days and 13 weeks were not different between groups. The impact of SNP was related to the time of treatment with respect to onset of MI –related pain. Mortality at 13 weeks was higher in the SNP group compared with the placebo group in patients in whom infusions were started within 9 h of the onset of pain but lower in the SNP group compared with placebo in patients in whom infusions were started after 9 h of the onset of pain.

A single-center retrospective review of patients admitted for ADHF who underwent right heart catheterization and were found to have a cardiac index ≤2.0 l/min/m^2 and elevated filling pressures compared outcomes in patients who were or were not treated with SNP [192]. Patients treated with SNP had greater improvement in hemodynamic measurements during hospitalization, higher rates of oral vasodilator prescription at discharge, and lower rates of all-cause mortality at a median follow up of 25.7 months. SNP use was not associated with a higher rate of inotrope use or worsening renal function during hospitalization.

In a series of single center studies, SNP and IV diuretics were used to achieve specific hemodynamic parameters in patients with advanced heart failure many of whom were felt refractory to heart failure medications and were referred for heart transplantation. Using this approach, patients with severe decompensated heart failure having low cardiac outputs and high filling pressures on right heart catheterization were treated with IV diuretics and sodium nitroprusside adjusted to achieve specific hemodynamic goals defined as: PCWP ≤ 15–18 mmHg, right atrial pressure ≤8 mmHg, decrease in mean pulmonary artery pressure by at least 20 %, improvement in cardiac index to ≥2.2 l/min/m^2 or systemic vascular resistance to 1000–1200 dynes/sec cm^{-5}, while maintaining a mean arterial pressure >65 mmHg

or systolic blood pressure ≥80 mmHg [44]. Parenteral therapy was replaced with oral vasodilator and diuretic therapy tailored to maintain hemodynamic goals. Using this approach, goals for cardiac output, pulmonary capillary wedge pressure, and systemic vascular resistance could be achieved by intravenous followed by oral therapy in the majority of patients [193].

Intensive reduction in systemic vascular resistance and ventricular filling pressures was accompanied by a reduction in LV end-diastolic and end-systolic volumes, no change in LFEF, a decrease in total stroke volume but a 40 % increase in forward stroke volume, and significant decreases in mitral and tricuspid regurgitation [45]. Improvements in hemodynamic parameters including near normal filling pressures were maintained at 8 months. Chronic hemodynamic improvement was accompanied by sustained symptomatic improvement [112]. Improvements in mitral and tricuspid regurgitation and estimated pulmonary artery pressures were sustained at 6 months on oral vasodilators and a flexible diuretic regimen. Further reductions in right atrial and left atrial volumes were also seen [113].

The HFSA, ACCF/AHA and ESC guidelines all endorse the use of nitroprusside to treat ADHF in the absence of symptomatic hypotension [8, 28, 118]. Nitroprusside is particularly useful in severely congested patients in whom rapid reduction of afterload is felt necessary – especially in the setting of hypertension or severe mitral regurgitation. Because of its powerful blood pressure lowering effect, SNP should be used in an intensive care unit setting where frequent blood pressures can be obtained. It can be rapidly titrated to achieve a specific systolic or mean blood pressure starting at doses as low as 0.1 mcg/kg/min and titrating up to as much as 5.0 mcg/kg/min.

Nesiritide

Nesiritide is a recombinant preparation of human B-type natriuretic peptide manufactured for intravenous administration. It has the same 32-amino acid sequence as endogenous BNP produced by the heart. Nesiritide is a balanced vasodilator with arterial and venous vasodilatory properties. Nesiritide binds to the natriuretic peptide receptor-A (NPR-A) which is widely expressed in kidney, lung, adipose, and vascular smooth muscle cells. (NPR-B receptors bind C-type natriuretic peptide and NPR-C receptors do not have a guanylate cyclase domain and function as clearance receptors.) The NPR-A receptor is linked to the cGMP-dependent signaling cascade and mediates many of the cardiovascular and renal effects of the natriuretic peptides. BNP binding to the NPR-A receptor activates the guanylyl cyclase–cyclic GMP–PKG pathway. The mean terminal half-life of nesiritide in patients with heart failure is approximately 18 min. Steady-state infusions of 0.01–0.03 mcg/kg/min increase baseline circulating BNP levels by three to six fold. BNP is metabolized by two mechanisms: binding to the NPR-C receptor with receptor-mediated internalization/degradation and proteolytic cleavage by neutral endopeptidases. Renal

clearance plays a minimal role in nesiritide metabolism and medication dosing does not need to be modified for any degree of renal insufficiency [153, 194–197].

Nesiritide infusion is associated with dose-related decreases in systemic vascular resistance, pulmonary vascular resistance, and right atrial and pulmonary capillary wedge pressures and increases in stroke volume and cardiac output without a change in heart rate [198–200]. Nesiritide has been reported to decrease aldosterone [198, 200] and endothelin-1 levels [201] with conflicting reports concerning the impact on plasma norepinephrine levels [198, 201]. Nesiritide exerts vasodilator effects on coronary conductance and resistance vessels, increases coronary blood flow despite a reduction in coronary perfusion pressure and decreases myocardial oxygen consumption [202]. Nesiritide infusion is not associated with an increase in ventricular arrhythmias [203].

The results of clinical trials that have assessed the effect of nesiritide on urine output have been conflicting. In a placebo-controlled trial in which diuretics were held for 4 h prior to and during study drug infusion, patients receiving nesiritide at infusion rates of 0.015 mcg/kg/min or 0.03 mcg/kg/min had significantly greater urine output over a 6-h period compared to patients receiving placebo [200]. In the same report, nesiritide infusions at 0.015 mcg/kg/min or 0.03 mcg/kg/min were compared with placebo but patients could receive diuretics and/or other vasodilators. Intravenous diuretics were given to significantly fewer patients in the nesiritide groups compared with the placebo group [200]. In the Nesiritide Administered Peri-Anesthesia in Patients Undergoing Cardiac Surgery (NAPA) trial, patients with an LVEF<40 % undergoing CABG with anticipated use of cardio-pulmonary bypass were randomized to receive fixed dose nesiritide at 0.01 mcg/kg/min or placebo for 24–96 h after induction of anesthesia [204]. Nesiritide was associated with greater urine output (2926 vs 2350 ml) during the initial 24 h after surgery and a shorter hospital stay. In a double-blind, placebo-controlled, crossover study of patients with decompensated heart failure who had an increase in creatinine of ≥0.2 mg/dL and ≥10 % above baseline within 6 months of enrollment, patients were randomized to a nesiritide bolus of 2 mcg/kg IV bolus followed by an infusion at 0.01 mcg/kg/min or placebo for 24 h on consecutive days [205]. There were no differences in GFR by iothalamate clearance, effective renal plasma flow by para-amino hippurate clearance, urine output, or sodium excretion for any time interval or for the entire 24-h period between the nesiritide and placebo study days.

The Renal Optimization Strategies Evaluation (ROSE) trial was a multicenter, double blind placebo-controlled trial of 360 patients hospitalized with acute heart failure and renal dysfunction (defined as an eGFR of 15–60 mL/min/1.73 m^2 by the MDRD equation) randomized to dopamine 2 mcg/kg/min, nesiritide 0.005 mcg/kg/min without a bolus, or placebo for 72 h. All patients received open label intravenous loop diuretic treatment with a recommended daily dose of 2.5 times their total daily outpatient diuretic dose. No difference was found between study groups with respect to the two primary end-points: 72-h cumulative urine volume and change in cystatin C level. In addition, there were no between group differences in secondary end-points of measures of decongestion, renal function or clinical outcomes [206].

The Vasodilator in the Management of Acute Heart Failure (VMAC) trial was a complex, multi-center, randomized double-blinded controlled study of nesiritide, nitroglycerine, and placebo added to standard therapy in 489 patients hospitalized for worsening heart failure [181]. The study compared the hemodynamic and clinical effects of nesiritide infusion at 0.01 mcg/kg/min after a bolus of 2 mcg/kg, IV nitroglycerine infusion at a rate determined by the investigator or placebo (see above for details). At 3 and 24 h, nesiritide lowered PCWP more than NTG, but there were no significant differences in patient reported dyspnea and only modest improvement in global clinical status in the nesiritide group.

A limitation of VMAC is that the mean dose of NTG was 42 mcg/min in the catheterized patients and 29 mcg/min in the non-catheterized patients, significantly below the optimal dose of 120–200 mg/min for the treatment of ADHF [161]. One of the sites in VMAC reported their single center results using aggressive up-titration of NTG that achieved a mean dose of 155 mcg/min at 3 h [207]. Nesiritide was associated with an early reduction in PCWP that was sustained over the 24-h study period. There was no evidence of nesiritide tolerance. High dose NTG was associated with a comparable reduction in PCWP that was delayed when compared with nesiritide. The NTG-associated decrease in PCWP was gradually attenuated despite continued up-titration reflecting the early development of NTG tolerance.

A subsequent retrospective pooled analysis of five small randomized trials of nesiritide of varying doses suggested that nesiritide increased the risk of worsening renal failure (defined by an increase in creatinine of greater than 0.5 mg/dL recorded at any time during the inpatient portion of the trial) [208]. Another retrospective pooled analysis of three small randomized trials of nesiritide of varying doses that reported 30-day mortality and did not require inotrope infusion as a control suggested that there was a trend toward increased mortality in the nesiritide treated patients that did not reach statistical significance [209, 210]. Two subsequent meta-analyses of randomized clinical trials of nesiritide did not show an increase in 30-day or 180-day all-cause mortality [211, 212] and did not show a clear relationship between mortality and nesiritide dose [212].

The Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure (ASCEND-HF) trial was a multicenter randomized placebo-controlled trial designed to assess the safety and efficacy of nesiritide added to standard therapy compared to placebo added to standard therapy in 7141 patients hospitalized for ADHF [213]. Patients were randomized in a 1:1 ratio to receive placebo or nesiritide. Nesiritide was administered as a continuous IV infusion at a dose of 0.01 mcg/kg/min for 24–164 h. At the discretion of the investigator, patients could receive an optional intravenous bolus of 2 mcg/kg prior to the initiation of the continuous infusion. Co-primary end-points were the change in self-reported dyspnea measured by a 7-point Likert scale at 6 and 24 h and the composite end-point of rehospitalization for heart failure or death within 30 days. Patients assigned to nesiritide more frequently reported improved dyspnea at 6 and 24 h but this difference was small and did not meet the prespecified level for significance. There was no difference in rehospitalization for heart failure or death from any cause at 30 days analyzed separately or as a composite end-point. There was also no difference in the rates of

worsening renal function defined as a more than a 25 % decrease in the eGFR calculated using the simplified MDRD equation at any time from study drug initiation through day 30 of the trial. The results from ASCEND-HF suggest that nesiritide can be used safely in patients with ADHF but cannot be recommended for routine use in a broad range of patients hospitalized for decompensated heart failure.

The HFSA, ACCF/AHA and ESC guidelines all endorse the use of nesiritide for the rapid improvement of congestive symptoms in patients with ADHF in the absence of symptomatic hypotension [8, 28, 118]. The recommended starting dose of nesiritide is 0.01 mcg/kg/min with or without an initial bolus of 2 mcg/kg. The dose can be increased by 0.005 mcg/kg/min every 3 h up to a maximum of 0.03 mcg/kg/min as tolerated by systemic blood pressure.

The primary side effects of nesiritide are headache and hypotension. In VMAC, headache occurred in 8 % of patients. Symptomatic hypotension was reported in 4 % of patients receiving nesiritide, was of mild to moderate severity in most patients, and resolved spontaneously after a decrease or discontinuation of medication or following an intravenous fluid bolus of ≤250 mL [181]. Symptomatic hypotension is dose-dependent and was reported in 11 % of patients with ADHF during infusion of 0.015 mcg/kg/min and in 17 % of patients during an infusion of 0.03 mcg/kg/min [200].

Inotropic Agents

The use of inotropic agents in patients hospitalized for ADHF is relatively common despite a lack of data from clinical trials that establishes safety and efficacy and despite observational data from large clinical registries that raise questions about safety. The most commonly used inotropic agents are dobutamine, dopamine, milrinone, and levosimendan. Dobutamine, dopamine and milrinone increase intracellular cyclic adenosine monophosphate (cAMP) and intracellular calcium concentration. Levosimendan is a calcium sensitizing agent with inotropic and vasodilatory effects. Levosimendan has not been approved for use in the U.S. or Canada. Intravenous inotropic agents may be used to relieve symptoms, improve hemodynamics and improve end-organ function in patients with acute decompensated heart failure with severe systolic dysfunction who have diminished peripheral perfusion and/or hypotension.

Dobutamine

Dobutamine was originally thought to be a selective β1 adrenergic receptor agonist. However, it has become clear that its pharmacologic effects are more complex. Dobutamine is a racemic mixture that stimulates β1, β2 and α1 adrenergic receptors. Its pharmacologic actions are a composite of the dose-related effects of each

enantiomer on adrenergic receptors. Its effects are not mediated through endogenous release of norepinephrine and it does not stimulate dopaminergic receptors. Both enantiomers have agonist effects on the β1 adrenergic receptor. (+)-dobutamine is 10 fold more potent than (−) - dobutamine with respect to β1 stimulation. Both isomers have mild agonist effects on the β2 receptor. (−)-dobutamine is an α1 agonist while (+)-dobutamine is a mixed α1 agonist/antagonist.

The primary pharmacologic effect of dobutamine is an increase in myocardial contractility mediated by β1 receptor stimulation. β1 stimulation increases adenylyl cyclase activity resulting in an increase in intracellular cAMP. An increase in intracellular cAMP facilitates calcium release from the sarcoplasmic reticulum and an increase in force generation by contractile proteins. The β1 effects result in positive inotropic effects with resulting increases in stroke volume and cardiac output and some reflex-mediated reduction in systemic vascular resistance. Dobutamine has relatively more inotropic than chronotropic effects when compared with isoproterenol. At equivalent inotropic doses, dobutamine enhances sinus node automaticity less than isoproterenol although has similar effects in increasing AV nodal and intraventricular conduction. The blunted chronotropic response relative to inotropic response is not well understood but may be related to a contribution of cardiac α1 receptor stimulation to inotrope effect. In the peripheral circulation, β2 stimulation can cause vasodilation at low doses. The α1 agonist effect of (−) – dobutamine on the arterial circulation is generally offset by the antagonist effect of (+)-dobutamine and the vasodilator effect of β2 stimulation. However, at higher doses, α-1 adrenergic receptor stimulation may cause venous and arterial vasoconstriction [214–217].

In most patients with heart failure, systolic dysfunction and low cardiac output, treatment with dobutamine results in an increase in stroke volume and cardiac output, a reduction in systemic vascular resistance and a modest reduction in filling pressures. The overall effect on blood pressure is variable depending on the impact on cardiac output, systemic vascular resistance and reflex sympathetic tone. In general, dobutamine causes little change in blood pressure and can be used safely in patients with hypotension. Pulmonary vascular resistance is generally not decreased. An increase in blood pressure may be seen at higher doses [214, 215, 218].

The effects of dobutamine on clinical outcomes have not been studied in prospective randomized controlled clinical trials. Substantial clinical experience suggests that dobutamine improves cardiac output, improves symptoms of low cardiac output and pulmonary congestion, and improves end-organ function in patients with low cardiac output syndrome in the setting of severe left ventricular systolic dysfunction.

Dobutamine has a half-life of 2 min. The onset of effect is rapid. Steady state concentrations are reached within 10 min of starting the infusion. Doses of 2–10 mcg/kg/minute are generally required to have an impact on cardiac output. The ESC guidelines recommend that dobutamine be started at infusion rates of 2–3 mcg/kg/min. The dose can be increased by 1–2 mcg/kg/min based on clinical and hemodynamic response. The maximum recommended dose is 15–20 mcg/kg per minute. However, if a desired response is not achieved with up

to 10 mcg/kg per minute, the addition of another inotrope or placement of an intra-aortic balloon pump should be considered. The response to dobutamine is commonly attenuated in patients receiving β-adrenergic blocking agents. In some studies of dobutamine using infusion durations of >24–72 h, cardiac output has been noted to return toward baseline in some patients raising the possibility of pharmacologic tolerance [214, 216].

Side effects of dobutamine include tachycardia (especially in patients with atrial fibrillation), atrial and ventricular arrhythmias, eosinophilia and hypersensitivity myocarditis [203, 219, 220]. Dobutamine increases myocardial oxygen consumption in patients with and without coronary artery disease [218, 221]. In patients with coronary artery disease, the increase in myocardial oxygen consumption may result in myocardial ischemia and worsening hemodynamics. Concern has been raised that dobutamine (and dopamine and milrinone) may cause additional cardiomyocyte damage and ultimately worsen heart failure by causing myocardial ischemia and, perhaps, direct myocyte toxicity. [216, 217, 222–224].

Dopamine

Dopamine is an endogenously produced catecholamine. It is a central neurotransmitter that plays an important role in the regulation of movement. It is also produced in the periphery by epithelial cells of the proximal tubule in the kidney and is thought to have local diuretic and natriuretic effects.

The cardiovascular effects of dopamine are mediated by a number of distinct cell surface receptors that vary in their affinity for dopamine and mediate distinct dose-dependent cardiovascular effects. At low dose (≤2 mcg/kg/min), dopamine acts primarily on the vascular dopamine type 1 (D1) receptors in the renal, mesenteric and coronary vasculature leading to vasodilation and natriuresis. D1 binding activates adenyl cyclase and increases intracellular cAMP leading to vasodilation. In addition, activation of D1 receptors in the proximal tubule and thick ascending limb of the loop of Henle inhibits the Na^+-H^+ exchanger and Na^+:K^+:$2Cl^-$ co-transporter facilitating the excretion of urinary sodium. Low-dose dopamine infusion results in an increase in renal blood flow, glomerular filtration rate and natriuresis.

At intermediate doses (2–5 mcg/kg/min), dopamine acts primarily on β1 receptors and facilitates release of norepinephrine from nerve terminals. At this dose, dopamine has a predominant inotropic and chronotropic effect. Cardiac output and heart rate are increased. Systolic blood pressure and pulse pressure are generally increased and diastolic blood pressure remains the same or increases slightly. There is generally little change in peripheral vascular resistance at these doses. At higher doses (>5 mcg/kg/min) dopamine activates α1 receptors which causes arterial vasoconstriction [214, 216, 217].

The effect of dopamine on renal physiology was evaluated in 13 patients with chronic heart failure [225]. Cardiac output, renal artery cross sectional area, renal blood flow, and renal vascular resistance were calculated at baseline and at

intravenous dopamine doses of 1, 2, 3, 5, and 10 mcg/kg/min. Cardiac output increased with increasing dose reaching statistical significance at doses of 5 and 10 μg/kg/min with the peak occurring at 10 mcg/kg/min. Renal artery cross-sectional area demonstrated a progressive increase with dose uptitration reaching statistical significance at doses of 5 and 10 μg/kg/min. Renal vascular resistance decreased reaching statistical significance at 2 mcg/kg/min with no difference seen from 2–10 mcg/kg/min. Renal blood flow progressively increased from 2–10 μg/kg/min. The increase in renal blood flow was proportionately larger than corresponding increases in cardiac output and was due primarily to dilation of large conductance and small resistance renal blood vessels.

Despite the demonstrated effect of dopamine on renal blood flow, it has been difficult to demonstrate a clinical benefit of low dose dopamine in prospective randomized clinical trials that studied patients with ADHF. The Dopamine in Acute Decompensated Heart Failure Trials (DAD-HF and DAD-HF II) evaluated the efficacy of adding dopamine to furosemide infusion in patients with ADHF [226, 227]. DAD-HF compared high dose furosemide (40 mg IV bolus followed by a 20 mg/h continuous infusion for 8 h) versus low dose furosemide (40 mg IV bolus followed by a 5 mg/h infusion for 8 h) plus dopamine 5 mcg/kg/min in sixty patients with ADHF. End-points included total diuresis and changes in dyspnea score during the 8-h protocol, worsening renal failure defined as a rise in serum creatinine >0.3 mg/dL from baseline to 24 h, electrolyte balance and 60-day post-discharge outcomes. The low-dose furosemide/dopamine protocol was equally effective as high dose furosemide with respect to diuresis and relief of dyspnea and was associated with less worsening renal failure and hypokalemia but no difference in 60-day mortality or rehospitalization rate. DAD-HF II was a three arm trial that randomized 161 patients with ADHF to an 8-h infusion(s) of: high dose furosemide (20 mg/h continuous infusion); low dose furosemide (5 mg/h continuous infusion) plus dopamine 5 mcg/kg/min; or low dose furosemide (5 mg/h continuous infusion) alone. All patients received furosemide 40 mg IV prior to randomization. No difference was found in the primary end-points of all-cause mortality and heart failure hospitalization at 60-days and one year. There was also no difference in urinary output over 24 h, dyspnea relief, or length of stay. Worsening renal function defined as a rise in serum creatinine ≥0.3 mg/dL from baseline to 24 h was more common in the high dose furosemide group than the low dose furosemide/dopamine or the low dose furosemide groups. The investigators concluded that the addition of low-dose dopamine was not associated with any clinical benefit.

The Renal Optimization Strategies Evaluation (ROSE) trial was a multicenter, double blind placebo-controlled trial of 360 patients hospitalized with acute heart failure and renal dysfunction (defined as an eGFR of 15–60 mL/min/1.73 m^2 by the MDRD equation) randomized to dopamine 2 mcg/kg/min, nesiritide 0.005 mcg/kg/min without a bolus, or placebo for 72 h (see above). No difference was found between study groups with respect to the two primary end-points: 72-h cumulative urine volume and change in cystatin C level. In addition, there were no between-group differences in secondary end-points of measures of decongestion, renal function or clinical outcomes [206].

The ACCF/AHA guidelines suggest that low dose dopamine ≤2 mcg/kg/min may be considered in addition to loop diuretics to improve diuresis and preserve renal function and renal blood flow [28]. The ESC guidelines suggest that dopamine at doses of 2–5 mcg/kg/min may be used as an inotrope in patients with heart failure, volume overload and hypotension [17]. Dopamine may be used to improve renal blood flow and diuresis in patients with decompensated heart failure who have an inadequate response to appropriately dosed intravenous loop diuretic. Dopamine dose should be based on estimated lean body weight and not on actual weight [216]. Dopamine should be administered through a central venous access site to avoid the risk of drug extravasation and ischemic necrosis of surrounding tissues associated with peripheral intravenous administration. Although dopamine increases cardiac output, it does not reduce left ventricular filling pressures and, in some patients, increases filling pressures. Dopamine causes more tachycardia than dobutamine and may precipitate angina in patients with coronary artery disease. It may cause atrial and ventricular arrhythmias [214].

Milrinone

Milrinone is a bipyridine derivative that selectively inhibits phosphodiesterase III (PDE3). Milrinone decreases intracellular cAMP degradation and increases intracellular cAMP which, in turn, increases intracellular calcium in cardiac and smooth muscle cells. Milrinone increases cardiac contractility and improves myocardial relaxation. Milrinone also causes systemic venous and arterial vasodilation and pulmonary arterial vasodilation. Milrinone increases cardiac output, lowers systemic and pulmonary vascular resistance, and decreases left and right ventricular filling pressures. The reductions in systemic and pulmonary vascular resistance and intracardiac filling pressures are greater than those seen with dobutamine at doses that produce similar increases in cardiac output [218]. Milrinone causes less tachycardia than dobutamine and, unlike dobutamine, causes a minimal increase in myocardial oxygen consumption [218, 228, 229]. The effect on systemic blood pressure depends on the increase in cardiac output and the reduction in systemic vascular resistance that occurs with milrinone administration. Vasodilation-mediated decreases in mean arterial pressure are relatively common and may limit the use of milrinone in some patients with low cardiac output and marginal arterial blood pressure. Unlike dobutamine, the effects of milrinone are not mediated by adrenergic receptors. As a result, milrinone may be used instead of dobutamine in patients with low cardiac output syndrome who are being treated with β-adrenergic blocking agents [216, 217].

The recommended dose of milrinone has been a 50 mcg/kg IV bolus followed by an infusion of 0.25–0.75 mcg/kg/min. However, bolus dosing has been associated with symptomatic hypotension. A study that compared the hemodynamic effects of a continuous infusion of 0.5 mcg/kg/min milrinone with or without an initial bolus demonstrated that the maximal effects on cardiac index and PCWP were seen

immediately after the initial IV bolus. However, improvement in pulmonary capillary wedge pressure and cardiac output were similar at 2 and 3 h, with or without a bolus [230]. The ACCF/AHA and HFSA guidelines do not recommend a loading dose [8, 28]. The HFSA guidelines recommend that an initial dose of 0.01 mcg/kg/min and final dose of 0.2–0.3 mcg/kg/min be considered [8]. The ACCF/AHA guidelines recommend a maintenance dose of 0.125–0.75 mcg/kg/min [28].

The elimination half-life of milrinone is 2.5 h but is nearly doubled in patients with severe heart failure. Milrinone is predominantly excreted by the kidney so dosage adjustments need to be made for patients with an eGFR <60 mL/min. Major side effects of milrinone include hypotension, atrial fibrillation and ventricular arrhythmias.

Levosimendan

Levosimendan differs from other inotropic agents in that its mechanism for increasing contractility does not involve an increase in intracellular cAMP. Levosimendan is a myofilament calcium sensitizer that interacts with Ca^{2+}-saturated cardiac troponin C (cTNC). cTNC acts as a calcium sensitive "switch" to turn myocardial force production on during systole and off during diastole. Levosimendan binding to cTNC facilitates prolonged interaction between cTNC and troponin I increasing the contractile force generated during systole. Levosimendan does not affect diastolic function. Levosimendan is a vasodilator of systemic, pulmonary and coronary arteries and systemic veins. Vasodilation is probably mediated by opening of adenosine triphosphate (ATP)-sensitive potassium channels in vascular smooth muscle cells which results in smooth muscle relaxation [231]. Levosimendan and its active metabolite OR-1896 are selective inhibitors of PDE3. PDE inhibition probably does not play a role in the vasodilatory or inotropic effects of levosimendan at doses used in clinical practice. The combined inotropic and vasodilatory effects result in an increased force of contraction, increased stroke volume and cardiac output, decreased preload and afterload and decreased PCWP. Levosimendan does not increase myocardial oxygen consumption [231]. The most common side effects are hypotension and headache. Tachycardia is unusual. The incidence of atrial fibrillation and hypokalemia are increased modestly. The elimination half-life of levosimendan is 1–1.5 h. However, the elimination half-life of OR-1896 is 75–80 h so that cardiovascular effects may persist for 75–80 h after discontinuation of infusion [232, 233].

Several adequately powered multicenter randomized controlled clinical trials have assessed the efficacy of levosimendan compared with either placebo or dobutamine in patients with ADHF.

The Survival of Patients With Acute Heart Failure in Need of Intravenous Inotropic Support (SURVIVE) study was a randomized, double-blind trial comparing the efficacy and safety of intravenous levosimendan or dobutamine in 1327 patients hospitalized with acute decompensated heart failure who required inotropic

support [234]. No difference was found between treatment groups in the primary end-point of all-cause mortality at 180 days. In addition, no differences were found in a number of secondary end-points including all-cause mortality at 31 days, number of days alive and out of the hospital during 180 days following randomization, patient global assessment, patient assessment of dyspnea at 24 h, and cardiovascular mortality at 180 days.

The Randomized EValuation of Intravenous Levosimendan Efficacy (REVIVE II) trial enrolled 600 patients hospitalized for treatment of ADHF who had an LVEF <35 % and who remained dyspneic at rest despite treatment with intravenous diuretics [235]. Patients were randomly assigned to receive a single infusion of levosimendan or placebo, each in addition to local standard treatments for ADHF. The primary end-point evaluated was the distribution of patients characterized as "Improved", "Unchanged", or "Worse" during the first 5 days after randomization based on a composite of patient self-reported global assessment at 6 h, 24 h and 5 days. There was a modest benefit in the primary end-point in the levosimendan group. There was a decrease in length of stay in the levosimendan group but no difference in mortality at 90 days. Treatment with levosimendan was associated with more hypotension and atrial fibrillation.

A meta-analysis of randomized controlled clinical trials of levosimendan evaluated the effect of levosimendan on mortality and length of stay compared to placebo or dobutamine. Data from 5480 patients in 45 randomized clinical trials were analyzed. In 23/48 trials, levosimendan was evaluated in patients with decompensated heart failure and in 17/48 trials, levosimendan was evaluated in patients who underwent cardiothoracic surgery. The analysis found a significant reduction in mortality associated with the use of levosimendan. In addition, a reduction in mortality was found with levosimendan use when studies comparing levosimendan to placebo and levosimendan to dobutamine were analyzed separately. A reduction in mortality was also seen when studies with at least 30, 90, and 180 days of follow up were analyzed. In addition, treatment with levosimendan was associated with a decrease in length of stay [236].

In 2000, levosimendan was approved for use in Sweden. Since then, the drug has been approved in 60 countries worldwide but it remains not licensed in the United States.

Use of Inotropes

The pattern of inotrope use has been described in several North American and European registries of patients admitted to the hospital with acute heart failure syndromes. In the ADHERE registry, 14 % of patients were treated with one or more inotropic agents although <3 % of the patients in the registry had a systolic blood pressure of <90 mmHg at hospital admission and almost 50 % had preserved systolic function. One or more inotropic agents were used in 8 % of patients with preserved systolic function (3 % dobutamine, 5 % dopamine and 1 % milrinone) and in

19 % of patients with reduced systolic function (11 % dobutamine; 10 % dopamine; 5 % milrinone). Only 8 % of patients who received either dobutamine or dopamine had a systolic blood pressure <90 mmHg. The mean systolic blood pressure on admission was 121.3 (±27.4) mmHg in patients who received milrinone and 124.0 (±29.3) mmHg in patients who received dobutamine [150].

In the OPTIMIZE-HF Registry, intravenous inotropic medications were used in 4 % of patients admitted for ADHF who had preserved systolic function and 12 % of patients with left ventricular systolic dysfunction [91]. Of the patients enrolled in OPTIMIZE-HF, 15 %, 6.5 %, 4.5 % and 3.2 % of patients were treated with an intravenous inotrope in the systolic blood pressure quartiles of <120 mmHg, 120–139 mmHg, 140–161 mmHg, and >161 mmHg, respectively [237]. In the EuroHeart Failure Survey II, of 3580 patients hospitalized with heart failure, ~25–30 % of patients were treated with an inotropic agent (10.2 % dobutamine; 11.3 % dopamine; 3.9 % levosimendan). Of patients admitted with "Decompensated Heart Failure" (as opposed to "Cardiogenic Shock" or "Pulmonary Oedema"), ~20–24 % of patients were treated with an inotrope (8.6 % dobutamine; 8.5 % dopamine; 4.4 % levosimendan) [238]. In an Italian survey, of 2807 patients hospitalized for ADHF, 25 % of patients were treated with an IV inotrope [239].

Several studies have suggested that the use of intravenous inotropic agents in patients with ADHF is associated with an increase in adverse events including symptomatic hypotension, atrial and ventricular arrhythmias and in-hospital and long-term mortality [150, 240–242]. A retrospective observational analysis of data from the ADHERE registry suggested that in-hospital mortality is increased in patients admitted for ADHF who are treated with intravenous inotropic agents. The risk factor and propensity score-adjusted odds ratio for in-hospital mortality was calculated for 15,230 of 65,180 patients in the registry who received nitroglycerine, nesiritide, dobutamine or milrinone during hospitalization for ADHF. The majority of patients included in this analysis had either normal or elevated blood pressure. Treatment with either nesiritide or nitroglycerine was associated with significantly lower in-hospital mortality than either dobutamine or milrinone. The covariate and propensity score adjusted odds ratio for mortality was 0.69 ($p < 0.005$) when nitroglycerine was compared with milrinone and 0.46 ($p < 0.005$) when nitroglycerine was compared with dobutamine [150].

A similar retrospective analysis was performed using data from the University Health System Consortium (UHC) Clinical Database Pharmacy (a database with information from 32 academic hospitals) [240]. 2130 patients were identified who were hospitalized for ADHF and treated with dobutamine, milrinone or nesiritide. Using logistic regression, the relationship between drug therapy and in-hospital mortality was assessed. In-hospital mortality was 10.2 %, 7.9 % and 2.9 % for patients treated with dobutamine, milrinone and nesiritide, respectively. The risk adjusted odds ratio for in-hospital mortality was 3.5 for dobutamine and 3.9 for milrinone when compared with nesiritide.

A retrospective observational analysis was performed using data from the ESCAPE Trial to assess the impact of inpatient inotrope use on 6 month outcomes [241]. Of the 433 patients enrolled, risk-adjusted hazard ratios for 6-month

mortality and mortality and rehospitalization were determined for the overall population and for patients treated with an intravenous vasodilator, inotrope or combination of inotrope and vasodilator. Overall 6-month mortality was 19 %. When compared to the overall cohort, risk adjusted HR for 6-month mortality was not significantly different for patients treated with vasodilators (HR 1.39, 95 % CI 0.64–3.00) but was significantly increased for patients treated with inotropes (HR 2.14, 95 % CI 1.10–4.15) and for patients treated with a combination of inotropes and vasodilators (HR 4.81, 95 % CI 2.34–9.90). The risk adjusted combined end-point of 6-month mortality or rehospitalization was not significantly increased for patients treated with vasodilators (HR1.2, CI 0.81–1.78) but was significantly increased for patients treated with inotropes (HR 1.96, CI 1.37–2.82) and patients treated with inotropes and vasodilators (HR 2.90, CI 1.88–4.48). On multivariable analysis, impaired renal function and right atrial pressure were significant predictors for the use of inotropes. Renal function and elevated PCWP were predictors for the use of vasodilators. However, the most powerful predictor of inotrope or vasodilator use was the study site and managing physician.

The Outcomes of a Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic Heart Failure (OPTIME-CHF) was a randomize, placebo-controlled, double blind trial that tested the hypothesis that short-term use of milrinone added to standard therapy in patients with chronic heart failure hospitalized for ADHF (but without "low output syndrome") would improve clinical outcomes [243]. The study randomized 951 patients hospitalized with ADHF who did not require intravenous inotropic support to receive a 48-h infusion of milrinone 0.5 mcg/kg/min or saline placebo. No loading dose was administered. The dose could be adjusted downward to 0.375 mcg/kg/min or upward to 0.75 mcg/kg/min at the discretion of the treating physician. Patients were ineligible if the treating physician judged that intravenous inotropic therapy was essential. The primary end-point was the total number of days hospitalized for cardiovascular causes within 60 days after randomization. There was no difference found in the primary endpoint. There were also no differences in in-hospital mortality, 60-day mortality or the composite of death or readmission. Sustained hypotension (systolic blood pressure less than 80 mmHg for greater than 30 min) requiring intervention and new atrial arrhythmias occurred more frequently in patients who received milrinone. There was also an important trend for an increase in ventricular tachycardia or ventricular fibrillation in the milrinone group that approached but did not reach statistical significance ($p = 0.06$). The authors concluded that milrinone was not indicated as adjunctive therapy in patients hospitalized for ADHF.

A post-hoc analysis of the OPTIME-CHF data was performed to assess whether there was an interaction between the effect of short-term milrinone therapy and the etiology of heart failure (ischemic vs. non-ischemic) [242]. Patients with ischemic cardiomyopathy were found to have been adversely affected by milrinone. Patients with ischemic cardiomyopathy who were treated with milrinone had an increase in the primary end-point of days in the hospital or death within 60 days, death or re-hospitalization at 60 days, and in-hospital mortality (5.0 % vs 1.6 %)

when compared to those treated with placebo. Conversely, patients with non-ischemic cardiomyopathy seemed to benefit from milrinone. Non-ischemic patients treated with milrinone as compared with those treated with placebo had lower rates of in-hospital mortality and death or rehospitalization at 60 days.

A number of mechanisms have been proposed to explain the increase in adverse outcomes seen in patients with ADHF who are treated with inotropic agents. These include: cAMP-induced atrial and ventricular arrhythmias; vasodilation with coronary hypoperfusion resulting in myocardial damage; increased myocardial oxygen consumption resulting in myocardial ischemia and myocardial injury; and direct myocyte toxicity possibly mediated by intracellular calcium overload [222, 224].

The ACCF/AHA, HFSA and ESC guidelines endorse the use of inotropes in patients with ADHF who have severe systolic dysfunction, significantly decreased cardiac output, diminished peripheral perfusion and end-organ dysfunction despite adequate or elevated filling pressures [8, 28, 118]. The goals of inotropic therapy are to relieve symptoms, maintain systemic perfusion and preserve end-organ function. Inotropes also may be indicated in fluid overloaded patients who remain volume overloaded despite intravenous diuretics and, if appropriate, intravenous vasodilators. Inotropes may be used as "bridge therapy" in Stage D patients who are awaiting mechanical circulatory support or heart transplantation.

The guidelines note the risk associated with inotropic therapy and recommend continuous heart rhythm monitoring and frequent blood pressure monitoring. The need for management in an intensive care or cardiac care unit should be assessed. Obtaining objective measurements of hemodynamic parameters using a PA catheter to guide therapy should be strongly considered. Lower doses of inotrope are recommended to minimize adverse effects. The continued need for inotropic support (and the possibility of discontinuation) should be regularly assessed. An attempt to wean inotropes should be made after optimization of guideline directed medical therapy.

If an inotrope is indicated in a patient being treated with a β-blocker, milrinone is the preferred agent as its positive inotropic effect is not mediated by β-adrenergic stimulation. There is little data to guide decisions concerning whether to continue chronic β-blocker therapy in a patient who requires inotropic support. It is reasonable to continue the β-blocker without a change in dose or decrease the dose of β-blocker with a plan to increase the dose if the patient improves and the inotrope can be discontinued. In the case of patients with cardiogenic shock, pulmonary edema, hypotension, or manifestations of severe end-organ hypoperfusion, it is reasonable to hold the β-blocker until the patient stabilizes and end-organ function improves [61].

Conclusions

Comprehensive guidelines for the management of ADHF have been published by the American College of Cardiology Foundation/American Heart Association (ACCF/AHA), the Heart Failure Society of America (HFSA), and the European

Society of Cardiology (ESC). In general, there are three phases in the evaluation and management of patients who present with ADHF including: initial assessment; ongoing assessment and treatment; and discharge planning. A critical part of the initial assessment is the evaluation for the presence of pulmonary or hemodynamic instability that may require emergent intervention. Assessment for ACS that may require emergent coronary artery angiography and coronary intervention is also an essential component of the initial assessment.

Initial treatment is focused on relieving respiratory distress and correcting hypoxia. Oxygen administered by nasal cannula or face mask is recommended in patients with hypoxia. The use of non-invasive positive pressure ventilation is recommended in patients with severe dyspnea, clinical evidence of pulmonary edema, or persistent hypoxia.

Pharmacologic therapy is focused on relieving pulmonary congestion. Intravenous loop diuretics are first-line therapy. Routine use of invasive hemodynamic monitoring is not indicated and should be reserved for patients in cardiogenic shock, patients who are unresponsive to initial medical therapy, or patients who develop clinically significant hypotension and/or significant worsening of renal function during initial treatment for ADHF. Assessment of the adequacy of decongestion can be challenging and is based on symptom relief and physical exam.

In the absence of hypotension, intravenous nitroglycerine, nitroprusside or nesiritide may be used in patients who do not respond adequately to parenteral diuretics. The use of intravenous inotropes is not indicated in most patients with ADHF except those with LV systolic dysfunction with cardiogenic shock, evidence of low cardiac output or end-organ dysfunction, hypotension or heart failure unresponsive to diuretics and parenteral vasodilators.

References

1. Park JH, Balmain S, Berry C, Morton JJ, McMurray JJ. Potentially detrimental cardiovascular effects of oxygen in patients with chronic left ventricular systolic dysfunction. Heart. 2010;96(7):533–8. doi:10.1136/hrt.2009.175257.
2. Vismara LA, Leaman DM, Zelis R. The effects of morphine on venous tone in patients with acute pulmonary edema. Circulation. 1976;54(2):335–7.
3. Grossmann M, Abiose A, Tangphao O, Blaschke TF, Hoffman BB. Morphine-induced venodilation in humans. Clin Pharmacol Ther. 1996;60(5):554–60.
4. Timmis AD, Rothman MT, Henderson MA, Geal PW, Chamberlain DA. Haemodynamic effects of intravenous morphine in patients with acute myocardial infarction complicated by severe left ventricular failure. Br Med J. 1980;280(6219):980–2.
5. Sacchetti A, Ramoska E, Moakes ME, McDermott P, Moyer V. Effect of ED management on ICU use in acute pulmonary edema. Am J Emerg Med. 1999;17(6):571–4. PubMed.
6. Hoffman JR, Reynolds S. Comparison of nitroglycerin, morphine and furosemide in treatment of presumed pre-hospital pulmonary edema. Chest. 1987;92(4):586–93. PubMed.
7. Peacock WF, Hollander JE, Diercks DB, Lopatin M, Fonarow G, Emerman CL. Morphine and outcomes in acute decompensated heart failure: an ADHERE analysis. Emerg Med J. 2008;25(4):205–9. doi:10.1136/emj.2007.050419.

8. Heart Failure Society of America, Lindenfeld J, Albert NM, Boehmer JP, Collins SP, Ezekowitz JA, Givertz MM, et al. HFSA 2010 Comprehensive Heart Failure Practice Guideline. Section 12: Evaluation and Management of Patients with Acute Decompensated Heart Failure. J Card Fail. 2010;16(6):e131–56. doi:10.1016/j.cardfail.2010.04.004.
9. Kato T, Suda S, Kasai T. Positive airway pressure therapy for heart failure. World J Cardiol. 2014;6(11):1175–91. doi:10.4330/wjc.v6.i11.1175.
10. Masip J, Roque M, Sánchez B, Fernández R, Subirana M, Expósito JA. Noninvasive ventilation in acute cardiogenic pulmonary edema: systematic review and meta-analysis. JAMA. 2005;294(24):3124–30.
11. Peter JV, Moran JL, Phillips-Hughes J, Graham P, Bersten AD. Effect of non-invasive positive pressure ventilation (NIPPV) on mortality in patients with acute cardiogenic pulmonary oedema: a meta-analysis. Lancet. 2006;367(9517):1155–63. Review.
12. Mehta S, Jay GD, Woolard RH, Hipona RA, Connolly EM, Cimini DM, et al. Randomized, prospective trial of bilevel versus continuous positive airway pressure in acute pulmonary edema. Crit Care Med. 1997;25(4):620–8.
13. Gray A, Goodacre S, Newby DE, Masson M, Sampson F, Nicholl J, 3CPO Trialists. Noninvasive ventilation in acute cardiogenic pulmonary edema. N Engl J Med. 2008;359(2):142–51. doi:10.1056/NEJMoa0707992.
14. Mariani J, Macchia A, Belziti C, Deabreu M, Gagliardi J, Doval H, et al. Noninvasive ventilation in acute cardiogenic pulmonary edema: a meta-analysis of randomized controlled trials. J Card Fail 2011;17(10):850-859. doi: 10.1016/j.cardfail.2011.05.010. Epub 2011 Jul 8.
15. Vital FM, Ladeira MT, Atallah AN. Non-invasive positive pressure ventilation (CPAP or bilevel NPPV) for cardiogenic pulmonary oedema. Cochrane Database Syst Rev. 2013;5:CD005351. doi:10.1002/14651858.CD005351.pub3.
16. Mal S, McLeod S, Iansavichene A, Dukelow A, Lewell M. Effect of out-of-hospital noninvasive positive-pressure support ventilation in adult patients with severe respiratory distress: a systematic review and meta-analysis. Ann Emerg Med. 2014;63(5):600–607.e1. doi:10.1016/j.annemergmed.2013.11.013. Epub 2013 Dec 15.
17. Dickstein K, Cohen-Solal A, Filippatos G, McMurray JJ, Ponikowski P, Poole-Wilson PA, ESC Committee for Practice Guidelines (CPG), et al. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2008: the Task Force for the diagnosis and treatment of acute and chronic heart failure 2008 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association of the ESC (HFA) and endorsed by the European Society of Intensive Care Medicine (ESICM). Eur Heart J. 2008;29(19):2388–442. doi:10.1093/eurheartj/ehn309. Epub 2008 Sep 17.
18. McMurray JJ, Adamopoulos S, Anker SD, Auricchio A, Böhm M, Dickstein K, et al; Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology, Bax JJ, Baumgartner H, Ceconi C, Dean V, Deaton C, et al; ESC Committee for Practice Guidelines. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. Eur J Heart Fail. 2012;14(8):803–69. doi: 10.1093/eurjhf/hfs105. No abstract available. Erratum in: Eur J Heart Fail. 2013 Mar;15(3):361
19. De Bruyne LKM. Mechanisms and management of diuretic resistance in congestive heart failure. Postgrad Med J. 2003;79(931):268–71.
20. Cleland JG, Coletta A, Witte K. Practical applications of intravenous diuretic therapy in decompensated heart failure. Am J Med. 2006;119(12 Suppl 1):S26–36.
21. Brater DC. Diuretic therapy. N Engl J Med. 1998;339(6):387–95.
22. Brater DC. Update in diuretic therapy: clinical pharmacology. Semin Nephrol. 2011;31(6):483–94. doi:10.1016/j.semnephrol.2011.09.003. Review.
23. Felker GM, Mentz RJ. Diuretics and ultrafiltration in acute decompensated heart failure. J Am Coll Cardiol. 2012;59(24):2145–53. doi:10.1016/j.jacc.2011.10.910.

24. Brater DC. Pharmacology of diuretics. Am J Med Sci. 2000;319(1):38–50.
25. Shankar SS, Brater DC. Loop diuretics: from the Na-K-2Cl transporter to clinical use. Am J Physiol Renal Physiol. 2003;284(1):F11–21.
26. Reilly RF, Jackson EK. Chapter 25. Regulation of Renal Function and Vascular Volume. In: Brunton LL, Chabner BA, Knollmann BC, editors. Goodman & Gilman's The Pharmacological Basis of Therapeutics. 12th ed. New York, NY: McGraw-Hill; 2011 .http://accessmedicine.mhmedical.com/content.aspx?bookid=374&Sectionid=41266232
27. ter Maaten JM, Valente MA, Damman K, Hillege HL, Navis G, Voors AA. Diuretic response in acute heart failure-pathophysiology, evaluation, and therapy. Nat Rev Cardiol. 2015;12(3):184–92. doi:10.1038/nrcardio.2014.215. Epub 2015 Jan 6.
28. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey Jr DE, Drazner MH, American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, et al. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. Circulation. 2013;128(16):e240–327. doi:10.1161/CIR.0b013e31829e8776. Epub 2013 Jun 5.
29. Leto L, Aspromonte N, Feola M. Efficacy and safety of loop diuretic therapy in acute decompensated heart failure: a clinical review. Heart Fail Rev. 2014;19(2):237–46. doi:10.1007/s10741-012-9354-7.
30. Huang X, Dorhout Mees EJ, Vos PF, Hamza S, Braam B. Everything we always wanted to know about furosemide but were afraid to ask. Am J Physiol Renal Physiol. 2016;310(10):F958–71. doi:10.1152/ajprenal.00476.2015. Epub 2016 Feb 24.
31. Gottlieb SS, Brater DC, Thomas I, Havranek E, Bourge R, Goldman S, et al. BG9719 (CVT-124), an A1 adenosine receptor antagonist, protects against the decline in renal function observed with diuretic therapy. Circulation. 2002;105(11):1348–53.
32. Liang KV, Williams AW, Greene EL, Redfield MM. Acute decompensated heart failure and the cardiorenal syndrome. Crit Care Med. 2008;36(1 Suppl):S75–88. doi:10.1097/01.CCM.0000296270.41256.5C.
33. Ares GR, Caceres PS, Ortiz PA. Molecular regulation of NKCC2 in the thick ascending limb. Am J Physiol Renal Physiol. 2011;301(6):F1143–59. doi:10.1152/ajprenal.00396.2011. Epub 2011 Sep 7.
34. Fonarow GC, Corday E, ADHERE Scientific Advisory Committee. Overview of acutely decompensated congestive heart failure (ADHF): a report from the ADHERE registry. Heart Fail Rev. 2004;9(3):179–85.
35. Buggey J, Mentz RJ, Pitt B, Eisenstein EL, Anstrom KJ, Velazquez EJ, O'Connor CM. A reappraisal of loop diuretic choice in heart failure patients. Am Heart J. 2015;169(3):323–33. doi:10.1016/j.ahj.2014.12.009. Epub 2015 Jan 6.
36. Knauf H, Mutschler E. Clinical pharmacokinetics and pharmacodynamics of torasemide. Clin Pharmacokinet. 1998;34(1):1–24.
37. Roush GC, Kaur R, Ernst ME. Diuretics: a review and update.Cardiovasc. Pharmacol Ther. 2014;19(1):5–13. doi:10.1177/1074248413497257. Epub 2013 Nov 15.
38. Wargo KA, Banta WM. A comprehensive review of the loop diuretics: should furosemide be first line? Ann Pharmacother. 2009;43(11):1836–47. doi:10.1345/aph.1M177. Epub 2009 Oct 20.
39. Felker M. Diuretic management in heart failure. Congest Heart Fail. 2010;16(Suppl 1):S68–72.
40. Vasko MR, Cartwright DB, Knochel JP, Nixon JV, Brater DC. Furosemide absorption altered in decompensated congestive heart failure. Ann Intern Med. 1985;102(3):314–8.
41. Stevenson LW, Tillisch JH. Maintenance of cardiac output with normal filling pressures in patients with dilated heart failure. Circulation. 1986;74(6):1303–8.
42. Raftery EB. Haemodynamic effects of diuretics in heart failure. Br Heart J. 1994;72(2 Suppl):S44–7. PubMed.

43. Nelson GI, Ahuja RC, Silke B, Okoli RC, Hussain M, Taylor SH. Haemodynamic effects of frusemide and its influence on repetitive rapid volume loading in acute myocardial infarction. Eur Heart J. 1983;4(10):706–11. PubMed PMID: 6653580.
44. Stevenson LW. Tailored therapy to hemodynamic goals for advanced heart failure. Eur J Heart Fail. 1999;1(3):251–7.
45. Stevenson LW, Bellil D, Grover-McKay M, Brunken RC, Schwaiger M, Tillisch JH, Schelbert HR. Effects of afterload reduction (diuretics and vasodilators) on left ventricular volume and mitral regurgitation in severe congestive heart failure secondary to ischemic or idiopathic dilated cardiomyopathy. Am J Cardiol. 1987;60(8):654–8.
46. Dikshit K, Vyden JK, Forrester JS, Chatterjee K, Prakash R, Swan HJ. Renal and extrarenal hemodynamic effects of furosemide in congestive heart failure after acute myocardial infarction. N Engl J Med. 1973;288(21):108. PubMed.
47. Verma SP, Silke B, Hussain M, Nelson GI, Reynolds GW, Richmond A, Taylor SH. First-line treatment of left ventricular failure complicating acute myocardial infarction: a randomised evaluation of immediate effects of diuretic, venodilator, arteriodilator, and positive inotropic drugs on left ventricular function. J Cardiovasc Pharmacol. 1987;10(1):38–46. PubMed.
48. Verma SP, Silke B, Reynolds G, Muller P, Frais MA, Taylor SH. Immediate effects of bumetanide on systemic haemodynamics and left ventricular volume in acute and chronic heart failure. Br J Clin Pharmacol. 1987;24(1):21–31. PubMed.
49. Pickkers P, Dormans TP, Russel FG, Hughes AD, Thien T, Schaper N, Smits P. Direct vascular effects of furosemide in humans. Circulation. 1997;96(6):1847–52. PubMed.
50. Smits P. Vascular effects of loop diuretics. Cardiovasc Res. 1996;32(6):988–97. PubMed.
51. Francis GS, Siegel RM, Goldsmith SR, Olivari MT, Levine TB, Cohn JN. Acute vasoconstrictor response to intravenous furosemide in patients with chronic congestive heart failure. Activation of the neurohumoral axis. Ann Intern Med. 1985;103(1):1–6. PubMed.
52. Johnson W, Omland T, Hall C, Lucas C, Myking OL, Collins C, et al. Neurohormonal activation rapidly decreases after intravenous therapy with diuretics and vasodilators for class IV heart failure. J Am Coll Cardiol. 2002;39(10):1623–9.
53. Salvador DR, Rey NR, Ramos GC, Punzalan FE. Continuous infusion versus bolus injection of loop diuretics in congestive heart failure. Cochrane Database Syst Rev. 2005;3:CD003178.
54. Felker GM, Lee KL, Bull DA, Redfield MM, Stevenson LW, Goldsmith SR, NHLBI Heart Failure Clinical Research Network, et al. Diuretic strategies in patients with acute decompensated heart failure. N Engl J Med. 2011;364(9):797–805. doi:10.1056/NEJMoa1005419.
55. Givertz MM, Postmus D, Hillege HL, Mansoor GA, Massie BM, Davison BA, et al. Renal function trajectories and clinical outcomes in acute heart failure. Circ Heart Fail. 2014;7(1):59–67. doi:10.1161/CIRCHEARTFAILURE.113.000556. Epub 2013 Nov 26.
56. Metra M, Nodari S, Parrinello G, Bordonali T, Bugatti S, Danesi R, et al. Worsening renal function in patients hospitalised for acute heart failure: clinical implications and prognostic significance. Eur J Heart Fail. 2008;10(2):188–95. doi:10.1016/j.ejheart.2008.01.011.
57. Aronson D, Burger AJ. The relationship between transient and persistent worsening renal function and mortality in patients with acute decompensated heart failure. J Card Fail. 2010;16(7):541–7. doi:10.1016/j.cardfail.2010.02.001. Epub 2010 Mar 19.
58. Testani JM, Chen J, McCauley BD, Kimmel SE, Shannon RP. Potential effects of aggressive decongestion during the treatment of decompensated heart failure on renal function and survival. Circulation. 2010;122(3):265–72. doi:10.1161/CIRCULATIONAHA. 109.933275. Epub 2010 Jul 6.
59. Wu MY, Chang NC, Su CL, Hsu YH, Chen TW, Lin YF, et al. Loop diuretic strategies in patients with acute decompensated heart failure: a meta-analysis of randomized controlled trials. J Crit Care. 2014;29(1):2–9. doi:10.1016/j.jcrc.2013.10.009. Epub 2013 Oct 29.
60. Alqahtani F, Koulouridis I, Susantitaphong P, Dahal K, Jaber BL. A meta-analysis of continuous vs intermittent infusion of loop diuretics in hospitalized patients. J Crit Care. 2014;29(1):10–7. doi:10.1016/j.jcrc.2013.03.015. Epub 2013 May 14.

61. Ezekowitz JA, Hernandez AF, Starling RC, Yancy CW, Massie B, Hill JA, et al. Standardizing care for acute decompensated heart failure in a large megatrial: the approach for the Acute Studies of Clinical Effectiveness of Nesiritide in Subjects with Decompensated Heart Failure (ASCEND-HF). Am Heart J. 2009;157(2):219–28. doi:10.1016/j.ahj.2008.10.002. Epub 2008 Nov 28.
62. Michalsen A, König G, Thimme W. Preventable causative factors leading to hospital admission with decompensated heart failure. Heart. 1998;80(5):437–41.
63. McKelvie RS, Moe GW, Ezekowitz JA, Heckman GA, Costigan J, Ducharme A, et al. The 2012 Canadian Cardiovascular Society heart failure management guidelines update: focus on acute and chronic heart failure. Can J Cardiol. 2013;29(2):168–81. doi:10.1016/j.cjca.2012.10.007. Epub 2012 Nov 30.
64. McMurray JJ, Teerlink JR, Cotter G, Bourge RC, Cleland JG, Jondeau G, VERITAS Investigators, et al. Effects of tezosentan on symptoms and clinical outcomes in patients with acute heart failure: the VERITAS randomized controlled trials. JAMA. 2007;298(17):2009–19.
65. Gheorghiade M, Konstam MA, Burnett Jr JC, Grinfeld L, Maggioni AP, Swedberg K, Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study With Tolvaptan (EVEREST) Investigators, et al. Short-term clinical effects of tolvaptan, an oral vasopressin antagonist, in patients hospitalized for heart failure: the EVEREST Clinical Status Trials. JAMA. 2007;297(12):1332–43. Epub 2007 Mar 25.
66. Metra M, Cleland JG, Weatherley BD, Dittrich HC, Givertz MM, Massie BM, et al. Dyspnoea in patients with acute heart failure: an analysis of its clinical course, determinants, and relationship to 60-day outcomes in the PROTECT pilot study. Eur J Heart Fail. 2010;12(5):499–507. doi:10.1093/eurjhf/hfq021. Epub 2010 Mar 12. 10.
67. Metra M, Teerlink JR, Felker GM, Greenberg BH, Filippatos G, Ponikowski P, et al. Dyspnoea and worsening heart failure in patients with acute heart failure: results from the Pre-RELAX-AHF study. Eur J Heart Fail. 2010;12(10):1130–9. doi:10.1093/eurjhf/hfq132. Epub 2010 Aug 22.
68. Felker GM, Leimberger JD, Califf RM, Cuffe MS, Massie BM, Adams Jr KF, et al. Risk stratification after hospitalization for decompensated heart failure. J Card Fail. 2004;10(6):460–6.
69. Knauf H, Mutschler E. Clinical pharmacokinetics and pharmacodynamics of torasemide. Clin Pharmacokinet. 1998;34(1):1–24. Review. Strom BL, Schinnar R, Apter AJ, Margolis DJ, Lautenbach E, Hennessy S, Bilker WB, Pettitt D. Absence of cross-reactivity between sulfonamide antibiotics and sulfonamide nonantibiotics. N Engl J Med. 2003;349(17):1628–35.
70. Strom B, Schinnar R, Apter AJ, Margolis DJ, Lautenbach E, Hennessy S, et al. Absence of cross-reactivity between sulfonamide antibiotics and sulfonamide nonantibiotics. N Engl J Med. 2003;349(17):1628–35. PubMed PMID 14573734.
71. Lee AG, Anderson R, Kardon RH, Wall M. Presumed "sulfa allergy" in patients with intracranial hypertension treated with acetazolamide or furosemide: cross-reactivity, myth or reality? Am J Ophthalmol. 2004;138(1):114–8.
72. Hemstreet BA, Page RL 2nd. Sulfonamide allergies and outcomes related to use of potentially cross-reactive drugs in hospitalized patients. Pharmacotherapy. 2006;26(4):551–7.
73. Bumex package insert. www.accessdata.fda.gov/drugsatfda_docs/label/2010/019225s024161.pdf
74. Torsemide package insert. www.accessdata.fda.gov/drudsatfda_docs/label/2012/020136s014lbl.pdf
75. Greenberg A. Diuretic complications. Am J Med Sci. 2000;319(1):10–24.
76. Rybak LP. Ototoxicity of loop diuretics. Otolaryngol Clin North Am. 1993;26(5):829–44.
77. Seligmann H, Podoshin L, Ben-David J, Fradis M, Goldsher M. Drug-induced tinnitus and other hearing disorders. Drug Saf. 1996;14(3):198–212.

78. Gerlag PG, van Meijel JJ. High-dose furosemide in the treatment of refractory congestive heart failure. Arch Intern Med. 1988;148(2):286–91.
79. Micromedex Solutions. Truven Health Analytics 2016.
80. Kassamali R, Sica DA. Acetazolamide: a forgotten diuretic agent. Cardiol Rev. 2011;19(6):276–8. doi:10.1097/CRD.0b013e31822b4939.
81. Knauf H, Mutschler E. Sequential nephron blockade breaks resistance to diuretics in edematous states. J Cardiovasc Pharmacol. 1997;29(3):367–72.
82. Khan MI. Treatment of refractory congestive heart failure and normokalemic hypochloremic alkalosis with acetazolamide and spironolactone. Can Med Assoc J. 1980;123(9):883–7.
83. Jentzer JC, DeWald TA, Hernandez AF. Combination of loop diuretics with thiazide-type diuretics in heart failure. J Am Coll Cardiol. 2010;56(19):1527–34. doi:10.1016/j.jacc.2010.06.034.
84. Masoumi A, Ortiz F, Radhakrishnan J, Schrier RW, Colombo PC. Mineralocorticoid receptor antagonists as diuretics: can congestive heart failure learn from liver failure? Heart Fail Rev. 2015;20(3):283–90. doi:10.1007/s10741-014-9467-2.
85. Bauersachs J, Jaisser F, Toto R. Mineralocorticoid receptor activation and mineralocorticoid receptor antagonist treatment in cardiac and renal diseases. Hypertension. 2015;65(2):257–63. doi:10.1161/HYPERTENSIONAHA.114.04488. Epub 2014 Nov 3.
86. McKelvie RS, Yusuf S, Pericak D, Avezum A, Burns RJ, Probstfield J, et al. Comparison of candesartan, enalapril, and their combination in congestive heart failure: randomized evaluation of strategies for left ventricular dysfunction (RESOLVD) pilot study. The RESOLVD Pilot Study Investigators. Circulation. 1999;100:1056–64.
87. Pitt B, Zannad F, Remme WJ, Cody R, Castaigne A, Perez A, Palensky J, Wittes J. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators. N Engl J Med. 1999;341(10):709–17.
88. van Vliet AA, Donker AJ, Nauta JJ, Verheugt FW. Spironolactone in congestive heart failure refractory to high-dose loop diuretic and low-dose angiotensin-converting enzyme inhibitor. Am J Cardiol. 1993;71(3):21A–8A.
89. Ferreira JP, Santos M, Almeida S, Marques I, Bettencourt P, Carvalho H. Mineralocorticoid receptor antagonism in acutely decompensated chronic heart failure. Eur J Intern Med. 2014;25(1):67–72. doi:10.1016/j.ejim.2013.08.711. Epub 2013 Sep 23.
90. Butler J, Ezekowitz JA, Collins SP, Givertz MM, Teerlink JR, Walsh MN, et al. Update on aldosterone antagonists use in heart failure with reduced left ventricular ejection fraction. Heart Failure Society of America Guidelines Committee. J Card Fail. 2012;18(4):265–81. doi:10.1016/j.cardfail.2012.02.005.
91. Fonarow GC, Stough WG, Abraham WT, Albert NM, Gheorghiade M, Greenberg BH, OPTIMIZE-HF Investigators and Hospitals, et al. Characteristics, treatments, and outcomes of patients with preserved systolic function hospitalized for heart failure: a report from the OPTIMIZE-HF Registry. J Am Coll Cardiol. 2007;50(8):768–77. PubMed.
92. Ambrosy AP, Pang PS, Khan S, Konstam MA, Fonarow GC, Traver B, et al. EVEREST Trial Investigators. Clinical course and predictive value of congestion during hospitalization in patients admitted for worsening signs and symptoms of heart failure with reduced ejection fraction: findings from the EVEREST trial. Eur Heart J. 2013;34(11):835–43. doi:10.1093/eurheartj/ehs444. Epub 2013 Jan 4.
93. Pang PS, Konstam MA, Krasa HB, Swedberg K, Zannad F, Blair JE, Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study with Tolvaptan (EVEREST) Investigators, et al. Effects of tolvaptan on dyspnoea relief from the EVEREST trials. Eur Heart J. 2009;30(18):2233–40. doi:10.1093/eurheartj/ehp253. Epub 2009 Jun 27.
94. Costanzo MR, Guglin ME, Saltzberg MT, Jessup ML, Bart BA, UNLOAD Trial Investigators. Ultrafiltration versus intravenous diuretics for patients hospitalized for acute decompensated heart failure. J Am Coll Cardiol. 2007;49(6):675–83. PubMed.
95. Mehta RH, Rogers JG, Hasselblad V, Tasissa G, Binanay C, Califf RM, O'Connor CM, Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization

Effectiveness (ESCAPE) Trial Investigators. Association of weight change with subsequent outcomes in patients hospitalized with acute decompensated heart failure. Am J Cardiol. 2009;103(1):76–81. doi:10.1016/j.amjcard.2008.08.041. Epub 2008 Oct 7.
96. Metra M, O'Connor CM, Davison BA, Cleland JG, Ponikowski P, Teerlink JR, et al. Early dyspnoea relief in acute heart failure: prevalence, association with mortality, and effect of rolofylline in the PROTECT Study. Eur Heart J. 2011;32(12):1519–34. doi:10.1093/eurheartj/ehr042. Epub 2011 Mar 8.
97. Kociol RD, McNulty SE, Hernandez AF, Lee KL, Redfield MM, Tracy RP, Braunwald E, O'Connor CM, Felker GM, NHLBI Heart Failure Network Steering Committee and Investigators. Markers of decongestion, dyspnea relief, and clinical outcomes among patients hospitalized with acute heart failure. Circ Heart Fail. 2013;6(2):240–5.
98. Gheorghiade M, Follath F, Ponikowski P, Barsuk JH, Blair JE, Cleland JG, European Society of Intensive Care Medicine, et al. Assessing and grading congestion in acute heart failure: a scientific statement from the acute heart failure committee of the heart failure association of the European Society of Cardiology and endorsed by the European Society of Intensive Care Medicine. Eur J Heart Fail. 2010;12(5):423–33. doi:10.1093/eurjhf/hfq045. Epub 2010 Mar 30.
99. Vaduganathan M, Greene SJ, Fonarow GC, Voors AA, Butler J, Gheorghiade M. Hemoconcentration-Guided Diuresis in Heart Failure. Am J Med. 2014;127(12):1154–9. doi:10.1016/j.amjmed.2014.06.009. pii: S0002-9343(14)00482-3. [Epub ahead of print].
100. Boyle A, Sobotka PA. Redefining the therapeutic objective in decompensated heart failure: hemoconcentration as a surrogate for plasma refill rate. J Card Fail. 2006;12(4):247–9.
101. van der Meer P, Postmus D, Ponikowski P, Cleland JG, O'Connor CM, Cotter G, et al. The predictive value of short-term changes in hemoglobin concentration in patients presenting with acute decompensated heart failure. J Am Coll Cardiol. 2013;61(19):1973–81. doi:10.1016/j.jacc.2012.12.050. Epub 2013 Mar 14.
102. Greene SJ, Gheorghiade M, Vaduganathan M, Ambrosy AP, Mentz RJ, Subacius H, EVEREST Trial investigators, et al. Haemoconcentration, renal function, and post-discharge outcomes among patients hospitalized for heart failure with reduced ejection fraction: insights from the EVEREST trial. Eur J Heart Fail. 2013;15(12):1401–11. doi:10.1093/eurjhf/hft110. Epub 2013 Jul 11.
103. Oh J, Kang SM, Hong N, Youn JC, Han S, Jeon ES, et al. Hemoconcentration is a good prognostic predictor for clinical outcomes in acute heart failure: data from the Korean Heart Failure (KorHF) Registry. Int J Cardiol. 2013;168(5):4739–43. doi:10.1016/j.ijcard.2013.07.241. Epub 2013 Aug 2.
104. Testani JM, Brisco MA, Chen J, McCauley BD, Parikh CR, Tang WH. Timing of hemoconcentration during treatment of acute decompensated heart failure and subsequent survival: importance of sustained decongestion. J Am Coll Cardiol. 2013;62(6):516–24. doi:10.1016/j.jacc.2013.05.027. Epub 2013 Jun 7.
105. Desai AS. Hemoglobin concentration in acute decompensated heart failure: a marker of volume status? J Am Coll Cardiol. 2013;61(19):1982–4. doi:10.1016/j.jacc.2013.02.021. Epub 2013 Mar 14.
106. Desai AS. Are serial BNP measurements useful in heart failure management? Serial natriuretic peptide measurements are not useful in heart failure management: the art of medicine remains long. Circulation. 2013;127(4):509–16. discussion 516. doi:10.1161/CIRCULATIONAHA.112.120493.
107. Doust JA, Pietrzak E, Dobson A, Glasziou P. How well does B-type natriuretic peptide predict death and cardiac events in patients with heart failure: systematic review. BMJ. 2005;330(7492):625.
108. Cheng V, Kazanagra R, Garcia A, Lenert L, Krishnaswamy P, Gardetto N, et al. A rapid bedside test for B-type peptide predicts treatment outcomes in patients admitted for decompensated heart failure: a pilot study. J Am Coll Cardiol. 2001;37(2):386–91.

109. Logeart D, Thabut G, Jourdain P, Chavelas C, Beyne P, Beauvais F, et al. Predischarge B-type natriuretic peptide assay for identifying patients at high risk of re-admission after decompensated heart failure. J Am Coll Cardiol. 2004;43(4):635–41.
110. Gackowski A, Isnard R, Golmard JL, Pousset F, Carayon A, Montalescot G, et al. Comparison of echocardiography and plasma B-type natriuretic peptide for monitoring the response to treatment in acute heart failure. Eur Heart J. 2004;25(20):1788–96.
111. Singer AJ, Birkhahn RH, Guss D, Chandra A, Miller CD, Tiffany B, et al. Rapid Emergency Department Heart Failure Outpatients Trial (REDHOT II): a randomized controlled trial of the effect of serial B-type natriuretic peptide testing on patient management. Circ Heart Fail. 2009;2(4):287–93. doi:10.1161/CIRCHEARTFAILURE.108.826685. Epub 2009 May 19.
112. Steimle AE, Stevenson LW, Chelimsky-Fallick C, Fonarow GC, Hamilton MA, Moriguchi JD, et al. Sustained hemodynamic efficacy of therapy tailored to reduce filling pressures in survivors with advanced heart failure. Circulation. 1997;96(4):1165–72. PubMed.
113. Hamilton MA, Stevenson LW, Child JS, Moriguchi JD, Walden J, Woo M. Sustained reduction in valvular regurgitation and atrial volumes with tailored vasodilator therapy in advanced congestive heart failure secondary to dilated (ischemic or idiopathic) cardiomyopathy. Am J Cardiol. 1991;67(4):259-263. PubMed.
114. Binanay C, Califf RM, Hasselblad V, O'Connor CM, Shah MR, Sopko G, ESCAPE Investigators and ESCAPE Study Coordinators, et al. Evaluation study of congestive heart failure and pulmonary artery catheterization effectiveness: the ESCAPE trial. JAMA. 2005;294(13):1625–33.
115. Rajaram SS, Desai NK, Kalra A, Gajera M, Cavanaugh SK, Brampton W, et al. Pulmonary artery catheters for adult patients in intensive care. Cochrane Database Syst Rev. 2013;2:CD003408. doi:10.1002/14651858.CD003408.pub3.
116. Shah MR, Hasselblad V, Stevenson LW, Binanay C, O'Connor CM, Sopko G, Califf RM. Impact of the pulmonary artery catheter in critically ill patients: meta-analysis of randomized clinical trials. JAMA. 2005;294(13):1664–70.
117. Harvey S, Harrison DA, Singer M, Ashcroft J, Jones CM, Elbourne D, PAC-Man study collaboration, et al. Assessment of the clinical effectiveness of pulmonary artery catheters in management of patients in intensive care (PAC-Man): a randomised controlled trial. Lancet. 2005;366(9484):472–7.
118. Collins SP, Lindsell CJ, Storrow AB, Abraham WT, ADHERE Scientific Advisory Committee, Investigators and Study Group. Prevalence of negative chest radiography results in the emergency department patient with decompensated heart failure. Ann Emerg Med. 2006;47(1):13–8. Epub 2005 Jun 20.
119. Gheorghiade M, Sopko G, De Luca L, Velazquez EJ, Parker JD, Binkley PF, et al. Navigating the crossroads of coronary artery disease and heart failure. Circulation. 2006;114(11):1202–13.
120. Ellison DH. Diuretic therapy and resistance in congestive heart failure. Cardiology. 2001;96(3–-4):132–43.
121. Valente MA, Voors AA, Damman K, Van Veldhuisen DJ, Massie BM, O'Connor CM, et al. Diuretic response in acute heart failure: clinical characteristics and prognostic significance. Eur Heart J. 2014;35(19):1284–93. doi:10.1093/eurheartj/ehu065. Epub 2014 Feb 28.
122. Testani JM, Brisco MA, Turner JM, Spatz ES, Bellumkonda L, Parikh CR, Tang WH. Loop diuretic efficiency: a metric of diuretic responsiveness with prognostic importance in acute decompensated heart failure. Circ Heart Fail. 2014;7(2):261–70. doi:10.1161/CIRCHEARTFAILURE.113.000895. Epub 2013 Dec 30.
123. Kazory A, Elkayam U. Cardiorenal interactions in acute decompensated heart failure: contemporary concepts facing emerging controversies. J Card Fail. 2014;20(12):1004–11. doi:10.1016/j.cardfail.2014.09.005. Epub 2014 Sep 16.
124. Maxwell MH, Breed ES, Schwartz IL. Renal venous pressure in chronic congestive heart failure. J Clin Invest. 1950;29(3):342–8.

125. Damman K, van Deursen VM, Navis G, Voors AA, van Veldhuisen DJ, Hillege HL. Increased central venous pressure is associated with impaired renal function and mortality in a broad spectrum of patients with cardiovascular disease. J Am Coll Cardiol. 2009;53(7):582–8. doi:10.1016/j.jacc.2008.08.080.
126. Damman K, Navis G, Smilde TD, Voors AA, van der Bij W, van Veldhuisen DJ, Hillege HL. Decreased cardiac output, venous congestion and the association with renal impairment in patients with cardiac dysfunction. Eur J Heart Fail. 2007;9(9):872–8. Epub 2007 Jun 22.
127. Mullens W, Abrahams Z, Francis GS, Sokos G, Taylor DO, Starling RC, et al. Importance of venous congestion for worsening of renal function in advanced decompensated heart failure. J Am Coll Cardiol. 2009;53(7):589–96. doi:10.1016/j.jacc.2008.05.068.
128. Cheatham ML, Safcsak K. Intraabdominal pressure: a revised method for measurement. J Am Coll Surg. 1998;186(3):368–9.
129. Malbrain ML. Different techniques to measure intra-abdominal pressure (IAP): time for a critical re-appraisal. Intensive Care Med. 2004;30(3):357–71. Epub 2004 Jan 17.
130. Mullens W, Abrahams Z, Skouri HN, Francis GS, Taylor DO, Starling RC, et al. Elevated intra-abdominal pressure in acute decompensated heart failure: a potential contributor to worsening renal function? J Am Coll Cardiol. 2008;51(3):300–6. doi:10.1016/j.jacc.2007.09.043.
131. Mullens W, Abrahams Z, Francis GS, Taylor DO, Starling RC, Tang WH. Prompt reduction in intra-abdominal pressure following large-volume mechanical fluid removal improves renal insufficiency in refractory decompensated heart failure. J Card Fail. 2008;14(6):508–14. doi:10.1016/j.cardfail.2008.02.010. Epub 2008 May 27.
132. Forman DE, Butler J, Wang Y, Abraham WT, O'Connor CM, Gottlieb SS, et al. Incidence, predictors at admission, and impact of worsening renal function among patients hospitalized with heart failure. J Am Coll Cardiol. 2004;43(1):61–7.
133. Krumholz HM, Chen YT, Vaccarino V, Wang Y, Radford MJ, Bradford WD, Horwitz RI. Correlates and impact on outcomes of worsening renal function in patients > or =65 years of age with heart failure. Am J Cardiol. 2000;85(9):1110–3.
134. Nohria A, Hasselblad V, Stebbins A, Pauly DF, Fonarow GC, Shah M, et al. Cardiorenal interactions: insights from the ESCAPE trial. J Am Coll Cardiol. 2008;51(13):1268–74. doi:10.1016/j.jacc.2007.08.072.
135. Aronson D, Abassi Z, Allon E, Burger AJ. Fluid loss, venous congestion, and worsening renal function in acute decompensated heart failure. Eur J Heart Fail. 2013;15(6):637–43. doi:10.1093/eurjhf/hft036. Epub 2013 Mar 8.
136. Ronco C, Cicoira M, McCullough PA. Cardiorenal syndrome type 1: pathophysiological crosstalk leading to combined heart and kidney dysfunction in the setting of acutely decompensated heart failure. J Am Coll Cardiol. 2012;60(12):1031–42. doi:10.1016/j.jacc.2012.01.077. Epub 2012 Jul 25.
137. Virzì GM, Clementi A, Brocca A, de Cal M, Vescovo G, Granata A, Ronco C. The hemodynamic and nonhemodynamic crosstalk in cardiorenal syndrome type 1. Cardiorenal Med. 2014;4(2):103–12. doi:10.1159/000362650. Epub 2014 May 14.
138. Husain-Syed F, McCullough PA, Birk HW, Renker M, Brocca A, Seeger W, Ronco C. Cardiopulmonary-renal interactions: a multidisciplinary approach. J Am Coll Cardiol. 2015;65(22):2433–48. doi:10.1016/j.jacc.2015.04.024.
139. van Meyel JJ, Smits P, Dormans T, Gerlag PG, Russel FG, Gribnau FW. Continuous infusion of furosemide in the treatment of patients with congestive heart failure and diuretic resistance. J Intern Med. 1994;235(4):329–34.
140. Dormans TP, van Meyel JJ, Gerlag PG, Tan Y, Russel FG, Smits P. Diuretic efficacy of high dose furosemide in severe heart failure: bolus injection versus continuous infusion. J Am Coll Cardiol. 1996;28(2):376–82.
141. Channer KS, McLean KA, Lawson-Matthew P, Richardson M. Combination diuretic treatment in severe heart failure: a randomised controlled trial. Br Heart J. 1994;71(2):146–50.

142. Rosenberg J, Gustafsson F, Galatius S, Hildebrandt PR. Combination therapy with metolazone and loop diuretics in outpatients with refractory heart failure: an observational study and review of the literature. Cardiovasc Drugs Ther. 2005;19(4):301–6.
143. Costanzo MR. Ultrafiltration in the management of heart failure. Curr Opin Crit Care. 2008;14(5):524–30. PubMed.
144. Costanzo MR, Jessup M. Treatment of congestion in heart failure with diuretics and extracorporeal therapies: effects on symptoms, renal function, and prognosis. Heart Fail Rev. 2012;17(2):313–24. PubMed.
145. Marenzi G, Lauri G, Grazi M, Assanelli E, Campodonico J, Agostoni P. Circulatory response to fluid overload removal by extracorporeal ultrafiltration in refractory congestive heart failure. J Am Coll Cardiol. 2001;38(4):963–8. PubMed.
146. Agostoni P, Marenzi G, Lauri G, Perego G, Schianni M, Sganzerla P, Guazzi MD. Sustained improvement in functional capacity after removal of body fluid with isolated ultrafiltration in chronic cardiac insufficiency: failure of furosemide to provide the same result. Am J Med. 1994;96(3):191–9. PubMed PMID 8154506.
147. Bart BA, Boyle A, Bank AJ, Anand I, Olivari MT, Kraemer M, et al. Ultrafiltration versus usual care for hospitalized patients with heart failure: the Relief for Acutely Fluid-Overloaded Patients With Decompensated Congestive Heart Failure (RAPID-CHF) trial. J Am Coll Cardiol. 2005;46(11):2043–6. PubMed.
148. Bart BA, Goldsmith SR, Lee KL, Givertz MM, O'Connor CM, Heart Failure Clinical Research Network. Ultrafiltration in decompensated heart failure with cardiorenal syndrome. N Engl J Med. 2012;367(24):2296–304. PubMed.
149. Silvers SM, Howell JM, Kosowsky JM, Rokos IC, Jagoda AS, American College of Emergency Physicians. Clinical policy: critical issues in the evaluation and management of adult patients presenting to the emergency department with acute heart failure syndromes. Ann Emerg Med. 2007;49(5):627–69. Epub 2007 Apr 3.
150. Abraham WT, Adams KF, Fonarow GC, Costanzo MR, Berkowitz RL, LeJemtel TH, ADHERE Scientific Advisory Committee and Investigators; ADHERE Study Group, et al. In-hospital mortality in patients with acute decompensated heart failure requiring intravenous vasoactive medications: an analysis from the Acute Decompensated Heart Failure National Registry (ADHERE). J Am Coll Cardiol. 2005;46(1):57–64.
151. Hamilton MA, Stevenson LW, Child JS, Moriguchi JD, Woo M. Acute reduction of atrial overload during vasodilator and diuretic therapy in advanced congestive heart failure. Am J Cardiol. 1990;65(18):1209–12.
152. Leier CV, Bambach D, Thompson MJ, Cattaneo SM, Goldberg RJ, Unverferth DV. Central and regional hemodynamic effects of intravenous isosorbide dinitrate, nitroglycerin and nitroprusside in patients with congestive heart failure. Am J Cardiol. 1981;48(6):1115–23.
153. Elkayam U, Janmohamed M, Habib M, Hatamizadeh P. Vasodilators in the management of acute heart failure. Crit Care Med. 2008;36(1 Suppl):S95–105. doi:10.1097/01.CCM.0000297161.41559.93.
154. Hollenberg SM. Vasodilators in acute heart failure. Heart Fail Rev. 2007;12(2):143–7.
155. Heart Failure Executive Committee, Peacock WF, Fonarow GC, Heart Failure Diagnosis Subcommittee, Ander DS, Maisel A, Hollander JE, Januzzi Jr JL, Yancy CW, Heart Failure Risk Stratification Subcommittee, Collins SP, Gheorghiade M, Weintraub NL, Storrow AB, Pang PS, Abraham WT, Hiestand B, Heart Failure Treatment Subcommittee, Kirk JD, Filippatos G, Gheorghiade M, Pang PS, Levy P, Amsterdam EA. Society of Chest Pain Centers Recommendations for the evaluation and management of the observation stay acute heart failure patient: a report from the Society of Chest Pain Centers Acute Heart Failure Committee. Crit Pathw Cardiol. 2008;7(2):83–6. doi:10.1097/01.hpc.0000317706.54479.a4.
156. Moazemi K, Chana JS, Willard AM, Kocheril AG. Intravenous vasodilator therapy in congestive heart failure. Drugs Aging. 2003;20(7):485–508.
157. Hunt SA, Abraham WT, Chin MH, Feldman AM, Francis GS, Ganiats TG, et al. 2009 focused update incorporated into the ACC/AHA 2005 Guidelines for the Diagnosis and

Management of Heart Failure in Adults: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines: developed in collaboration with the International Society for Heart and Lung Transplantation. Circulation. 2009;119(14):e391–479. doi:10.1161/CIRCULATIONAHA.109.192065. Epub 2009 Mar 26.
158. Herling IM. Intravenous nitroglycerin: clinical pharmacology and therapeutic considerations. Am Heart J. 1984;108:141–8.
159. De Caterina R, Dorso CR, Tack-Goldman K, Weksler BB. Nitrates and endothelial prostacyclin production: studies in vitro. Circulation. 1985;71(1):176–82.
160. Chen Z, Zhang J, Stamler JS. Identification of the enzymatic mechanism of nitroglycerin bioactivation. Proc Natl Acad Sci U S A. 2002;99(12):8306–11. Epub 2002 Jun 4.
161. Elkayam U, Bitar F, Akhter MW, Khan S, Patrus S, Derakhshani M. Intravenous nitroglycerin in the treatment of decompensated heart failure: potential benefits and limitations. J Cardiovasc Pharmacol Ther. 2004;9(4):227–41.
162. Elkayam U. Nitrates in the treatment of congestive heart failure. Am J Cardiol. 1996;77(13):41C–51C.
163. Armstrong PW, Armstrong JA, Marks GS. Pharmacokinetic-hemodynamic studies of intravenous nitroglycerin in congestive cardiac failure. Circulation. 1980;62(1):160–6.
164. Magrini F, Niarchos AP. Ineffectiveness of sublingual nitroglycerin in acute left ventricular failure in the presence of massive peripheral edema. Am J Cardiol. 1980;45(4):841–7.
165. Kulick D, Roth A, McIntosh N, Rahimtoola SH, Elkayam U. Resistance to isosorbide dinitrate in patients with severe chronic heart failure: incidence and attempt at hemodynamic prediction. J Am Coll Cardiol. 1988;12(4):1023–8.
166. Katz SD, Biasucci L, Sabba C, Strom JA, Jondeau G, Galvao M, et al. Impaired endothelium-mediated vasodilation in the peripheral vasculature of patients with congestive heart failure. J Am Coll Cardiol. 1992;19(5):918–25.
167. Mehra A, Shotan A, Ostrzega E, Hsueh W, Vasquez-Johnson J, Elkayam U. Potentiation of isosorbide dinitrate effects with N-acetylcysteine in patients with chronic heart failure. Circulation. 1994;89(6):2595–600.
168. Packer M, Lee WH, Kessler PD, Gottlieb SS, Medina N, Yushak M. Prevention and reversal of nitrate tolerance in patients with congestive heart failure. N Engl J Med. 1987;317(13):799–804.
169. Daiber A, Mülsch A, Hink U, Mollnau H, Warnholtz A, Oelze M, Münzel T. The oxidative stress concept of nitrate tolerance and the antioxidant properties of hydralazine. Am J Cardiol. 2005;96(7B):25i–36i. Epub 2005 Aug 8.
170. Hink U, Oelze M, Kolb P, Bachschmid M, Zou MH, Daiber A, et al. Role for peroxynitrite in the inhibition of prostacyclin synthase in nitrate tolerance. J Am Coll Cardiol. 2003;42(10):1826–34.
171. Dakak N, Makhoul N, Flugelman MY, Merdler A, Shehadeh H, Schneeweiss A, et al. Failure of captopril to prevent nitrate tolerance in congestive heart failure secondary to coronary artery disease. Am J Cardiol. 1990;66(5):608–13.
172. Elkayam U, Kulick D, McIntosh N, Roth A, Hsueh W, Rahimtoola SH. Incidence of early tolerance to hemodynamic effects of continuous infusion of nitroglycerin in patients with coronary artery disease and heart failure. Circulation. 1987;76(3):577–84.
173. Dupuis J, Lalonde G, Lemieux R, Rouleau JL. Tolerance to intravenous nitroglycerin in patients with congestive heart failure: role of increased intravascular volume, neurohumoral activation and lack of prevention with N-acetylcysteine. J Am Coll Cardiol. 1990;16(4):923–31.
174. Elkayam U, Roth A, Henriquez B, Weber L, Tonnemacher D, Rahimtoola SH. Hemodynamic and hormonal effects of high-dose transdermal nitroglycerin in patients with chronic congestive heart failure. Am J Cardiol. 1985;56(8):555–9.

175. Dupuis J, Lalonde G, Bichet D, Rouleau JL. Captopril does not prevent nitroglycerin tolerance in heart failure. Can J Cardiol. 1990;6(7):281–6.
176. Bauer JA, Fung HL. Concurrent hydralazine administration prevents nitroglycerin-induced hemodynamic tolerance in experimental heart failure. Circulation. 1991;84(1):35–9.
177. Daiber A, Oelze M, Coldewey M, Kaiser K, Huth C, Schildknecht S, et al. Hydralazine is a powerful inhibitor of peroxynitrite formation as a possible explanation for its beneficial effects on prognosis in patients with congestive heart failure. Biochem Biophys Res Commun. 2005;338(4):1865–74. Epub 2005 Nov 11.
178. Elkayam U, Bitar F. Effects of nitrates and hydralazine in heart failure: clinical evidence before the african american heart failure trial. Am J Cardiol. 2005;96(7B):37i–43i. Epub 2005 Aug.
179. Taylor AL, Ziesche S, Yancy C, Carson P, D'Agostino Jr R, Ferdinand K, African-American Heart Failure Trial Investigators, et al. Combination of isosorbide dinitrate and hydralazine in blacks with heart failure. N Engl J Med. 2004;351(20):2049–57. Epub 2004 Nov 8.
180. Cotter G, Metzkor E, Kaluski E, Faigenberg Z, Miller R, Simovitz A, et al. Randomised trial of high-dose isosorbide dinitrate plus low-dose furosemide versus high-dose furosemide plus low-dose isosorbide dinitrate in severe pulmonary oedema. Lancet. 1998;351(9100):389–93.
181. Publication Committee for the VMAC Investigators (Vasodilatation in the Management of Acute CHF). Intravenous nesiritide vs nitroglycerin for treatment of decompensated congestive heart failure: a randomized controlled trial. JAMA. 2002;287(12):1531–40.
182. Elkayam U, for the VMAC Study Group. Superior hemodynamic effect of nesiritide (B-type natriuretic peptide) compared to high dose nitroglycerin (NTG) in patients with decompensated heart failure. NAIP 5th Annual Meeting; 2002 Apr, p 7.
183. Fung HL, Bauer JA. Mechanisms of nitrate tolerance. Cardiovasc Drugs Ther. 1994;8(3):489–99. PubMed.
184. Michel T, Hoffman BB. Chapter 27. Treatment of Myocardial Ischemia and Hypertension. In: Brunton LL, Chabner BA, Knollmann BC, editors. Goodman & Gilman's The Pharmacological Basis of Therapeutics. 12th ed. New York, NY: McGraw-Hill; 2011 .http://accessmedicine.mhmedical.com/content.aspx?bookid=374&Sectionid=41266234. Accessed August 04, 2015.
185. Hottinger DG, Beebe DS, Kozhimannil T, Prielipp RC, Belani KG. Sodium nitroprusside in 2014: a clinical concepts review. J Anaesthesiol Clin Pharmacol. 2014;30(4):462–71. doi:10.4103/0970-9185.142799.
186. Carlson MD, Eckman PM. Review of vasodilators in acute decompensated heart failure: the old and the new. J Card Fail. 2013;19(7):478–93. doi:10.1016/j.cardfail.2013.05.007.
187. Packer M, Meller J, Medina N, Gorlin R, Herman MV. Rebound hemodynamic events after the abrupt withdrawal of nitroprusside in patients with severe chronic heart failure. N Engl J Med. 1979;301(22):1193–7.
188. Reade MC, Davies SR, Morley PT, Dennett J, Jacobs IC, Australian Resuscitation Council. Review article: management of cyanide poisoning. Emerg Med Australas. 2012;24(3):225–38. doi:10.1111/j.1742-6723.2012.01538.x. Epub 2012 Feb 21.
189. Guiha NH, Cohn JN, Mikulic E, Franciosa JA, Limas CJ. Treatment of refractory heart failure with infusion of nitroprusside. N Engl J Med. 1974;291(12):587–92.
190. Hockings BE, Cope GD, Clarke GM, Taylor RR. Randomized controlled trial of vasodilator therapy after myocardial infarction. Am J Cardiol. 1981;48(2):345–52.
191. Cohn JN, Franciosa JA, Francis GS, Archibald D, Tristani F, Fletcher R, et al. Effect of short-term infusion of sodium nitroprusside on mortality rate in acute myocardial infarction complicated by left ventricular failure: results of a Veterans Administration cooperative study. N Engl J Med. 1982;306(19):1129–35.

192. Mullens W, Abrahams Z, Francis GS, Skouri HN, Starling RC, Young JB, et al. Sodium nitroprusside for advanced low-output heart failure. J Am Coll Cardiol. 2008;52(3):200–7. doi:10.1016/j.jacc.2008.02.083.
193. Stevenson LW, Dracup KA, Tillisch JH. Efficacy of medical therapy tailored for severe congestive heart failure in patients transferred for urgent cardiac transplantation. Am J Cardiol. 1989;63(7):461–4.
194. Levin ER, Gardner DG, Samson WK. Natriuretic peptides. N Engl J Med. 1998;339(5):321–8.
195. Elkayam U, Akhter MW, Tummala P, Khan S, Singh H. Nesiritide: a new drug for the treatment of decompensated heart failure. J Cardiovasc Pharmacol Ther. 2002;7(3):181–94.
196. Potter LR, Yoder AR, Flora DR, Antos LK, Dickey DM. Natriuretic peptides: their structures, receptors, physiologic functions and therapeutic applications. Handb Exp Pharmacol. 2009;191:341–66. doi:10.1007/978-3-540-68964-5_15.
197. Potter LR. Natriuretic peptide metabolism, clearance and degradation. FEBS J. 2011;278(11):1808–17. doi:10.1111/j.1742-4658.2011.08082.x. Epub 2011 Apr 7.
198. Abraham WT, Lowes BD, Ferguson DA, Odom J, Kim JK, Robertson AD, et al. Systemic hemodynamic, neurohormonal, and renal effects of a steady-state infusion of human brain natriuretic peptide in patients with hemodynamically decompensated heart failure. J Card Fail. 1998;4(1):37–44.
199. Mills RM, LeJemtel TH, Horton DP, Liang C, Lang R, Silver MA, et al. Sustained hemodynamic effects of an infusion of nesiritide (human b-type natriuretic peptide) in heart failure: a randomized, double-blind, placebo-controlled clinical trial. Natrecor Study Group. J Am Coll Cardiol. 1999;34(1):155–62.
200. Colucci WS, Elkayam U, Horton DP, Abraham WT, Bourge RC, Johnson AD, et al. Intravenous nesiritide, a natriuretic peptide, in the treatment of decompensated congestive heart failure. Nesiritide Study Group. N Engl J Med. 2000;343(4):246–53.
201. Aronson D, Horton DP, Burger AJ. Effect of nesiritide, B-type natriuretic peptide, on endothelin-1 in patients with decompensated congestive heart failure. J Am Coll Cardiol. 2001;37(2 Suppl A):1A–648A.
202. Michaels AD, Klein A, Madden JA, Chatterjee K. Effects of intravenous nesiritide on human coronary vasomotor regulation and myocardial oxygen uptake. Circulation. 2003;107(21):2697–701. Epub 2003 May 12.
203. Burger AJ, Horton DP, LeJemtel T, Ghali JK, Torre G, Dennish G, Prospective Randomized Evaluation of Cardiac Ectopy with Dobutamine or Natrecor Therapy, et al. Effect of nesiritide (B-type natriuretic peptide) and dobutamine on ventricular arrhythmias in the treatment of patients with acutely decompensated congestive heart failure: the PRECEDENT study. Am Heart J. 2002;144(6):1102–8.
204. Mentzer Jr RM, Oz MC, Sladen RN, Graeve AH, Hebeler Jr RF, Luber Jr JM, Smedira NG, NAPA Investigators. Effects of perioperative nesiritide in patients with left ventricular dysfunction undergoing cardiac surgery: the NAPA Trial. J Am Coll Cardiol. 2007;49(6):716–26. Epub 2006 Dec 11.
205. Wang DJ, Dowling TC, Meadows D, Ayala T, Marshall J, Minshall S, et al. Nesiritide does not improve renal function in patients with chronic heart failure and worsening serum creatinine. Circulation. 2004;110(12):1620–5. Epub 2004 Aug 30.
206. Chen HH, Anstrom KJ, Givertz MM, Stevenson LW, Semigran MJ, Goldsmith SR, NHLBI Heart Failure Clinical Research Network, et al. Low-dose dopamine or low-dose nesiritide in acute heart failure with renal dysfunction: the ROSE acute heart failure randomized trial. JAMA. 2013;310(23):2533–43. doi:10.1001/jama.2013.282190.
207. Elkayam U, Akhter MW, Singh H, Khan S, Usman A. Comparison of effects on left ventricular filling pressure of intravenous nesiritide and high-dose nitroglycerin in patients with decompensated heart failure. Am J Cardiol. 2004;93(2):237–40.
208. Sackner-Bernstein JD, Skopicki HA, Aaronson KD. Risk of worsening renal function with nesiritide in patients with acutely decompensated heart failure. Circulation. 2005;111(12):1487–91. Epub 2005 Mar 21.

209. Sackner-Bernstein JD, Kowalski M, Fox M, Aaronson K. Short-term risk of death after treatment with nesiritide for decompensated heart failure: a pooled analysis of randomized controlled trials. JAMA. 2005;293(15):1900–5.
210. Aaronson KD, Sackner-Bernstein J. Risk of death associated with nesiritide in patients with acutely decompensated heart failure. JAMA. 2006;296(12):1465–6.
211. Arora RR, Venkatesh PK, Molnar J. Short and long-term mortality with nesiritide. Am Heart J. 2006;152(6):1084–90.
212. Abraham WT, Trupp RJ, Jarjoura D. Nesiritide in acute decompensated heart failure: a pooled analysis of randomized controlled trials. Clin Cardiol. 2010;33(8):484–9. doi:10.1002/clc.20793.
213. O'Connor CM, Starling RC, Hernandez AF, Armstrong PW, Dickstein K, Hasselblad V, et al. Effect of nesiritide in patients with acute decompensated heart failure. N Engl J Med. 2011;365(1):32–43. doi:10.1056/NEJMoa1100171.
214. Westfall TC, Westfall DP. Chapter 12. Adrenergic Agonists and Antagonists. In: Brunton LL, Chabner BA, Knollmann BC, editors. Goodman & Gilman's The Pharmacological Basis of Therapeutics. 12th ed. New York, NY: McGraw-Hill; 2011 .http://accessmedicine.mhmedical.com/content.aspx?bookid=374&Sectionid=41266218. Accessed March 28, 2015.
215. Leier CV, Unverferth DV. Drugs five years later. Dobutamine. Ann Intern Med. 1983;99(4):490–6.
216. Bayram M, De Luca L, Massie MB, Gheorghiade M. Reassessment of dobutamine, dopamine, and milrinone in the management of acute heart failure syndromes. Am J Cardiol. 2005;96(6A):47G–58G.
217. Shin DD, Brandimarte F, De Luca L, Sabbah HN, Fonarow GC, Filippatos G, et al. Review of current and investigational pharmacologic agents for acute heart failure syndromes. Am J Cardiol. 2007;99(2A):4A–23A. Epub 2006 Nov 27.
218. Monrad ES, Baim DS, Smith HS, AS L. Milrinone, dobutamine, and nitroprusside: comparative effects on hemodynamics and myocardial energetics in patients with severe congestive heart failure. Circulation. 1986;73(3 Pt 2):III168–74.
219. El-Sayed OM, Abdelfattah RR, Barcelona R, Leier CV. Dobutamine-induced eosinophilia. Am J Cardiol. 2004;93(8):1078–9.
220. Takkenberg JJ, Czer LS, Fishbein MC, Luthringer DJ, Quartel AW, Mirocha J, et al. Eosinophilic myocarditis in patients awaiting heart transplantation. Crit Care Med. 2004;32(3):714–21.
221. Beanlands RS, Bach DS, Raylman R, Armstrong WF, Wilson V, Montieth M, et al. Acute effects of dobutamine on myocardial oxygen consumption and cardiac efficiency measured using carbon-11 acetate kinetics in patients with dilated cardiomyopathy. J Am Coll Cardiol. 1993;22(5):1389–98.
222. Schulz R, Rose J, Martin C, Brodde OE, Heusch G. Development of short-term myocardial hibernation. Its limitation by the severity of ischemia and inotropic stimulation. Circulation. 1993;88(2):684–95.
223. Nikolaidis LA, Hentosz T, Doverspike A, Huerbin R, Stolarski C, Shen YT, Shannon RP. Catecholamine stimulation is associated with impaired myocardial O(2) utilization in heart failure. Cardiovasc Res. 2002;53(2):392–404.
224. Teerlink JR, Metra M, Zacà V, Sabbah HN, Cotter G, Gheorghiade M, Cas LD. Agents with inotropic properties for the management of acute heart failure syndromes. Traditional agents and beyond. Heart Fail Rev. 2009;14(4):243–53. doi:10.1007/s10741-009-9153-y.
225. Elkayam U, Ng TM, Hatamizadeh P, Janmohamed M, Mehra A. Renal vasodilatory action of dopamine in patients with heart failure: magnitude of effect and site of action. Circulation. 2008;117(2):200–5. Epub 2008 Jan 2.
226. Giamouzis G, Butler J, Starling RC, Karayannis G, Nastas J, Parisis C, et al. Impact of dopamine infusion on renal function in hospitalized heart failure patients: results of the Dopamine in Acute Decompensated Heart Failure (DAD-HF) Trial. J Card Fail. 2010;16(12):922–30. doi:10.1016/j.cardfail.2010.07.246.

227. Triposkiadis FK, Butler J, Karayannis G, Starling RC, Filippatos G, Wolski K, et al. Efficacy and safety of high dose versus low dose furosemide with or without dopamine infusion: the Dopamine in Acute Decompensated Heart Failure II (DAD-HF II) trial. Int J Cardiol. 2014;172(1):115–21. doi:10.1016/j.ijcard.2013.12.276. Epub 2014 Jan 10.
228. Baim DS. Effect of phosphodiesterase inhibition on myocardial oxygen consumption and coronary blood flow. Am J Cardiol. 1989;63(2):23A–6A.
229. Banfor PN, Preusser LC, Campbell TJ, Marsh KC, Polakowski JS, Reinhart GA, et al. Comparative effects of levosimendan, OR-1896, OR-1855, dobutamine, and milrinone on vascular resistance, indexes of cardiac function, and O2 consumption in dogs. Am J Physiol Heart Circ Physiol. 2008;294(1):H238–48. Epub 2007 Nov 2.
230. Baruch L, Patacsil P, Hameed A, Pina I, Loh E. Pharmacodynamic effects of milrinone with and without a bolus loading infusion. Am Heart J. 2001;141(2):266–73.
231. Papp Z, Édes I, Fruhwald S, De Hert SG, Salmenperä M, Leppikangas H, et al. Levosimendan: molecular mechanisms and clinical implications: consensus of experts on the mechanisms of action of levosimendan. Int J Cardiol. 2012;159(2):82–7. doi:10.1016/j.ijcard.2011.07.022. Epub 2011 Jul 23.
232. Kivikko M, Antila S, Eha J, Lehtonen L, Pentikäinen PJ. Pharmacokinetics of levosimendan and its metabolites during and after a 24-hour continuous infusion in patients with severe heart failure. Int J Clin Pharmacol Ther. 2002;40(10):465–71.
233. Kivikko M, Lehtonen L. Levosimendan: a new inodilatory drug for the treatment of decompensated heart failure. Curr Pharm Des. 2005;11(4):435–55.
234. Mebazaa A, Nieminen MS, Packer M, Cohen-Solal A, Kleber FX, Pocock SJ, SURVIVE Investigators, et al. Levosimendan vs dobutamine for patients with acute decompensated heart failure: the SURVIVE Randomized Trial. JAMA. 2007;297(17):1883–91.
235. Cleland JG, Freemantle N, Coletta AP, Clark AL. Clinical trials update from the American Heart Association: REPAIR-AMI, ASTAMI, JELIS, MEGA, REVIVE-II, SURVIVE, and PROACTIVE. Eur J Heart Fail. 2006;8(1):105–10.
236. Landoni G, Biondi-Zoccai G, Greco M, Greco T, Bignami E, Morelli A, et al. Effects of levosimendan on mortality and hospitalization. A meta-analysis of randomized controlled studies. Crit Care Med. 2012;40(2):634–46. doi:10.1097/CCM.0b013e318232962a.
237. Gheorghiade M, Abraham WT, Albert NM, Greenberg BH, O'Connor CM, She L, OPTIMIZE-HF Investigators and Coordinators, et al. Systolic blood pressure at admission, clinical characteristics, and outcomes in patients hospitalized with acute heart failure. JAMA. 2006;296(18):2217–26.
238. Nieminen MS, Brutsaert D, Dickstein K, Drexler H, Follath F, Harjola VP, EuroHeart Survey Investigators, Heart Failure Association, European Society of Cardiology, et al. EuroHeart Failure Survey II (EHFS II): a survey on hospitalized acute heart failure patients: description of population. Eur Heart J. 2006;27(22):2725–36. Epub 2006 Sep 25.
239. Tavazzi L, Maggioni AP, Lucci D, Cacciatore G, Ansalone G, Oliva F, Porcu M, Italian survey on Acute Heart Failure Investigators. Nationwide survey on acute heart failure in cardiology ward services in Italy. Eur Heart J. 2006;27(10):1207–15. Epub 2006 Apr 7. PMID:16603579[PubMed - indexed for MEDLINE 1.
240. Arnold LM, Crouch MA, Carroll NV, Oinonen MJ. Outcomes associated with vasoactive therapy in patients with acute decompensated heart failure. Pharmacotherapy. 2006;26(8):1078–85.
241. Elkayam U, Tasissa G, Binanay C, Stevenson LW, Gheorghiade M, Warnica JW, et al. Use and impact of inotropes and vasodilator therapy in hospitalized patients with severe heart failure. Am Heart J. 2007;153(1):98–104.
242. Felker GM, Benza RL, Chandler AB, Leimberger JD, Cuffe MS, Califf RM, OPTIME-CHF Investigators, et al. Heart failure etiology and response to milrinone in decompensated heart failure: results from the OPTIME-CHF study. J Am Coll Cardiol. 2003;41(6):997–1003.
243. Cuffe MS, Califf RM, Adams Jr KF, Benza R, Bourge R, Colucci WS, Outcomes of a Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic Heart Failure (OPTIME-CHF) Investigators, et al. Short-term intravenous milrinone for acute exacerbation of chronic heart failure: a randomized controlled trial. JAMA. 2002;287(12):1541–7.

Chapter 12
Acute Decompensated Heart Failure: Treatment with Guideline Directed Medical Therapy and Discharge Planning

Daniel Fishbein

Initiation or Continuation of Guideline Directed Medical Therapy (GDMT)

A number of medications including ACE inhibitors, ARBs, β-blockers, mineralocorticoid receptor antagonists (MRAs), and the combination of hydralazine/isosorbide dinitrate (in black patients) have been shown, in prospective randomized placebo-controlled clinical trials, to improve symptoms, decrease mortality and decrease hospitalization in ambulatory patients with heart failure with reduced ventricular systolic function [1–11]. Randomized studies of these agents have not been conducted in patients hospitalized for ADHF. The ACCF/AHA guidelines recommend that heart failure medications be carefully reviewed on admission and that appropriate changes be made during hospitalization. Chronic maintenance therapy with GDMT should, in general, be continued during hospitalization for ADHF and GDMT should be initiated in patients with ADHF and HFrEF who are not receiving chronic heart failure medications [12]. The HFSA guidelines emphasize that hospitalization for ADHF is an "excellent opportunity" to optimize a patient's chronic oral medical regimen [13]. The ESC guidelines recommend that GDMT should be continued on admission or should be started as soon as possible in patients with HFrEF [14].

D. Fishbein, MD
University of Washington Medical Center, Department of Medicine, Division of Cardiology, 1959 NE Pacific Street, #356422, Seattle, WA 98195, USA
e-mail: dfishbein@cardiology.washington.edu

H. Eisen (ed.), *Heart Failure*, DOI 10.1007/978-1-4471-4219-5_12

Angiotensin Converting Enzyme Inhibitors (ACEI) or Angiotensin Receptor Blockers (ARB)

An attempt should be made during heart failure hospitalization to increase the ACEI or ARB dose to recommended target doses (lisinopril 20–35 mg daily, captopril 50 mg tid, enalapril 10–20 mg bid; losartan 150 qd, candesartan 32 mg qd, valsartan 160 mg bid) as tolerated by blood pressure, serum potassium concentration and renal function. An increased dose of ACE inhibitor or ARB may not be tolerated in patients who have low intracardiac filling pressures as a result of over diuresis. A reduction in the dose of ACEI and ARB should be considered in patients admitted with significant renal dysfunction or hyperkalemia. MRAs should be discontinued before ACEI or ARB in patients with hyperkalemia. An attempt to reinitiate or up titrate these medications should be subsequently considered depending on whether renal function or hyperkalemia improve during hospitalization.

The recommended starting doses of ACE inhibitor or ARB in hospitalized patients not receiving heart failure medications on admission are: captopril 6.25 mg tid, enalapril 2.5 mg bid, lisinopril 2.5–5.0 mg qd; losartan 50 mg qd, valsartan 40 mg bid, or candesartan 4–8 mg daily [14]. It is reasonable to consider initiating an ACE inhibitor or ARB at half of the recommended starting dose in patients with borderline blood pressure or renal insufficiency. Caution should be used when treating a patient with significant hyperkalemia (K^+ >5.0 mmol/L), significant renal dysfunction (creatinine >2.5 mg/dL or eGFR < 30 mL/min/1.73 m^2), or symptomatic or significant asymptomatic hypotension (systolic blood pressure <90 mmHg). In general, ACEIs or ARBs are not initiated in these settings. The dose of ACE inhibitor or ARB can be cautiously increased daily in the absence of hypotension, worsening renal function or hyperkalemia [12, 14].

Beta-Blockers

In general, β-blockers should not be held nor the dose reduced unless the patient has severe pulmonary congestion, evidence of marginal or low cardiac output or hypotension or if the ADHF hospitalization is felt to have been precipitated by β-blocker initiation or recent dose increase. Data from the Carvedilol or Metoprolol European Trial (COMET) [15], the ESCAPE trial [16], and the OPTIMIZE-HF program [17] all suggest that patients admitted to the hospital for ADHF who have their outpatient chronic β-blocker stopped or who are discharged on a significantly lower dose have a significantly higher risk-adjusted one and 2 year mortality (COMET); a significantly higher risk adjusted rate of rehospitalization or death at 60–90 days (ESCAPE), and a significantly higher risk and propensity adjusted 60–90 day post-discharge mortality (OPTIMIZE-HF).

The ACCF and ESC recommend that β-blocker therapy should be initiated when parenteral diuretics, intravenous vasodilators and inotropic agents have been

successfully discontinued [12, 14]. The patient should be hemodynamically stable and volume status should be optimized prior to β-blocker initiation. The initial dose of β-blocker should be small (carvedilol 3.125 mg bid, metoprolol succinate 12.5–25 mg qd, bisoprolol 1.25 mg qd). Caution should also be used when initiating β-blockers in patients who have required treatment with inotropes earlier in their hospitalization [12]. The Initiation Management Predischarge: Process for Assessment of Carvedilol Therapy in Heart Failure (IMPACT-HF) trial was a prospective randomized open-label study in 363 β-blocker naïve patients stabilized after hospitalization for ADHF who were randomized to pre-discharge initiation of β-blocker therapy or post-discharge initiation at the physician's discretion [18]. Patients who had been treated with inotropic therapy during the HF hospitalization were excluded from entering the trial. The primary end-point, treatment with a β-blocker at 60 days after discharge, was significantly greater in the pre-discharge initiation group (91.2 % vs 73.4 %). No difference was found between groups with respect to side effects or hospital length of stay. Data from the OPTIMIZE-HF registry found that only 56.9 % of patients who were eligible for β-blocker therapy were receiving a β-blocker at admission; the mean total daily dose of carvedilol or metoprolol in patients who were receiving a β-blocker was less than half the recommended dose; there was little change in dose during hospitalization or within the first 60–90 days after discharge; and only 17.5 % and 7.9 % of patients discharged on a β-blocker were at the recommended target dose of carvedilol or metoprolol succinate, respectively [19].

Mineralocorticoid Receptor Antagonists (MRAs)

The MRAs spironolactone and eplerenone have been shown to improve survival in patients with HFrEF and are recommended GDMT in patients with systolic dysfunction. Despite this, data from the Get with the Guidelines-Heart Failure quality improvement registry suggest that only one third of patients eligible for aldosterone antagonist therapy receive an MRA at discharge following hospitalization for ADHF [20]. The ACCF/AHA and ESC guidelines recommend that treatment with an MRA be either continued or initiated in patients with reduced ejection fraction hospitalized for ADHF [12, 14]. The ACCF/AHA guidelines recommend that an MRA should be initiated only if the serum potassium is less than 5 mEq/L [12]. The starting dose for patients with an eGFR $\geq$ 50 mL/min/1.73 m^2 is 12.5–25 mg qd for spironolactone and 25 mg qd for eplerenone. For patients with an eGFR 30 to 49 mL/min/1.73 m^2, the initial dose should be eplerenone 25 mg once every other day or spironolactone 12.5 mg once daily or every other day. MRAs should not be used in patients being treated with both an ACEI and an ARB. Potassium supplementation should be decreased on initiation of an MRA. Potassium and renal function need to be followed carefully in the hospitalized patient because of ongoing changes in volume status, diuretic dose, ACE inhibitor or ARB dose, systemic perfusion and renal function.

Hydralazine and Nitrates (H/NTG)

Black patients with HFrEF may benefit from the addition of hydralazine and nitrates. The African- American Heart Failure Trial (A-HeFT) randomized 1050 self-identified black patients with systolic dysfunction and NYHA Class III or IV heart failure symptoms who were receiving standard therapy for heart failure for at least three months to receive either a fixed dose of isosorbide dinitrate plus hydralazine or placebo [1]. The study was terminated prematurely because of a significantly lower mortality in the hydralazine/nitrate group compared to the control group (6.2 % vs 10.2 %; HR 0.57). In addition, there was a 33 % relative risk reduction in the rate of first hospitalization for heart failure and an improvement in quality of life score assessed by the Minnesota Living with Heart Failure questionnaire. Both the ACCF/AHA and HFSA guidelines recommend the combination of hydralazine/nitrates as part of GDMT in self-identified black patients with symptomatic HFrEF [12, 13]. Despite these guidelines, an analysis from the Get with The Guidelines-Heart Failure registry found that of 11,185 African American patients admitted with HFrEF who were eligible for hydralazine/nitrate therapy, only 22.4 % received H/NTG on discharge [21].

An attempt should be made to insure that the doses of GDMT be optimized during the heart failure hospitalization and after discharge. A study of initiation and persistence of GDMT in 107,092 patients discharged after first hospitalization for heart failure in Denmark from 1995–2004 demonstrated that treatment with ACEI or ARB, β-blocker or MRA was initiated in 43 %, 27 % and 19 % of patients, respectively. Patients who did not have therapy initiated by 90 days after discharge had a low probability of later medication initiation. Persistence of treatment was high once initiated but treatment dosages were below recommended targets and, with the exception of carvedilol, were generally not increased after discharge [22].

Implantable Cardioverter Defibrillator and Cardiac Resynchronization Therapy

Hospitalization allows for consultation with an electrophysiologist for evaluation for implantable cardioverter defibrillator (ICD) and/or cardiac resynchronization (CRT) therapy [13, 23]. Patients with HFrEF should be screened for ICD therapy for primary prevention of sudden cardiac arrest. ICD therapy is indicated in: patients with nonischemic dilated cardiomyopathy, NYHA FC II or III symptoms and an LVEF ≤35 %; patients with an LVEF ≤35 % due to prior MI who are at least 40 days post-MI and have NYHA FC II-III symptoms; patients with LV dysfunction due to prior MI who are at least 40 days post-MI, have an LVEF ≤ 30 %, and are NYHA FC I; and patients with nonsustained VT due to prior MI, LVEF ≤ 40 %, and

inducible VF or sustained VT at electrophysiology study. Ideally, device implantation should be delayed until patients are receiving optimal medical therapy, are no longer volume overloaded and are hemodynamically stable. The benefit of implanting a primary prevention ICD during hospitalization for ADHF has not been evaluated [24–26].

Approximately 40 % of patients with HFrEF hospitalized for ADHF have a wide QRS complex. Cardiac resynchronization therapy may improve symptoms and survival in patients who have LVEF ≤ 35 %, sinus rhythm, LBBB with a QRS duration ≥150 ms, and NYHA class II, III, or ambulatory IV symptoms on GDMT. CRT should be considered after discharge if the patient remains symptomatic despite appropriate GDMT [26–31].

Discharge Planning

The optimal timing for hospital discharge has not been prospectively evaluated. In general, patients should have resolution of heart failure symptoms at rest and with minimal activity; should be hemodynamically stable without lightheadedness at rest or with activity; should have stable kidney and liver function; should have normal electrolytes; should be on optimal GDMT; should have the cause of heart failure established; should have conditions/precipitating factors that worsen heart failure identified and corrected; and should have volume status as normal as possible [32, 33]. Patients with atrial fibrillation should have a controlled ventricular response. Hypertension should be well controlled.

In general, patients should be observed for 24 h after the transition from intravenous to oral diuretics. Patients may become congested again during this period. It is also possible that, with better GDMT and resolution of congestion, the dose of oral diuretic will be overestimated based on the preadmission or intravenous dose and will need to be decreased prior to discharge. Patients who have been treated with parenteral vasodilator or inotropic therapy should be observed for at least 24 h after these medications are stopped to insure that the patient is clinically stable, does not develop recurrent findings of hypoperfusion, is not hypotensive, and remains diuretic responsive and euvolemic.

Discharge criteria from the HFSA 2010 Comprehensive Heart Failure Practice Guidelines are summarized in Table 12.1 [34].

The transition from the inpatient to the outpatient setting is a vulnerable time for patients who have been hospitalized for ADHF. Hospitalization for heart failure may reflect an important change in cardiac function and pathophysiology and may indicate that the trajectory of the patient's underlying disease has changed. Patients are frequently discharged on a medical regimen that is different from and more complex than their regimen on admission. Patients are also discharged at a time when vital signs, volume status, renal function, appetite, salt and water intake, and

Table 12.1 Discharge criteria for patients hospitalized for ADHF

Recommended for all HF patients	Exacerbating factors addressed
	Near optimal volume status observed
	Transition from intravenous to oral diuretic successfully completed
	Patient and family education completed, including clear discharge instructions
	LVEF documented
	Smoking cessation counseling initiated
	Near optimal pharmacologic therapy achieved, including ACE inhibitor and beta blocker (for patients with reduced LVEF), or intolerance documented (Sections 7 and 11)
	Follow-up clinic visit scheduled, usually for 7–10 days
Should be considered for patients with advanced HF or recurrent admissions for HF	Oral medication regimen stable for 24 h
	No intravenous vasodilator or inotropic agent for 24 h
	Ambulation before discharge to assess functional capacity after therapy
	Plans for post-discharge management (scale present in home, visiting nurse or telephone follow up generally no longer than 3 days after discharge)
	Referral for disease management, if available

Reprinted with permission from Lindenfeld et al. [13]

the absorption, metabolism and effect of medications are changing. In addition, the majority of patients with heart failure have multiple comorbidities that are associated with an increased risk of mortality and preventable hospitalization and that are frequently not addressed during the ADHF hospitalization [35].

Important components of discharge planning are reviewed below [33, 36]:

Patient Education

The education of patients, family members and care-providers is an essential component of discharge planning. Patients should be educated about:

1. the dose, frequency and potential side effects of each medication; patients should be able to identify their medications and understand the reason for taking each medication; patients should receive explicit instructions about medication adjustment.
2. warning signs and symptoms of worsening heart failure
3. self-management skills including monitoring daily weights, controlling sodium intake, and monitoring blood pressure
4. recommended level of activity

5. clear guidelines for reporting signs and symptoms of heart failure, change in weight, and abnormal blood pressure to the appropriate care provider
6. factors that may aggravate heart failure
7. follow up in anticoagulation clinic in patients taking warfarin

In a randomized controlled trial of 223 patients hospitalized with ADHF, the addition of a 60 minute one-on-one teaching session with a nurse educator to the standard discharge process resulted in fewer days hospitalized or death within the first 180 days after discharge, a lower risk of rehospitalization or death, fewer heart failure hospitalizations, increased self-care measures and a reduced cost of care [37]. In a smaller study, patients hospitalized for ADHF were randomized to an in-hospital educational program conducted by a multidisciplinary team (nurse or educator and a pharmacist) or standard care. Patients randomized to the educational program showed higher knowledge scores at discharge, an improvement in quality of life measured by the MLWHF Questionnaire and trends toward better compliance with ACEI and β-blocker therapy [38].

Discharge on GDMT

Insuring that patients are discharged on appropriate heart failure medications reduces mortality and rehospitalization. An analysis from the National Heart Care Project (an initiative by the Centers for Medicare & Medicaid Services designed to improve the quality of care for Medicare beneficiaries hospitalized with heart failure) looked at 17,456 patients age ≥ 65 years who had systolic dysfunction and no contraindication to ACEI or ARB who survived hospitalization for heart failure. ACEI were prescribed to only 68 % of this ideal cohort. 78 % of patients were prescribed either an ACEI or ARB. ACEI prescription was associated with a lower risk-adjusted 1-year mortality rate (HR 0.86) [39].

The relationship between the five ACC/AHA performance measures for patients hospitalized with heart failure (discharge instructions, evaluation of left ventricular systolic function, ACEI or ARB for LV systolic dysfunction, adult smoking cessation counseling and anticoagulation at discharge for atrial fibrillation) and sixty- to ninety-day mortality and combined mortality/rehospitalization rates were evaluated in 5791 patients in the Follow-up Cohort in the OPTIMIZE-HF registry [40]. None of the 5 measures was significantly associated with risk-adjusted 60–90 day post-discharge mortality using multivariable and propensity-adjusted analysis. ACEI or ARB use at discharge was associated with a significant decrease in risk-adjusted 60–90 day mortality or rehospitalization (HR 0.51). Beta-blocker use at discharge, which was also evaluated, was associated with a significant reduction in 60–90 day mortality [HR 0.48] and combined mortality or rehospitalization (HR 0.73).

A hospital based discharge medication program was initiated by Intermountain Health Care, a non-profit integrated health system including 20 hospitals that serves ~60 % of the population of Utah and southern Idaho. The intent of this program was to insure that appropriate medications for secondary prevention were prescribed at discharge to all patients hospitalized for acute myocardial infarction, coronary heart disease, heart failure or atrial fibrillation. The measure for patients with HF was the prescription for an ACEI (or ARB if intolerant) at discharge. The proportion of HF patients who received a prescription for ACEI or ARB increased from ~64 % before the initiation of the program to > 90 % after. This was associated with statistically significant reductions in 30 day and 1 year mortality (HR of 0.76 and 0.77, respectively) and 30 day and 1 year readmission (HR of 0.84 and 0.91, respectively) [41].

Comorbidities

Addressing the long-term management of common comorbid conditions should be part of transitional care planning [35, 36]. Community acquired pneumonia, influenza and other respiratory infections are among the most common precipitants of hospitalization for ADHF [42, 43]. Influenza and pneumococcal vaccination remain significantly underutilized in heart failure patients. The prevalence of vaccination varies widely by region and country from 22 % – 37 % for influenza vaccine and 1 % to 22 % for pneumococcal vaccine [44–46]. Patients hospitalized for ADHF should have their immunization status for influenza and pneumococcal disease reviewed and updated [47–49].

Patient Safety

Systems of care that insure patient safety should be adopted by all hospitals. This includes the adoption of "Safe Practices" endorsed by the National Quality Forum [50]. This document emphasizes the importance of accurate and timely communication of clinical information among patient caregivers, medication reconciliation, and the important components of safe discharge practices.

Written Discharge Instructions and Discharge Summary

All patients should be provided with written discharge instructions that address: discharge medications, activity level, diet, weight monitoring, follow-up appointments and what to do if symptoms worsen. In addition, clear and specific care

information should be transmitted in a timely manner from the cardiologist to all of the patient's current health care providers and should address new medication initiation and dose up-titration, adverse effects of new medications, need for laboratory monitoring, and follow up plan [36, 51].

Post-discharge Follow Up

There is significant variation among institutions with respect to time from discharge to physician follow up [52]. The ACCF/AHA guidelines recommend scheduling an early follow-up visit within 7–14 days and an early telephone follow-up within 3 days of hospital discharge [33] The HFSA practice guidelines recommend a follow-up clinic visit in 7–10 days after hospital discharge [34].

Before discharge, at the first post-discharge visit and at all subsequent visits, the following should be addressed: the initiation, titration and optimization of GDMT; assessment of vital signs, volume status and systemic perfusion; assessment of electrolytes and renal function; screening for common causes of worsening heart failure; and reinforcement of HF education including medication adherence and self-monitoring [53].

Multidisciplinary Disease Management Programs

The ACCF/AHA, HFSA, Canadian Cardiovascular Society and ESC guidelines endorse the use of multidisciplinary heart failure disease management programs (DMP) for patients discharged after hospitalization for ADHF, especially those at high risk for hospital readmission [33, 34, 36, 54]. These programs generally include comprehensive discharge planning plus post-discharge support. The ESC Guidelines recommend that the key characteristics of a heart failure DMP include [54]:

1. using a team approach
2. providing inpatient and outpatient services
3. discharge planning, education and counseling strategies which promote self-care
4. ongoing optimization of medical therapy
5. prescription of a flexible diuretic regimen
6. close attention to clinical deterioration
7. vigilant follow-up and enhanced access to care.

Multiple meta-analyses of DMPs have confirmed that these programs reduce all-cause mortality at 12 months, reduce HF-related readmissions at 12 months and improve quality of life [55–58]. Yu and colleagues compared randomized controlled

clinical trials of DMPs that were and were not effective in improving discharge outcomes in an effort to identify the essential characteristics of DMPs that resulted in improved outcomes [57]. They concluded that to be effective, DMPs should be multifaceted and should include: an in-hospital phase of care; intensive patient education; self-care supportive strategies; optimization of GDMT; and ongoing surveillance for and management of clinical deterioration. Another meta-analysis suggested that DMPs that employ case management interventions where patients are intensively monitored by telephone calls and home visits (usually by a specialist nurse), were especially effective in improving outcomes [58]. Strategies that employ follow-up by a specialized multidisciplinary team are also especially effective [55].

There has been increasing interest in structured telephone support (STS) and especially in home telemonitoring (TM). STS is monitoring and/or self-care management delivered using simple telephone technology. Home telemonitoring is a form of non-invasive, remote patient monitoring that involves the use of electronic devices and telecommunication technologies (e.g., monitoring devices, hand-held or wearable technologies, and intelligent sensors) for the digital transmission of physiologic and other disease-related data from the patient's home to a health care center providing care and clinical feedback. Several meta-analyses have demonstrated that STS reduces HF-related hospitalizations and probably all-cause mortality while TM reduces HF-related hospitalizations and all-cause mortality [59–61]. Both interventions improve quality of life, functional class, patient-knowledge and self-care [59].

A comprehensive systematic review and meta- analysis of transitional care interventions to prevent readmissions for people hospitalized with heart failure contracted by the Agency for Healthcare Research and Quality was recently published [62]. This analysis found that a high-intensity home-visiting program reduced all-cause readmission and the composite of all-cause readmission or death at 30 days and 3–6 months and decreased HF-specific readmission over 3–6 months. Multidisciplinary HF (MDS-HF) clinic interventions reduced all-cause readmission. STS interventions reduced HF-specific readmission but not all cause readmission. Home-visiting programs, MDS-HF clinics, and STS interventions reduced mortality. Neither telemonitoring nor nurse-led clinic interventions reduced readmission or mortality.

Palliative Care

The ACCF/AHA and Canadian Cardiovascular Society (CCS) endorse early involvement of palliative care, especially in patients with advanced heart failure [33, 63, 64]. Palliative care needs to be distinguished from hospice. Palliative care is specialized multidisciplinary care that focuses on improving the quality of life for people of any age who are living with any serious illness. Hospice is a system of interdisciplinary care that is focused on improving quality of life and relieving

suffering in the dying patient in the last months of life [65]. Palliative care should be considered in all patients with advanced heart failure to help identify and manage physical, psychological, and spiritual issues, to assist with decisions concerning advanced heart failure therapies, and to help with advance and end-of-life directives. Palliative care should be considered for many patients hospitalized with ADHF and should not be reserved for only patients at the end of life.

Risk for Rehospitalization

Transitional care is especially important in patients at high risk for rehospitalization. This includes patients with advanced age, previous hospitalizations for heart failure, multiple concomitant comorbidities, limited social support, frailty, cognitive and functional impairment or depression [66, 67]. A review of 26 unique readmission risk prediction models found that they performed poorly in discriminating which patients were at risk for rehospitalization [68]. Data from the EVEREST trial suggests that findings of persistent congestion identified a population at high risk for readmission [69]. Cognitive impairment measured by the Mini Cog exam in patients hospitalized for ADHF was found to be strongly associated with the composite end-point of rehospitalization or mortality (HR = 1.90) [70]. Cognitive impairment was identified as the most important predictor of post-discharge outcomes among 55 variables analyzed.

Other Issues

Treatment Based on Systolic Blood Pressure

Current practice guidelines emphasize the use of parenteral loop diuretics in the initial treatment of ADHF. Several expert panels have suggested that initial blood pressure be integrated into the initial treatment paradigm [71–73]. There is data that suggests that volume redistribution rather than volume overload causes acute decompensation in patients with ADHF who present with hypertension. In some of these patients, an acute increase in systemic vascular resistance results in an acute reduction in stroke volume and an acute elevation in PCWP with the rapid development of dyspnea with or without flash pulmonary edema. These patients generally do not have gradually progressive symptoms prior to hospitalization and have less evidence of edema and systemic venous congestion on presentation [74–76]. Mobilization of venous fluid from the splanchnic circulation may also play a role in these patients [77].

A consensus document from the Society of Academic Emergency Medicine / HFSA Acute Heart Failure Working Group has proposed that presenting systolic

blood pressure be incorporated into the initial treatment paradigm by dividing patients into three groups: (1) hypertensive (SBP > 140 mmHg); (2) normotensive (SBP 100–140 mmHg); and (3) hypotensive (SBP < 100 mmHg). Patients in the hypertensive group would be treated with low dose diuretics and higher dose vasodilators. Patients in the normotensive group would be treated with diuretics and moderate dose vasodilators. Patients in the hypotensive group would be treated with diuretics and inotropes as needed [72]. There have been no prospective randomized trials that have evaluated a treatment strategy based on initial systolic blood pressure but several reports suggest that performing a randomized trial evaluating this approach is feasible [78–80].

Improving Survival After Hospitalization for ADHF

Hospitalization for ADHF is an event that identifies a patient at high risk for dying in the next year. In patients with chronic heart failure, HF hospitalization is a marker of disease progression and probably reflects a change in the trajectory of the underlying heart disease. A retrospective analysis from the Candesartan in Heart failure: Assessment of reduction in Mortality and morbidity (CHARM) trials assessed the risk after discharge from a first hospitalization for HF compared to patients who were not hospitalized for HF using time-updated Cox proportional-hazards models [81]. After adjustment for predictors of death, mortality rate was found to be increased after HF hospitalization with a HR of 3.15. Longer duration of hospitalization and repeat hospitalization increased the risk of dying. A retrospective analysis from the Digitalis Investigation Group (DIG) trial assessed the effect of incident HF hospitalization on subsequent mortality compared with no HF hospitalization in a propensity matched population [82]. Using matched Cox regression analysis, patients in the HF hospitalization group had a significantly increased risk of subsequent mortality compared with the no HF hospitalization group with a HR of 2.49. The HR for CV and HF mortality were 2.88 and 5.22, respectively. An analysis using health care utilization databases from British Columbia confirmed that the number of HF hospitalizations is a strong predictor of mortality in community HF patients with median survivals after the first, second, third and fourth hospitalizations of 2.4, 1.4, 1.0, and 0.6 years, respectively [83].

A number of clinical trials of newer medications that have attempted to show an impact on post-discharge outcomes have largely been negative. Agents that have been studied and shown to be ineffective include milrinone [84], nesiritide [85], the selective vasopressin (V_2) receptor antagonist tolvaptan [86, 87], levosimendan [88], the direct renin inhibitor aliskerin [89], the adenosine A_1 receptor antagonist rolofylline [90], and the endothelin receptor antagonist tezosentan [91]. There is substantial data that discharge on an ACEI and a β-blocker improves survival and decreases hospitalization [39–41, 92–94].

The Prospective Comparison of ARNI [Angiotensin Receptor–Neprilysin Inhibitor] with ACEI [Angiotensin-Converting–Enzyme Inhibitor] to Determine

Impact on Global Mortality and Morbidity in Heart Failure (PARADIGM-HF) Trial randomized 8442 patients with NYHA FC II, III or IV heart failure to receive a combination of valsartan and the neprilysin inhibitor sacubitril or enalapril [95–97]. The primary end-point of the trial was the composite of cardiovascular death and heart failure hospitalization. Neprilysin is a neutral endopeptidase inhibitor that degrades several endogenous vasoactive peptides including natriuretic peptides, bradykinin and adrenomedullin. Sacubitril inhibits neprilysin (but not ACE or aminopeptidase P) and increases the levels of natriuretic peptides, bradykinin and adrenomedullin. In PARADIGM-HF, when compared with enalapril, the combination of valsartan and sacubitril reduced the primary end-point by 20 %. Death from any cause was reduced by 16 %, cardiovascular death by 20 %, and HF hospitalization by 21 %. Symptoms and physical limitations of heart failure were decreased. This combination was well tolerated with lower proportions of hyperkalemia, renal impairment and cough compared with enalapril.

This study was not conducted with patients hospitalized for ADHF. The combination has been approved by the FDA for use in patients with chronic heart failure (NYHA Class II-IV) and reduced ejection fraction to reduce the risk of cardiovascular death and hospitalization for heart failure in place of ACEI or ARB. The combination is marketed as Entresto. There has not been a consensus document that addresses whether patients with ADHF should be started on Entresto instead of ACEI or ARB or switched from ACEI or ARB to Entresto during HF hospitalization.

Ongoing Drug Development

A number of new drugs with novel mechanisms of action are being evaluated in ongoing clinical trials in patients with ADHF [98, 99].

Relaxin/Serelaxin

Relaxin is a naturally occurring vasoactive peptide hormone that is produced by the placenta and corpus luteum and also by the failing myocardium. It acts on a G-protein coupled receptor, RXFP1, which is abundantly expressed in the cardiovascular, renal, and reproductive systems. Activation of RXFPI increases the production of cAMP with a resulting increase in nitric oxide production. In addition, relaxin has anti-inflammatory and anti-fibrotic effects and causes upregulation of vascular matrix metallo-proteinase-2 activity all of which result in vasodilation and increased vessel compliance [98–100].

In the Preliminary study of RELAXin in Acute Heart Failure (Pre-RELAX-AHF), 234 patients with acute heart failure, evidence of congestion on CXR, elevated BNP or NT-BNP, systolic blood pressure > 125 mmHg, and mild-moderate renal insufficiency were treated with standard care and randomized to a 48-h

infusion of placebo or one of four doses of relaxin [101]. When compared to placebo, treatment with relaxin was associated with dyspnea improvement at 6, 12, and 24 h by Likert scale and through day 14 by visual analogue scale. In addition, patients treated with relaxin had a shorter length of stay, greater days alive and out of the hospital, and reduced risk of cardiovascular death or HF readmission.

The RELAXin in Acute Heart Failure (RELAX-AHF) Trial randomized 1161 patients with the same clinical characteristics as Pre-RELAX-AHF to receive standard care plus a 48-h infusion of placebo or serelaxin 30 mcg/kg per day [102]. Serelaxin is recombinant human relaxin-2. Serelaxin is identical in structure to naturally occurring relaxin and is formulated as a sterile solution for infusion. The study had two primary end-points that evaluated dyspnea improvement. Serelaxin improved the change in the visual analogue scale area under the curve (VAS AUC) from baseline to day 5. Serelaxin had no significant effect on the proportion of patients with moderate or marked dyspnea improvement measured by Likert scale during the first 24 h. Serelaxin had no effect on cardiovascular death or HF readmission at 60 days or days alive and out of the hospital at 60 days. Treatment with serelaxin was associated with fewer deaths at 180 days. Several phase three trials of serelaxin are ongoing.

Ularitide

Urodilatin is a natriuretic peptide that is synthesized and secreted by distal renal tubular cells. Following intraluminal secretion, it binds to NPR-A receptors in the inner medullary collecting duct regulating renal sodium resorption and water homeostasis via cGMP-dependent signal transduction. Intravenous urodilatin increases diuresis and natriuresis and reduces pulmonary capillary wedge pressure (PCWP) and systemic vascular resistance [98, 99, 103].

Ularitide is a synthetically derived form of urodilatin. The SIRIUS II trial was a phase 2, randomized, double-blind, placebo controlled, dose-finding study in 221 patients with acute decompensation of chronic heart failure with dyspnea at rest or with minimal activity, cardiac index ≤ 2.5 L/min/m^2, and pulmonary capillary wedge pressure $\geq$18 mmHg. Patients received standard care and were randomized to a 24-h infusion of placebo or one of three doses of ularitide. At 6 h, patients treated with ularitide demonstrated a significant decrease in PCWP, improved dyspnea score, decreased systemic vascular resistance and increased cardiac index [104].The Efficacy and Safety of Ularitide for the Treatment of Acute Decompensated Heart Failure (TRUE-AHF) is an ongoing phase 3 trial designed to assess the effect of a 48-h continuous IV infusion of ularitide (15 ng/kg/min) versus placebo on the clinical status of patients with acute decompensated heart failure [43].

Istaroxime

Istaroxime is a novel steroidal intravenous inotropic agent unrelated to cardiac glycosides. The drug has unique inotropic/lusitropic properties [42, 98, 105]. Istaroxime inhibits Na^+/K^+ ATPase and stimulates sarcoplasmic reticulum Ca^{2+}adenosine triphosphatase isoform 2a. This affects cytosolic accumulation of calcium during systole resulting in an inotropic response and rapid sequestration of calcium during diastole resulting in a lusitropic response.

The Hemodynamic, Echocardiographic and Neurohormonal Effects of Istaroxime, a Novel Inotropic Agent: A Randomized Controlled Trial in Patients with Heart Failure (HORIZON-HF) trial randomized 121 patients with acute decompensated heart failure and LVEF ≤ 35 % on standard heart failure therapy to a 6-h infusion of placebo or one of three doses of istaroxime [106]. Patients underwent pulmonary artery catheterization within 48 h of admission and prior to randomization. Comprehensive 2-dimensional, Doppler, and tissue Doppler echocardiography were performed immediately before and within the last 30 minutes of study drug infusion. The primary end-point of the trial was change in PCWP from baseline compared to placebo after the 6-h infusion. Istaroxime significantly reduced PCWP, left ventricular end-diastolic pressure and heart rate and increased systolic blood pressure and cardiac index. There were no changes in neurohormones, renal function or troponin I. In addition, istaroxime improved systolic and diastolic function by echo parameters with evidence of increased contractility and decreased diastolic stiffness.

Omecamtiv Mecarbil (OM)

Omecamtiv Mecarbil is a small-molecule, cardiac-selective myosin activator. OM increases the number of myosin heads interacting with actin resulting in the generation of greater contractile force. OM improves myocardial contractility by prolonging systolic ejection time without changing myocardial oxygen consumption, myocyte calcium levels or the rate of left ventricular pressure development (LV dP/dt). In contrast, dobutamine increases LV dP/dt, decreases systolic ejection time, and increases myocardial oxygen consumption [98, 99, 106]. In healthy men, OM infusion resulted in dose-related increases in systolic ejection time, associated with increases in stroke volume, fractional shortening, and ejection fraction without changes in diastolic function [13]. In the phase II Acute Treatment with Omecamtiv Mecarbil to Increase Contractility in Acute Heart Failure (ATOMIC-AHF) study, patients admitted with acute heart failure, LVEF ≤ 40 %, dyspnea and elevated natriuretic peptides were randomized to receive a 48-h infusion of placebo or one of three doses of OM [107]. The primary end-point was dyspnea relief at 6, 24 and 48 h using a patient-reported 7-level Likert scale. OM did not improve the primary

endpoint. There were plasma concentration-related increases in left ventricular systolic ejection time ($p < 0.0001$) and decreases in end-systolic dimension ($p < 0.05$).

The Chronic Oral Study of Myosin Activation to Increase Contractility in Heart Failure (COSMIC-HF) trial is multicenter, Phase 2 trial designed to evaluate an oral modified release formulation of OM in chronic heart failure patients with reduced ejection fraction [108]. The trial consists of two parts, a dose escalation phase and a larger and longer expansion phase. The primary end-points for the expansion phase are to assess the maximum and pre-dose plasma concentration of OM. The secondary end-points are to assess changes from baseline in systolic ejection time, stroke volume, left ventricular end-systolic diameter, left ventricular end-diastolic diameter, heart rate and N-terminal pro-brain natriuretic peptide at week 20, as well as the safety and tolerability of OM including incidence of adverse events from baseline to week 24.

Conclusions

Hospitalization for ADHF identifies a patient at increased risk for dying in the next year. Initiation and optimization of guideline directed medical therapy is an important component of treatment of the hospitalized patient and to date, the only pharmacologic intervention that has been demonstrated to decrease post-discharge mortality and HF hospitalization.

Careful discharge planning is an important component of care in the patient hospitalized with ADHF. Patient education should address the dose, frequency and potential side effects of each medication, self-management skills, and guidelines for reporting signs and symptoms of worsening heart failure. All patients should be provided with written discharge instructions. Multidisciplinary heart failure disease management programs appear to be helpful in improving outcomes, especially in patients at high risk for hospital readmission.

References

1. Taylor AL, Ziesche S, Yancy C, Carson P, D'Agostino R Jr, Ferdinand K, et al. African-American Heart Failure Trial Investigators. Combination of isosorbide dinitrate and hydralazine in blacks with heart failure. N Engl J Med 2004;351(20):2049-2057. Epub 2004 Nov 8.
2. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. The SOLVD Investigators. N Engl J Med. 1991;325(5):293–302.
3. Effects of enalapril on mortality in severe congestive heart failure. Results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). The CONSENSUS Trial Study Group. N Engl J Med. 1987;316(23):1429–35.
4. Heran BS, Musini VM, Bassett K, Taylor RS, Wright JM. Angiotensin receptor blockers for heart failure. Cochrane Database Syst Rev 2012;(4):CD003040. doi:10.1002/14651858.CD003040.pub2.

5. Granger CB, McMurray JJ, Yusuf S, Held P, Michelson EL, Olofsson B, CHARM Investigators and Committees, et al. Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function intolerant to angiotensin-converting-enzyme inhibitors: the CHARM-Alternative trial. Lancet. 2003;362(9386):772–6.
6. Cohn JN, Tognoni G, Valsartan Heart Failure Trial Investigators. A randomized trial of the angiotensin-receptor blocker valsartan in chronic heart failure. N Engl J Med. 2001;345(23):1667–75.
7. Packer M, Coats AJ, Fowler MB, Katus HA, Krum H, Mohacsi P, Carvedilol Prospective Randomized Cumulative Survival Study Group, et al. Effect of carvedilol on survival in severe chronic heart failure. N Engl J Med. 2001;344(22):1651–8.
8. Hjalmarson A, Goldstein S, Fagerberg B, Wedel H, Waagstein F, Kjekshus J, et al. Effects of controlled-release metoprolol on total mortality, hospitalizations, and well-being in patients with heart failure: the Metoprolol CR/XL Randomized Intervention Trial in congestive heart failure (MERIT-HF). MERIT-HF Study Group JAMA. 2000;283(10):1295–302.
9. The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II): a randomised trial. Lancet. 1999 Jan 2;353(9146):9–13.
10. Pitt B, Remme W, Zannad F, Neaton J, Martinez F, Roniker B, et al. Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study Investigators. Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. N Engl J Med 2003;348(14):1309-1321. Epub 2003 Mar 31.
11. Pitt B, White H, Nicolau J, Martinez F, Gheorghiade M, Aschermann M, et al. EPHESUS Investigators. Eplerenone reduces mortality 30 days after randomization following acute myocardial infarction in patients with left ventricular systolic dysfunction and heart failure. J Am Coll Cardiol. 2005;46(3):425–31.
12. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE Jr, Drazner MH, et al. American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. Circulation 2013;128(16):e240-e327. doi: 10.1161/CIR.0b013e31829e8776. Epub 2013 Jun 5.
13. Lindenfeld J, Albert NM, Boehmer JP, Collins SP, Ezekowitz JA, Givertz MM, et al. Heart Failure Society of America, HFSA 2010 Comprehensive Heart Failure Practice Guideline. Section 12: Evaluation and Management of Patients with Acute Decompensated Heart Failure. J Card Fail. 2010;16(6):e131–56. doi:10.1016/j.cardfail.2010.04.004.
14. Collins SP, Lindsell CJ, Storrow AB, Abraham WT. ADHERE Scientific Advisory Committee, Investigators and Study Group. Prevalence of negative chest radiography results in the emergency department patient with decompensated heart failure. Ann Emerg Med 2006;47(1):13-18. Epub 2005 Jun 20.
15. Metra M, Torp-Pedersen C, Cleland JG, Di Lenarda A, Komajda M, Remme WJ, COMET investigators. et al. Should beta-blocker therapy be reduced or withdrawn after an episode of decompensated heart failure? Results from COMET. Eur J Heart Fail. 2007;9(9):901-909. Epub 2007 Jun 19.
16. Butler J, Young JB, Abraham WT, Bourge RC, Adams Jr KF, Clare R, O'Connor C, ESCAPE Investigators. Beta-blocker use and outcomes among hospitalized heart failure patients. J Am Coll Cardiol. 2006;47(12):2462–9.
17. Fonarow GC, Abraham WT, Albert NM, Stough WG, Gheorghiade M, Greenberg BH, et al. OPTIMIZE-HF Investigators and Coordinators. Influence of beta-blocker continuation or withdrawal on outcomes in patients hospitalized with heart failure: findings from the OPTIMIZE-HF program. J Am Coll Cardiol. 2008;52(3):190–9. doi:10.1016/j.jacc.2008.03.048.
18. Gattis WA, O'Connor CM, Gallup DS, Hasselblad V, Gheorghiade M; IMPACT-HF Investigators and Coordinators. Predischarge initiation of carvedilol in patients hospitalized for decompensated heart failure: results of the Initiation Management Predischarge: Process

for Assessment of Carvedilol Therapy in Heart Failure (IMPACT-HF) trial. J Am Coll Cardiol. 2004;43(9):1534–41.
19. Fonarow GC, Abraham WT, Albert NM, Stough WG, Gheorghiade M, Greenberg BH, et al. Dosing of beta-blocker therapy before, during, and after hospitalization for heart failure (from Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure). Am J Cardiol. 2008;102(11):1524–9. doi: 10.1016/j.amjcard.2008.07.045. Epub 2008 Sep 6.
20. Albert NM, Yancy CW, Liang L, Zhao X, Hernandez AF, Peterson ED, et al. Use of aldosterone antagonists in heart failure. JAMA. 2009;302(15):1658–65. doi:10.1001/jama.2009.1493.
21. Golwala HB, Thadani U, Liang L, Stavrakis S, Butler J, Yancy CW, et al. Use of hydralazine-isosorbide dinitrate combination in African American and other race/ethnic group patients with heart failure and reduced left ventricular ejection fraction. J Am Heart Assoc. 2013;2(4):e000214. doi:10.1161/JAHA.113.000214.
22. Gislason GH, Rasmussen JN, Abildstrom SZ, Schramm TK, Hansen ML, Buch P, et al. Persistent use of evidence-based pharmacotherapy in heart failure is associated with improved outcomes. Circulation 2007;116(7):737-744. Epub 2007 Jul 23.
23. Michel T, Hoffman BB. Chapter 27. Treatment of myocardial ischemia and hypertension. In: Brunton LL, Chabner BA, Knollmann BC. eds. Goodman & Gilman's the pharmacological basis of therapeutics12. New York: McGraw-Hill; 2011. http://accessmedicine.mhmedical.com/content.aspx?bookid=374&Sectionid=41266234. Accessed August 04, 2015
24. Moss AJ, Zareba W, Hall WJ, Klein H, Wilber DJ, Cannom DS, et al. Multicenter Automatic Defibrillator Implantation Trial II Investigators. Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. N Engl J Med 2002;346(12):877-883. Epub 2002 Mar 19.
25. Bardy GH, Lee KL, Mark DB, Poole JE, Packer DL, Boineau R, et al. Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) Investigators. Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure. N Engl J Med. 2005;352(3):225–37.
26. Epstein AE, DiMarco JP, Ellenbogen KA, Estes NA , Freedman RA, et al; American College of Cardiology Foundation; American Heart Association Task Force on Practice Guidelines; Heart Rhythm Society.2012 ACCF/AHA/HRS focused update incorporated into the ACCF/AHA/HRS 2008 guidelines for device-based therapy of cardiac rhythm abnormalities: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. Circulation. 2013;127(3):e283–352. doi: 10.1161/CIR.0b013e318276ce9b. Epub 2012 Dec 19.
27. Bristow MR, Saxon LA, Boehmer J, Krueger S, Kass DA, De Marco T, et al. Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION) Investigators. Cardiac-resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure. N Engl J Med. 2004;350(21):2140–50.
28. Cleland JG, Daubert JC, Erdmann E, Freemantle N, Gras D, Kappenberger L, Tavazzi L. Cardiac Resynchronization-Heart Failure (CARE-HF) Study Investigators. The effect of cardiac resynchronization on morbidity and mortality in heart failure. N Engl J Med 2005;352(15):1539-1549. Epub 2005 Mar 7.
29. Moss AJ, Hall WJ, Cannom DS, Klein H, Brown MW, Daubert JP, et al, MADIT-CRT Trial Investigators. Cardiac-resynchronization therapy for the prevention of heart-failure events. N Engl J Med 2009;361(14):1329-1338. doi: 10.1056/NEJMoa0906431. Epub 2009 Sep 1.
30. Tang AS, Wells GA, Talajic M, Arnold MO, Sheldon R, Connolly S, Resynchronization-Defibrillation for Ambulatory Heart Failure Trial Investigators. et al. Cardiac-resynchronization therapy for mild-to-moderate heart failure. N Engl J Med 2010;363(25):2385-2395. doi: 10.1056/NEJMoa1009540. Epub 2010 Nov 14.
31. Linde C, Abraham WT, Gold MR, St John Sutton M, Ghio S, Daubert C. REVERSE (REsynchronization reVErses Remodeling in Systolic left vEntricular dysfunction) Study Group. Randomized trial of cardiac resynchronization in mildly symptomatic heart failure patients and in asymptomatic patients with left ventricular dysfunction and previous heart

failure symptoms. J Am Coll Cardiol 2008;52(23):1834-1843. doi: 10.1016/j.jacc.2008.08.027. Epub 2008 Nov 7.
32. Go AS, Mozaffarian D, Roger VL, Benjamin EJ, Berry JD, Blaha MJ, et al. American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics--2014 update: a report from the American Heart Association. Circulation 2014;129(3):e28-e292. doi: 10.1161/01.cir.0000441139.02102.80. Epub 2013 Dec 18.
33. Dickstein K, Cohen-Solal A, Filippatos G, McMurray JJ, Ponikowski P, Poole-Wilson PA, et al; ESC Committee for Practice Guidelines (CPG). ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2008: the Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2008 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association of the ESC (HFA) and endorsed by the European Society of Intensive Care Medicine (ESICM). Eur Heart J. 2008 ;29(19):2388-2442. doi: 10.1093/eurheartj/ehn309. Epub 2008 Sep 17.
34. National 2012. Heart Lung and Blood Institute. People Science Health. What is heart failure? Available from: http://www.nhlbi.nih.gov/health/health-topics/topics/hf/ Accessed Feb 2012.
35. Hall MJ, DeFrances CJ, Williams SN, et al. National hospital discharge survey: 2007 summary. National health statistics reports; no 29. National Center for Health Statistics: Hyattsville; 2010 .Available from: http://www.cdc.gov/nchs/data/nhsr/nhsr029.pdf
36. Gheorghiade M, Pang PS. Acute heart failure syndromes. J Am Coll Cardiol. 2009;53(7):557–73. doi:10.1016/j.jacc.2008.10.041.
37. Gheorghiade M, Zannad F, Sopko G, Klein L, Piña IL, Konstam MA, et al. International Working Group on Acute Heart Failure Syndromes. Acute heart failure syndromes: current state and framework for future research. Circulation. 2005;112(25):3958–68.
38. Fang J, Mensah GA, Croft JB, Keenan NL. Heart failure-related hospitalization in the U.S., 1979 to 2004. J Am Coll Cardiol. 2008;52(6):428–34. doi:10.1016/j.jacc.2008.03.061.
39. Chen J, Normand SL, Wang Y, Krumholz HM. National and regional trends in heart failure hospitalization and mortality rates for Medicare beneficiaries, 1998-2008. JAMA. 2011;306(15):1669–78. doi:10.1001/jama.2011.1474.
40. Fonarow GC, Abraham WT, Albert NM, Gattis WA, Gheorghiade M, Greenberg B, et al. Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure (OPTIMIZE-HF): rationale and design. Am Heart J. 2004;148(1):43–51.
41. Adams KF, Fonarow GC, Emerman CL, LeJemtel TH, Costanzo MR, Abraham WT, ADHERE Scientific Advisory Committee and Investigators, et al. Characteristics and outcomes of patients hospitalized for heart failure in the United States: rationale, design, and preliminary observations from the first 100,000 cases in the Acute Decompensated Heart Failure National Registry (ADHERE). Am Heart J. 2005;149(2):209–16.
42. Fonarow GC, Heywood JT, Heidenreich PA, Lopatin M, Yancy CW, ADHERE Scientific Advisory Committee and Investigators. Temporal trends in clinical characteristics, treatments, and outcomes for heart failure hospitalizations, 2002 to 2004: findings from Acute Decompensated Heart Failure National Registry (ADHERE). Am Heart J. 2007;153(6):1021–8.
43. Fonarow GC, Corday E, ADHERE Scientific Advisory Committee. Overview of acutely decompensated congestive heart failure (ADHF): a report from the ADHERE registry. Heart Fail Rev. 2004;9(3):179–85.
44. Cleland JG, Swedberg K, Cohen-Solal A, Cosin-Aguilar J, Dietz R, Follath F, et al. The Euro Heart Failure Survey of the EUROHEART survey programme. A survey on the quality of care among patients with heart failure in Europe. The Study Group on Diagnosis of the Working Group on Heart Failure of the European Society of Cardiology. The Medicines Evaluation Group Centre for Health Economics University of York. Eur J Heart Fail. 2000;2(2):123–32.
45. Cleland JG, Swedberg K, Follath F, Komajda M, Cohen-Solal A, Aguilar JC, et al. Study Group on Diagnosis of the Working Group on Heart Failure of the European Society of Cardiology. The EuroHeart Failure survey programme-- a survey on the quality of care

among patients with heart failure in Europe. Part 1: patient characteristics and diagnosis. Eur Heart J. 2003;24(5):442–63.
46. Komajda M, Follath F, Swedberg K, Cleland J, Aguilar JC, Cohen-Solal A, et al. Study Group on Diagnosis of the Working Group on Heart Failure of the European Society of Cardiology. The EuroHeart Failure Survey programme--a survey on the quality of care among patients with heart failure in Europe. Part 2: treatment. Eur Heart J. 2003;24(5):464–74.
47. Nieminen MS, Brutsaert D, Dickstein K, Drexler H, Follath F, Harjola VP, et al. EuroHeart Survey Investigators; Heart Failure Association, European Society of Cardiology. EuroHeart Failure Survey II (EHFS II): a survey on hospitalized acute heart failure patients: description of population. Eur Heart J 2006;27(22):2725-2736. Epub 2006 Sep 25.
48. Fonarow GC, Abraham WT, Albert NM, Stough WG, Gheorghiade M, Greenberg BH, OPTIMIZE-HF Investigators and Hospitals, et al. Age- and gender-related differences in quality of care and outcomes of patients hospitalized with heart failure (from OPTIMIZE-HF). Am J Cardiol. 2009;104(1):107–15. doi:10.1016/j.amjcard.2009.02.057.
49. Gheorghiade M, Abraham WT, Albert NM, Greenberg BH, O'Connor CM, She L, et al. OPTIMIZE-HF Investigators and Coordinators. Systolic blood pressure at admission, clinical characteristics, and outcomes in patients hospitalized with acute heart failure. JAMA. 2006;296(18):2217–26.
50. Yancy CW, Lopatin M, Stevenson LW, De Marco T, Fonarow GC, ADHERE Scientific Advisory Committee and Investigators. Clinical presentation, management, and in-hospital outcomes of patients admitted with acute decompensated heart failure with preserved systolic function: a report from the Acute Decompensated Heart Failure National Registry (ADHERE) Database. J Am Coll Cardiol. 2006;47(1):76–84 PubMed PMID 16386668.
51. Fonarow GC, Stough WG, Abraham WT, Albert NM, Gheorghiade M, Greenberg BH, OPTIMIZE-HF Investigators and Hospitals, et al. Characteristics, treatments, and outcomes of patients with preserved systolic function hospitalized for heart failure: a report from the OPTIMIZE-HF Registry. J Am Coll Cardiol. 2007;50(8):768–77 PubMed PMID 17707182.
52. Lenzen MJ, Scholte OP, Reimer WJ, Boersma E, Vantrimpont PJ, Follath F, Swedberg K, et al. Differences between patients with a preserved and a depressed left ventricular function: a report from the EuroHeart Failure Survey. Eur Heart J. 2004;25(14):1214–20.
53. Grady KL, Dracup K, Kennedy G, Moser DK, Piano M, Stevenson LW, et al. Team management of patients with heart failure: A statement for healthcare professionals from The Cardiovascular Nursing Council of the American Heart Association. Circulation. 2000;102(19):2443–56 PubMed PMID 11067802.
54. Yancy CW, Abraham WT, Albert NM, Clare R, Stough WG, Gheorghiade M, et al. Quality of care of and outcomes for African Americans hospitalized with heart failure: findings from the OPTIMIZE-HF (Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients With Heart Failure) registry. J Am Coll Cardiol. 2008;51(17):1675–84. doi:10.1016/j.jacc.2008.01.028.
55. Jencks SF, Williams MV, Coleman EA. Rehospitalizations among patients in the Medicare fee-for-service program. N Engl J Med. 2009;360(14):1418–28. doi:10.1056/NEJMsa0803563.
56. Heidenreich PA, Sahay A, Kapoor JR, Pham MX, Massie B. Divergent trends in survival and readmission following a hospitalization for heart failure in the Veterans Affairs health care system 2002 to 2006. J Am Coll Cardiol. 2010;56(5):362–8. doi:10.1016/j.jacc.2010.02.053.
57. Bueno H, Ross JS, Wang Y, Chen J, Vidán MT, Normand SL, et al. Trends in length of stay and short-term outcomes among Medicare patients hospitalized for heart failure, 1993-2006. JAMA. 2010;303(21):2141–7. doi:10.1001/jama.2010.748.
58. Tuppin P, Cuerq A, de Peretti C, Fagot-Campagna A, Danchin N, Juillière Y. et al. Two-year outcome of patients after a first hospitalization for heart failure: A national observational study. Arch Cardiovasc Dis 2014;107(3):158-168. doi: 10.1016/j.acvd.2014.01.012. Epub 2014 Mar 21.

59. Jessup M, Abraham WT, Casey DE, Feldman AM, Francis GS, Ganiats TG, et al. 2009 focused update: ACCF/AHA Guidelines for the Diagnosis and Management of Heart Failure in Adults: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines: developed in collaboration with the International Society for Heart and Lung Transplantation. Circulation 2009;119(14):1977-2016. doi: 10.1161/CIRCULATIONAHA.109.192064. Epub 2009 Mar 26.
60. Kaul P, Ezekowitz JA, Armstrong PW, Leung BK, Savu A, Welsh RC, et al. Incidence of heart failure and mortality after acute coronary syndromes. Am Heart J. 2013 ;165(3):379-385. doi: 10.1016/j.ahj.2012.12.005. Epub 2013 Jan 22.
61. Steg PG, Dabbous OH, Feldman LJ, Cohen-Solal A, Aumont MC, López-Sendón J, Global Registry of Acute Coronary Events Investigators. et al. Determinants and prognostic impact of heart failure complicating acute coronary syndromes: observations from the Global Registry of Acute Coronary Events (GRACE). Circulation 2004;109(4):494-499. Epub 2004 Jan 26.
62. Weintraub NL, Collins SP, Pang PS, Levy PD, Anderson AS, Arslanian-Engoren C, American Heart Association Council on Clinical Cardiology and Council on Cardiopulmonary, Critical Care, Perioperative and Resuscitation. et al. Acute heart failure syndromes: emergency department presentation, treatment, and disposition: current approaches and future aims: a scientific statement from the American Heart Association. Circulation. 2010;122(19):1975-1996. doi: 10.1161/CIR.0b013e3181f9a223. Epub 2010 Oct 11.
63. Campbell RT, Jhund PS, Castagno D, Hawkins NM, Petrie MC, McMurray J. What have we learned about patients with heart failure and preserved ejection fraction from DIG-PEF, CHARM-preserved, and I-PRESERVE? J J Am Coll Cardiol 2012;60(23):2349-2356. doi: 10.1016/j.jacc.2012.04.064. Epub 2012 Nov 7.
64. Clark AL, Cleland JG. Causes and treatment of oedema in patients with heart failure. Nat Rev Cardiol 2013;10(3):156-170. doi: 10.1038/nrcardio.2012.191. Epub 2013 Jan 15.
65. ter Maaten JM, Valente MA, Damman K, Hillege HL, Navis G, Voors AA. Diuretic response in acute heart failure-pathophysiology, evaluation, and therapy. Nat Rev Cardiol 2015;12(3):184-192. doi: 10.1038/nrcardio.2014.215. Epub 2015 Jan 6.
66. Ronco C, Cicoira M, McCullough PA. Cardiorenal syndrome type 1: pathophysiological crosstalk leading to combined heart and kidney dysfunction in the setting of acutely decompensated heart failure. J Am Coll Cardiol 2012;60(12):1031-1042. doi: 10.1016/j.jacc.2012.01.077. Epub 2012 Jul 25.
67. Gehlbach BK, Geppert E. The pulmonary manifestations of left heart failure. Chest. 2004;125(2):669–82.
68. Guazzi M. Alveolar gas diffusion abnormalities in heart failure. J Card Fail 2008;14(8):695-702. doi: 10.1016/j.cardfail.2008.06.004. Epub 2008 Jul 18.
69. Uhley HN, Leeds SE, Sampson JJ, Friedman M. Role of pulmonary lymphatics in chronic pulmonary edema. Circ Res. 1962;11:966–70.
70. Mackersie RC, Christensen J, Lewis FR. The role of pulmonary lymphatics in the clearance of hydrostatic pulmonary edema. J Surg Res. 1987;43(6):495–504.
71. Hochberg I, Abassi Z, Azzam ZS. Patterns of alveolar fluid clearance in heart failure. Int J Cardiol 2008;130(2):125-130. doi: 10.1016/j.ijcard.2008.03.015. Epub 2008 Jun 24.
72. Guazzi M, Phillips SA, Arena R, Lavie CJ. Endothelial dysfunction and lung capillary injury in cardiovascular diseases. Prog Cardiovasc Dis 2015;57(5):454-462. doi: 10.1016/j.pcad.2014.11.003. Epub 2014 Nov 12.
73. Chaudhry S, Wang Y, Concato J, Gill TM, Krumholz HM. Patterns of weight change preceding hospitalization for heart failure. Circulation 2007;116(14):1549-1554. Epub 2007 Sep 10.
74. Adamson PB, Magalski A, Braunschweig F, Böhm M, Reynolds D, Steinhaus D, et al. Ongoing right ventricular hemodynamics in heart failure: clinical value of measurements derived from an implantable monitoring system. J Am Coll Cardiol. 2003;41(4):565–71.

75. Ohlsson A, Steinhaus D, Kjellström B, Ryden L, Bennett T. Central hemodynamic responses during serial exercise tests in heart failure patients using implantable hemodynamic monitors. Eur J Heart Fail. 2003;5(3):253–9.
76. Adamson PB, Kjellström B, Braunschweig F, Magalski A, Linde C, Kolodiezj A, et al. Ambulatory hemodynamic monitoring from an implanted device: components of continuous 24-hour pressures that correlate to supine resting conditions and acute right heart catheterization. Congest Heart Fail. 2006;12(1):14–9.
77. Aaron MF, Aranda JM, Renlund DG, Fonarow GC, Feldman DS, Cho YK, et al.. The Effect of Postural Changes on Intracardiac Filling Pressures[abstract]. J Card Fail. 2008; 14: S28.
78. Zile MR, Bennett TD, St John Sutton M, Cho YK, Adamson PB, Aaron MF, et al. Transition from chronic compensated to acute decompensated heart failure: pathophysiological insights obtained from continuous monitoring of intracardiac pressures. Circulation 2008;118(14):1433-1441. doi: 10.1161/CIRCULATIONAHA.108.783910. Epub 2008 Sep 15.
79. Zile MR, Adamson PB, Cho YK, Bennett TD, Bourge RC, Aaron MF, et al. Hemodynamic factors associated with acute decompensated heart failure: part 1 – insights into pathophysiology. J Card Fail 2011;17(4):282-291. doi: 10.1016/j.cardfail.2011.01.010. Epub 2011 Feb 26.
80. Milo-Cotter O, Adams KF, O'Connor CM, Uriel N, Kaluski E, Felker GM, et al. Acute heart failure associated with high admission blood pressure--a distinct vascular disorder? Eur J Heart Fail 2007;9(2):178-183. Epub 2006 Jul 31.
81. Cotter G, Moshkovitz Y, Milovanov O, Salah A, Blatt A, Krakover R, et al. Acute heart failure: a novel approach to its pathogenesis and treatment. Eur J Heart Fail. 2002;4(3):227–34.
82. Kaluski E, Kobrin I, Zimlichman R, Marmor A, Krakov O, Milo O, et al. RITZ-5: randomized intravenous TeZosentan (an endothelin-A/B antagonist) for the treatment of pulmonary edema: a prospective, multicenter, double-blind, placebo-controlled study. J Am Coll Cardiol. 2003;41(2):204–10.
83. Mebazaa A, Pang PS, Tavares M, Collins SP, Storrow AB, Laribi S, et al. The impact of early standard therapy on dyspnoea in patients with acute heart failure: the URGENT-dyspnoea study. Eur Heart J 2010;31(7):832-841. doi: 10.1093/eurheartj/ehp458. Epub 2009 Nov 11.
84. Balmain S, Padmanabhan N, Ferrell WR, Morton JJ, McMurray JJ. Differences in arterial compliance, microvascular function and venous capacitance between patients with heart failure and either preserved or reduced left ventricular systolic function. Eur J Heart Fail 2007;9(9):865-871. Epub 2007 Jul 19.
85. Cotter G, Metra M, Milo-Cotter O, Dittrich HC, Gheorghiade M. Fluid overload in acute heart failure--re-distribution and other mechanisms beyond fluid accumulation. Eur J Heart Fail. 2008;10(2):165–9. doi:10.1016/j.ejheart.2008.01.007.
86. Cotter G, Felker GM, Adams KF, Milo-Cotter O, O'Connor CM. The pathophysiology of acute heart failure--is it all about fluid accumulation? Am Heart J. 2008;155(1):9–18.
87. Felker GM, Leimberger JD, Califf RM, Cuffe MS, Massie BM, Adams Jr KF, et al. Risk stratification after hospitalization for decompensated heart failure. J Card Fail. 2004;10(6):460–6.
88. Fonarow GC, Adams Jr KF, Abraham WT, Yancy CW, ADHERE Scientific Advisory Committee, Study Group, and Investigators, Boscardin WJ. Risk stratification for in-hospital mortality in acutely decompensated heart failure: classification and regression tree analysis. JAMA. 2005;293(5):572–80.
89. Lee DS, Austin PC, Rouleau JL, Liu PP, Naimark D, Tu JV. Predicting mortality among patients hospitalized for heart failure: derivation and validation of a clinical model. JAMA. 2003;290(19):2581–7.
90. Collins S, Storrow AB, Kirk JD, Pang PS, Diercks DB, Gheorghiade M.Beyond pulmonary edema: diagnostic, risk stratification, and treatment challenges of acute heart failure management in the emergency department. Ann Emerg Med 2008;51(1):45-57. Epub 2007 Sep 14.

91. Collins S, Storrow AB, Albert NM, Butler J, Ezekowitz J, Felker GM, SAEM/HFSA Acute Heart Failure Working Group. et al. Early management of patients with acute heart failure: state of the art and future directions. A consensus document from the society for academic emergency medicine/heart failure society of America acute heart failure working group. J Card Fail 2015;21(1):27-43. doi: 10.1016/j.cardfail.2014.07.003. Epub 2014 Jul 18.
92. Stevenson LW, Perloff JK. The limited reliability of physical signs for estimating hemodynamics in chronic heart failure. JAMA. 1989;261(6):884–8 PubMed PMID 2913385.
93. Kay JM, Edwards FR. Ultrastructure of the alveolar-capillary wall in mitral stenosis. Pathobiology. 1973;111(4):239–45.
94. Kingsbury MP, Huang W, Donnelly JL, Jackson E, Needham E, Turner MA, Sheridan DJ. Structural remodelling of lungs in chronic heart failure. Basic Res Cardiol 2003;98(5):295-303. Epub 2003 May 16.
95. Huang W, Kingsbury MP, Turner MA, Donnelly JL, Flores NA, Sheridan DJ. Capillary filtration is reduced in lungs adapted to chronic heart failure: morphological and haemodynamic correlates. Cardiovasc Res. 2001;49(1):207–17.
96. Davies SW, Bailey J, Keegan J, Balcon R, Rudd RM, Lipkin DP. Reduced pulmonary microvascular permeability in severe chronic left heart failure. Am Heart J. 1992;124(1):137–42.
97. Rossi JS, Flaherty JD, Fonarow GC, Nunez E, Gattis Stough W, Abraham WT, et al. Influence of coronary artery disease and coronary revascularization status on outcomes in patients with acute heart failure syndromes: a report from OPTIMIZE-HF (Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure). Eur J Heart Fail 2008;10(12):1215-1223. doi: 10.1016/j.ejheart.2008.09.009. Epub 2008 Nov 8.
98. Flaherty JD, Bax JJ, De Luca L, Rossi JS, Davidson CJ, Filippatos G, Acute Heart Failure Syndromes International Working Group, et al. Acute Heart Failure Syndromes in Patients With Coronary Artery Disease Early Assessment and Treatment. J Am Coll Cardiol. 2009;53(3):254–63 PubMed PMID 19147042.
99. Thygesen K, Alpert JS, White HD. Joint ESC/ACCF/AHA/WHF Task Force for the Redefinition of Myocardial Infarction, Jaffe AS, Apple FS, Galvani M, Katus HA, Newby LK, Ravkilde J, et al. Universal definition of myocardial infarction. Circulation 2007;116(22):2634-2653. Epub 2007 Oct 19.
100. Kociol RD, Pang PS, Gheorghiade M, Fonarow GC, O'Connor CM, Felker GM. Troponin elevation in heart failure prevalence, mechanisms, and clinical implications. J Am Coll Cardiol. 2010;56(14):1071–8. doi:10.1016/j.jacc.2010.06.016.
101. Peacock 4th WF, De Marco T, Fonarow GC, Diercks D, Wynne J, Apple FS, ADHERE Investigators, Wu AH. Cardiac troponin and outcome in acute heart failure. N Engl J Med. 2008;358(20):2117–26. doi:10.1056/NEJMoa0706824 .PMID: 18480204 [PubMed - indexed for MEDLINE]
102. You JJ, Austin PC, Alter DA, Ko DT, Tu JV. Relation between cardiac troponin I and mortality in acute decompensated heart failure. Am Heart J. 2007;153(4):462–70.
103. Cleland JG, Pennell DJ, Ray SG, Coats AJ, Macfarlane PW, Murray GD, Carvedilol hibernating reversible ischaemia trial: marker of success investigators, et al. Myocardial viability as a determinant of the ejection fraction response to carvedilol in patients with heart failure (CHRISTMAS trial): randomised controlled trial. Lancet. 2003;362(9377):14–21.
104. Beohar N, Erdogan AK, Lee DC, Sabbah HN, Kern MJ, Teerlink J, et al. Acute heart failure syndromes and coronary perfusion. J Am Coll Cardiol. 2008;52(1):13–6. doi:10.1016/j.jacc.2008.03.037.
105. Drazner MH, Hellkamp AS, Leier CV, Shah MR, Miller LW, Russell SD, et al. Value of clinician assessment of hemodynamics in advanced heart failure: the ESCAPE trial. Circ Heart Fail. 2008;1(3):170–7. doi:10.1161/CIRCHEARTFAILURE.108.769778.
106. Ely JW, Osheroff JA, Chambliss ML, Ebell MH. Approach to leg edema of unclear etiology. J Am Board Fam Med. 2006;19(2):148–60.

107. Leier CV, Silver MA, Massie BM, Young JB, Fowler MB, Ventura HO, Hershberger RE. Nuggets, pearls, and vignettes of master heart failure clinicians. Part 1--the medical history. Congest Heart Fail. 2001;7(5):245–9.
108. Payvar S, Spertus JA, Miller AB, Casscells SW, Pang PS, Zannad F, Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study with Tolvaptan (EVEREST) Investigators. et al. Association of low body temperature and poor outcomes in patients admitted with worsening heart failure: a substudy of the Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study with Tolvaptan (EVEREST) trial. Eur J Heart Fail 2013;15(12):1382-1389. doi: 10.1093/eurjhf/hft113. Epub 2013 Jul 15.

Chapter 13
Cardiac-Oncology: Management of the Patient with Heart Failure After Chemotherapy

Ashwani Gupta and Howard J. Eisen

Introduction

The survival of patients diagnosed with malignancy has improved drastically over the last few decades [1]. This has led to increased recognition of adverse events related to chemotherapeutic drugs, especially cardiovascular effects. Cardiovascular disease is the 2nd most common cause of mortality in these patients after the malignancy itself [2]. Cardiomyopathy is the most common cardiovascular side effect of chemotherapy. Various chemotherapeutic agents have been associated with the development of cardiomyopathy. A detailed list of these agents is provided in Table 13.1.

Chemotherapy-induced cardiomyopathy has been broadly classified into two types- Type I (non-reversible) and Type II (reversible) [3]. However, this distinction is not always mutually exclusive- type II dysfunction may not always be reversible and type I may reverse with cessation of the offending agent and heart failure (HF) therapy. Also, both types may co-exist, especially in patients receiving more than one cardiotoxic drug. Differences between type I and II cardiomyopathy are described in Table 13.2.

A. Gupta, MBBS
Division of Cardiology, Department of Internal Medicine, Hahnemann University Hospital, Broad and Vine Street, Philadelphia, PA 19102, USA
e-mail: drashwani@gmail.com

H.J. Eisen, MD (✉)
Division of Cardiology, Drexel University College of Medicine, Hahnemann University Hospital, 245 North 15th Street, Mailstop#1012, Philadelphia, PA 19102, USA
e-mail: heisen@drexelmed.edu

H. Eisen (ed.), *Heart Failure*, DOI 10.1007/978-1-4471-4219-5_13

Table 13.1 List of chemotherapeutic agents associated with cardiomyopathy

1. **Anthracyclines** — Doxorubicin, Daunorubicin, Epirubicin, Idarubicin, Mitoxantrone
2. **Monoclonal antibodies against HER2** — Trastuzumab
3. **Alkylating agents** — Cyclophosphamide, Ifosfamide
4. **Antimicrotubule agents** — Paclitaxel
5. **Angiogenesis inhibitors** — Bevacizumab
6. **Tyrosine kinase inhibitors** — Sunitinib, sorefinib, imatinib, lapatinib
7. **Pyrimidine analogues** — 5-Flourouracil, Capecitabine

Table 13.2 Differences between Type I and Type II chemotherapy induced cardiomyopathy

Type I	Type II
Myocardial cell death	Myocardial cell dysfunction
Reversible	Non-reversible
Related to cumulative dose	Not related to cumulative dose
Agent cannot be reintroduced without risk	Agent can be reintroduced with minimal risk
Biopsy shows myocardial damage	Minimal changes on biopsy
Drugs like anthracyclines, alkylating agents, microtubule inhibitors	Drugs like trastuzumab, angiogenesis inhibitors, pyrimidine analogues, tyrosine kinase inhibitors

Definition

The definition of chemotherapy-induced cardiomyopathy has not been precisely defined. Various trials have employed different definitions of this entity. The Cardiac Review and Evaluation Committee (CRCE) has established the following criterion to diagnose chemotherapy induced cardiac dysfunction [4]:

1. Decrease in left ventricular ejection fraction (LVEF), which is either global or worse in the septum
2. Symptoms of congestive heart failure
3. Signs of congestive heart failure, including but not limited to, S3 gallop, tachycardia or both
4. A symptomatic decline in LVEF of at least 5 % or asymptomatic decline in LVEF of at least 10 % to an absolute LVEF of <55 %

Anthracyclines

Anthracyclines still remain the cornerstone of many modern chemotherapeutic regimens, with doxorubicin being the most widely used agent. These agents intercalate between specific bases in the DNA and inhibit DNA and RNA synthesis. Cardiotoxicity with these agents was recognized very early and found to be dose-dependent [5]. Initial studies, performed in 1970s, recommended a maximum total

doxorubicin dose 550 mg/m^2 [6]. However, these studies were limited by lack of evaluation for asymptomatic LV dysfunction. Recent studies report incidence of LV dysfunction to be as high as 50 % with long-term follow up [7]. Swain et al. [8] reported incidence of cardiomyopathy at 5 %, 16 % and 26 % respectively, with cumulative doses of 400, 500 and 550 mg/m^2. Hence, currently the cumulative dose is usually limited to 400–450 mg/m^2. However, there is no safe dose and cardiomyopathy has been reported with doses as low as 250 mg/m^2, especially in children [9].

Three different manifestations of anthracycline-mediated cardiotoxicity have been described [10]:

1. Acute — Acute cardiotoxicity is rare, occurring in <1 % patients and manifests within hours to weeks as arrhythmias, acute heart failure, myocardial ischemia, or pericarditis/myocarditis-like syndrome. Most patients recover completely from this acute cardiotoxicity. However, long terms effects are not known.
2. Early-onset chronic — This manifestation occurs within the 1st year of treatment and incidence is reported at 1.6–2.1 %. It typically presents as dilated cardiomyopathy and may persist, or even progress, after discontinuation of the offending agent.
3. Late-onset chronic — This is the most common form and is seen in about 1.6–5 % patients. It typically occurs years after chemotherapy and presents as progressive dilated cardiomyopathy, heart failure, or arrhythmias.

Various risk factors have been described for the development of anthracycline-mediated cardiomyopathy (Table 13.3) [11]. The most important risk factor is the total cumulative dose. Other major risk factors include extremes of age, pre-existing cardiovascular disease, concomitant use of other cardiotoxic drugs and chest irradiation.

Anthracyclines produce progressive and irreversible type I cardiomyopathy. Cardiac biopsy typically shows patchy areas of interstitial fibrosis, vacuolation and rarely frank necrosis [12]. The pathophysiology of anthracycline-medicated cardiomyopathy is not clearly understood and multiple mechanisms have been hypothesized [13]. The most commonly accepted hypothesis is generation of excessive reactive oxygen species (ROS) and free radical induced myocyte damage. Various mechanisms have been hypothesized for excess free radical production, including mitochondrial dysfunction, increased endothelial nitric oxide synthase production, iron dependent redox cycling, and NAD(P)H dependent mechanisms [13]. However, recent literature suggests that the ROS hypothesis may not fully explain the anthracycline-induced cardiotoxicity [13]. Other hypothesized mechanisms include inhibition of topoisomerase II, DNA cross-linking, decreased ATP production, direct damage to the mitochondria and cell membranes, and increased apoptosis.

Several attempts have been made to reduce doxorubicin cardiotoxicity:

1. Structural modification of anthracyclines —

   Many studies have focused on the development of chemotherapeutic agents, with reduced cardiotoxicty, while preserving antitumor efficacy. Unfortunately, thus far, the development of such an agent has remained unsuccessful. Epirubicin

Table 13.3 Risk factors for anthracycline-mediated cardiomyopathy

1. Cumulative anthracycline dose
2. Mode of administration (rate of infusion, type of agent, individual dose)
3. Age — Children <15 years and elderly >70 years
4. Chest irradiation
5. Pre-existing cardiovascular disease
6. Hypertension
7. Use of other cardiotoxic drugs (e.g., trastuzumab, cyclophosphamide, paclitaxel)
8. Female sex
9. Trisomy 21
10. HFE gene mutation

drew initial interest due to its reduced cardiotoxicity when compared mg-for-mg with doxorubicin. However, subsequent studies demonstrated epirubicin as a less potent chemotherapeutic agent compared to doxorubicin with similar cardiotoxicity at functionally equivalent doses of epirubicin [14].

2. Different vehicle —

   A liposomal-encapsulated doxorubicin remains restricted to the circulating blood and does not cross capillary junctions into normal organs. However, it easily penetrates into the tumor due to increased capillary permeability. It has been shown to reduce cardiotoxicity while still retaining its anti-neoplastic effects [15]. However, more data is still required and increased cost limits its use.

3. Different protocols —

Continuous infusion reduces the risk of cardiotoxicity by decreasing the peak level of the drug [16]. However, it is associated with increased cost, need for an indwelling catheter and increased inconvenience to the patient. There is also a concern for reduction in antineoplastic effects.

Trastuzumab

Trastuzumab is a monoclonal antibody active against human epidermal growth factor (HER2) receptor, which is overexpressed in 25 % of breast cancers. However, trastuzumab significantly increases the risk of cardiomyopathy. A meta-analysis of randomized clinical trials with use of trastuzumab as an adjuvant chemotherapeutic agent showed a 1.6 % absolute increase in incidence of symptomatic heart failure and 7.2 % increase in LV systolic dysfunction [17]. Another trial in patients with metastatic breast cancer showed a 19 % increased risk of cardiomyopathy when trastuzumab was used in combination with anthracycline and cyclophosphamide, and a 12 % increased risk when added to paclitaxel [18]. Analysis of the SEER-Medicare database showed a 32.1 % incidence of cardiomyopathy in patients receiving trastuzumab and a 41.9 % incidence in patients receiving anthracycline

Table 13.4 Risk factors for development of trastuzumab-induced cardiomyopathy

1. Age> 50 years
2. Hypertension
3. Concomitant use of anthracyclines or paclitaxel
4. Pre-existing cardiovascular disease
5. Smoking

plus trastuzumab, which is much higher than previously reported trials [19]. Most protocols recommend use of trastuzumab sequentially with anthracyclines. However, even sequential use is associated with an increased risk of cardiomyopathy, though much less than concomitant use [20] (See Table 13.4).

Trastuzumab produces type II cardiomyopathy, which is not dose dependent and potentially reversible. There is no visible myocyte damage on histology and changes are visible only on electron microscopy [21]. Some authors have re-challenged patients with trastuzumab without recurrence of cardiomyopathy in most patients [4]. However, many authors have questioned its reversible nature and reported a 20–40 % incidence of persistent LV dysfunction [22]. MRI studies have shown evidence of delayed gadolinium enhancement despite recovery of cardiac function, suggesting persistent myocardial damage [23]. Long-term studies are needed to better define the natural history of trastuzumab-induced cardiomyopathy.

The mechanism of trastuzumab-induced cardiomyopathy is not well understood, but inhibition of ErbB2 is thought to be the main mechanism. ErbB2 is a critical component of multiple anti-apoptotic pathways and is necessary for myocyte survival and repair. Trastuzumab binds to the ErbB2 on cardiac myocytes and blocks the cardioprotective ErbB2-ErbB4 signaling pathway [24]. Removal of trastuzumab leads of resumption of these pathways and recovery of cardiac damage. The synergistic cardiotoxic effects of anthracycline and trastuzumab can be explained by myocyte damage due to anthracyclines and blockage of repair mechanisms by trastuzumab [25].

A few approaches to reduce trastuzumab-induced cardiotoxicity are under investigation:

1. Second generation monoclonal antibodies —
   Lapatinib, a HER1 and HER2 receptor inhibitor, appears to be associated with much lower risk of cardiomyopathy than trastuzumab [26]. Other second-generation anti-HER2 therapies are being developed and three agents – neratinib, trastuzumab-DM1 and pertuzumab, are currently under investigation.
2. Anthracycline-sparing protocols —
   The BCIRG 006 trial demonstrated that the anthracycline-sparing chemotherapy protocols with trastuzumab alone were associated with significantly decreased risk of cardiomyopathy while preserving antitumor efficacy [27]. However, data regarding anti-neoplastic efficacy without anthracyclines is still conflicting [28].

3. Shorter treatment duration —
   Preliminary data shows that shorter regimens of trastuzumab are associated with a lower incidence of cardiomyopathy [29]. However, larger long-term studies are required to assess cardiotoxicity and anti-tumor efficacy.

Alkylating Agents

Cyclophosphamide is activated in the liver and its active metabolite crosslinks DNA, disrupting cell division. It has been associated with increased risk of cardiomyopathy, especially in combination with an anthracycline or cisplatin [30]. Other risk factors include advanced age and mediastinal irradiation. The mechanism of cardiotoxicity is not very well established and appears to be related to the strength of the individual dose, rather than cumulative dose [30]. Ifosamide has also been rarely associated with cardiomyopathy [31].

Antimicrotubule Agents

Paclitaxel, alone, has not been implicated as a cause of cardiomyopathy. However, it reduces the elimination of doxorubicin and increases its toxicity [32]. Paclitaxel should be avoided immediately before doxorubicin administration and within the next hour. The most common cardiovascular side-effect of paclitaxel is transient asymptomatic bradycardia [33].

Flouropyramidines

5-Flourouracil (5-FU) and its oral prodrug capecitabine have been associated with cardiotoxicity. The most common cardiac side effect is myocardial ischemia, likely related to coronary vasospasm [34]. Cardiomyopathy from these agents is rare and limited to a few case reports. It appears to have a type II pattern, with recovery of cardiac function in most cases after cessation of the agent [35].

Angiogenesis Inhibitors

Bevacizumab is a recombinant monoclonal antibody against the vascular endothelial growth factor (VEGF) receptor. It has primarily been associated with an increased risk of thrombotic events. The risk of cardiomyopathy is very low and

follows the reversible type II pattern [36]. The most probable hypothesis is the loss of protective effects of VEGF against endothelial dysfunction caused by excess oxidative stress.

Tyrosine Kinase Inhibitors

The most common cardiovascular effect of tyrosine kinase inhibitors is hypertension. Sunitinib has been associated with a 6–8 % incidence of HF and up to a 19 % incidence of cardiomyopathy, especially in patients with pre-existing coronary artery disease and cardiac risk factors, like hypertension [37]. Imatinib, an inhibitor of the Bcr-Abl protein, is used in the treatment of chronic myelogenous leukemia and has been associated with HF as well [38]. It is hypothesized to induce cardiotoxicity by the activation of the endoplasmic reticulum stress response pathways. Electron microscopy of cardiac biopsies demonstrates membrane whorls, pleomorphic mitochondria, effaced cristae, glycogen accumulation, lipid droplets, and vacuoles [38]. However, data is limited to animal studies and a few small case series.

Diagnosis

Traditionally, the detection of cardiotoxicity has relied on detection of reduction in LVEF. Multiple-gated acquisition (MUGA) scan and transthoracic echocardiography are the two most commonly used modalities. Baseline LVEF should always be obtained before initiation of chemotherapy. The values obtained from different modalities are not interchangeable and, hence, the same modality should continually be used throughout the chemotherapy protocol for an assessment and comparison of LVEF.

MUGA Scan

Historically, MUGA scan has been the modality of choice to assess LVEF prior recent advances in echocardiography. MUGA scan has the advantage of lower inter-observer variability and generation of an exact LVEF number [39]. However, it exposes the patients to ionizing radiation (approximately 7.8 mSv/exam) [40] and does not provide any information regarding valvular disorders, pericardial diseases, and diastolic parameters. Currently, most centers use echocardiography as the primary modality for LVEF assessment. MUGA scan continues to be used at many centers due to the oncologists' familiarity with the test and interpretation of its results. MUGA scan use should be limited in patients with poor acoustic windows or with pre-existing cardiomyopathy prior to the initiation of chemotherapy.

Transthoracic Echocardiography

Transthoracic echocardiography is the most commonly used modality for assessment of LVEF in patients receiving chemotherapy. Echocardiography is readily accessible, portable, inexpensive, and does not expose patients to ionizing radiation. It also provides additional information regarding valvular disorders, diastolic dysfunction, and pericardial disorders. Its disadvantages include larger inter-observer variability, dependence on complex geometric models and lack of good acoustic windows in many patients. Inter-observer variability and need for assumptions regarding ventricular geometry can be reduced by using 3D transthoracic echocardiography [41]. A small study with real time 3D transthoracic echocardiogram showed good correlation with MRI and MUGA scans in patients receiving chemotherapy [23]. Poor acoustic windows can be improved by the use of contrast agents, which better delineate the endocardial borders and reduce intra- and inter-observer variability [42]. Ideally, 3D echocardiography or contrast-enhanced echocardiography should be used as the modality of choice in screening patients for chemotherapy-induced cardiomyopathy.

Multiple indices of diastolic function have been evaluated in patients undergoing cardiotoxic chemotherapy [43]. Diastolic dysfunction usually precedes systolic dysfunction and early detection can potentially reduce the future risk of cardiomyopathy. However, none of the diastolic parameters have been found to have any significant association with development of future cardiac dysfunction [44].

Another modality used for early detection of cardiac dysfunction is the assessment of cardiac reserve by exercise or pharmacological stress echocardiography. Small studies have shown that reduction in cardiac reserve can be seen as early as after first cycle of chemotherapy and it can predict future cardiovascular events [45]. However, data regarding use of stress echocardiography are very limited.

The newest development in echocardiography is speckled and strain imaging. Multiple small trials have shown that these modalities can detect systolic dysfunction earlier than standard parameters and predict long term development of cardiomyopathy [46, 47]. Larger trials are still required before these modalities become standard of care. The major concern with these highly sensitive techniques is that many patients may never develop clinically significant cardiac dysfunction and life-saving therapies may be withheld unnecessarily.

Endomyocardial Biopsy

An endomyocardial biopsy can show typical features of cell damage from agents with type I cardiotoxicity. It was the gold standard to diagnose chemotherapy-induced cardiotoxicity. Billingham et al. [12] performed the pivotal trials assessing the histopathological changes following anthracycline exposure and developed a four point scoring system to characterize the extent of myocardial damage.

However, it is an invasive procedure with significant risks and is not routinely used these days, especially with recent advances in other modalities of non-invasive imaging.

Cardiac MRI

Cardiac MRI (CMR) is currently the gold standard for assessment of LVEF [48]. CMR can also identify regions of non-transmural cardiac injury by delayed gadolinium enhancement. Anthracycline-induced cardiomyopathy characteristically demonstrates a delayed enhancement in the anterolateral wall and trastuzumab-induced cardiomyopathy shows a subepicardial delayed enhancement in the lateral wall [23]. CMR also provides detailed structural information, including right-sided chambers. However, CMR is not widely available and is expensive. CMR cannot be used in patients with metal devices or implants and gadolinium use is contraindicated in patients with reduced renal function.

Cardiac Biomarkers

Reduction in LVEF is a late development in the cascade of development of cardiomyopathy and early identification is critical. Several cardiac biomarkers have been studied to identify early cardiac damage. However, utmost caution must be exercised as a false positive result can withhold lifesaving therapy. A good biomarker must be easy to measure, accurate, reproducible, and most importantly, should have high specificity to limit likelihood of false positive results. Biomarkers should be used as an adjunct to the previously described modalities of cardiac assessment [49].

Troponin I is the most studied biomarker as a predictor of development of cardiomyopathy. Elevation of troponin I levels can predict cardiac damage earlier than currently used modalities [50]. One study involving 703 patients receiving anthracyclines showed a 30 % incidence of troponin I elevation and 9 % patients had persistent elevation even at 1 month [51]. Biomarker measurements were done before starting chemotherapy and immediately after. The testing was repeated at 12, 24, 36 and 72 h and again at 1 month. Cardiovascular endpoints were seen in 1 %, 37 % and 84 % patients, respectively, in troponin I negative, transient positive and persistent troponin I positive patients at 1 month. The positive and negative predictive value of troponin I was 84 % and 99 %, respectively. However, this has not been validated in repeated larger trials. A consensus regarding optimal timing of troponin I measurement has also not been reached.

Serum atrial natriuretic peptide (ANP), B-type natriuretic peptide (BNP) and N-terminal proBNP (NT-proBNP) have not been validated as a screening tool in patients receiving cardiotoxic drugs [52, 53]. The studies with these markers have

been small, heterogeneous, single center trials and results have been conflicting. A few newer biomarkers have also shown promise in identification of cardiac damage, including, heart-type fatty acid-binding protein (H-FABP) [54] and glycogen phosphorylase BB (GPBB) [55].

Screening

Screening guidelines have been published by various societies for anthracycline and trastuzumab-induced cardiomyopathy. However, there is a lack of consensus amongst various guidelines. Nuclear cardiology guidelines regarding screening for anthracycline-mediated cardiomyopathy are shown in Table 13.5 [56]. The Children's Oncology Group's Long-Term Follow-up Guidelines for Survivors of Childhood, Adolescent, and Young Adult Cancers (COG LTFU guidelines) recommend assessment of LV function by either echocardiogram or MUGA scan every 1–5 years (depending on the presence of risk factors for cardiotoxicity) [57].

The screening guidelines for trastuzumab-induced cardiomyopathy are slightly different. The National Comprehensive Cancer Network Guidelines recommend LVEF assessment at baseline and then every 3 months for the duration of chemotherapy [58]. The Cardiac Guideline Consensus Committee suggests that LVEF can be assessed every 3 months if EF is greater than 40 %. If the LVEF is less than 40 %, trastuzumab should be withheld and LVEF assessment should be done every month [59].

Cardiac Protection

All patients receiving chemotherapy are considered *at risk* for development of HF. The most useful method to reduce cardiotoxicity is by limiting the cumulative dose and avoiding the co-administration of multiple cardiotoxic drugs. Anthracycline-induced cardiomyopathy is thought to be primarily due to free radical production and many anti-oxidants have been studied to provide cardioprotection. However, data for most of these compounds have been discrepant and disappointing. Dexrazoxane, an iron chelator, is the only FDA approved agent for cardioprotection during anthracycline therapy [60]. A Cochrane meta-analysis showed significant benefit of dexrazoxane in prevention of cardiotoxicity with a hazard ratio of 0.29 (95 % CI 0.20–0.41) [61]. It has been shown to reduce subclinical myocyte damage during chemotherapy as well, as evidenced by reduced incidence of troponin I elevation. However, there are some concerns regarding the reduction of anti-tumor efficacy by anthracyclines, increased myelosuppression and higher risk of second malignancy [61]. Therefore, current guidelines recommend use of dexrazoxane only in patients who have already received $\geq$300 mg/m^2 of doxorubicin and would benefit from further doses of doxorubicin. Dexrazoxane is not approved for use in children.

Table 13.5 Guidelines for monitoring of LVEF by Equilibirum Radionuclinde Angiography (ERNA)

If baseline LVEF ≥50 %
Baseline ERNA before starting chemotherapy
Next ERNA at cumulative doxorubicin dose 250–300 mg/m^2
Next ERNA at cumulative dose 450 mg/m^2 (at 400 mg/m^2 if high-risk)
Next ERNA prior to every dose >450 mg/m^2
Discontinue if LVEF decreases by ≥10 % from baseline AND reaches ≤50 %
If baseline LVEF <50 %
Baseline ERNA before starting chemotherapy
Serial ERNA prior to every subsequent dose
Discontinue if LVEF decreases by ≥10 % from baseline OR reaches ≤30 %
If baseline LVEF<30 %
Chemotherapy is not recommended

There has been limited data regarding role of standard HF drugs as cardioprotective agents. Small studies with use of carvedilol and valsartan have shown some cardioprotective effect [62, 63]. Cardinale et al. [64] randomized patients with positive troponin I levels at 1 month after chemotherapy to enalapril and placebo. The study found no reduction in LVEF in patients receiving enalapril, compared with a 43 % incidence in the control group. The recently published OVERCOME trial showed a small, but statistically significant benefit in preserving LVEF with prophylactic administration of enalapril and carvedilol [65]. However, larger multi-center trials are still needed. Many other agents are being evaluated as cardioprotective agents during chemotherapy.

Management

Data regarding management of chemotherapy-induced cardiomyopathy is limited and there are no well-defined recommendations. Most patients with cancer are excluded from major trials and, if included, they form a very small percentage of patients in most large trials. Traditionally, these patients were believed to respond poorly to standard HF therapy and had a very poor prognosis with 2-year mortality up to 60 % [66]. However, these historic beliefs were based on studies with diuretics and digitalis as the mainstay of HF therapy. Currently, patients with chemotherapy-induced cardiomyopathy should be treated with the same guidelines as other causes of cardiomyopathy. Although ACE inhibitors, ARBs and beta-blockers have never been systematically studied in these patients, these agents should be prescribed in every patient, if possible, and titrated up to the maximal tolerated dose. Recent trials show that the most critical variable for recovery of LVEF is the time to initiation of

HF therapy. Cardinal et al. [67] showed the likelihood of LVEF recovery are highest if HF therapy is started within 2 months, compared to no chances of complete recovery if started after 6 months and not even partial recovery if started after 12 months. They found an approximately fourfold decrease in chances of complete recovery with doubling of time to initiation of HF therapy.

Small studies have shown significant benefit of cardiac resynchronization therapy (CRT) in patients meeting criterion [68]. A larger trial regarding use of CRT in these patients called MADIT-CHIC (Multicenter Automated Defibrillator Implantation Trial- Chemotherapy Induced Cardiomyopathy) is currently ongoing and will provide further information regarding benefit of CRT in these patients [69].

Orthotopic heart transplant (OHT) is also an option for these patients after confirmed complete remission. Between October 1987 and October 2011, only 0.8 % transplants (total 453 transplants) were performed in the United States for doxorubicin-induced cardiomyopathy [70]. However, the number of OHT performed per year for chemotherapy-induced cardiomyopathy has been constantly increasing. There was no difference in all-cause mortality or mortality from malignancy between patients receiving OHT for chemotherapy-induced cardiomyopathy and all other causes of cardiomyopathy [70]. However, data regarding recurrence of malignancy or development of new malignancy is very limited. Data from the International Society of Heart and Lung Transplantation (ISHLT) Registry between January 2000 and December 2008 showed an increased risk of malignancy in patients with chemotherapy-induced cardiomyopathy compared to other causes of non-ischemic cardiomyopathy (5 % vs 2 % respectively, p value = 0.006) [71]. There was no effect on short or long-term survival and only 5 % cases of malignancy occurred within the 1st year of OHT with only one case of recurrence of breast cancer.

Patients with trastuzumab-induced cardiomyopathy should be assessed for recovery of LV function, with concomitant increase of guideline-proven HF medications. Most patients recover their cardiac function within 1–2 months. If LV function recovers, patients can be rechallenged with trastuzumab with careful monitoring. If the EF falls again, trastuzumab should be stopped and not reinitiated again unless it is the only lifesaving therapy [20].

Takotsubo Cardiomyopathy

Stress induced cardiomyopathy, also known as Takotsubo cardiomyopathy, is an acute reversible cardiomyopathy triggered by an acute stress [72]. Recently, there have been multiple reports of Takotsubo cardiomyopathy after chemotherapy. It has been reported with use of rituximab [73], 5-Flourouracil (5-FU) [74], vascular endothelial growth factor receptor antagonists, especially bevacizumab [75] and the tubulin-depolymerization agent combrestatin [76]. The strongest association appears to be with administration of 5-FU [72].

Cardiac-Oncology

The early detection and management of chemotherapy-induced cardiomyopathy will define the future of field of cardiac-oncology. Both cardiology and oncology are highly specialized fields and management of these overlapping, complicated disease processes requires the coordination of both specialists. Many signs and symptoms of heart failure are similar to side effects of chemotherapy and radiation, including fatigue, shortness of breath, dyspnea on exertion, lower extremity edema, etc. The decreased activity of patients undergoing chemotherapy can lead to a delay in the detection of cardiovascular disease in this patient population [77]. The management of these patients becomes even more difficult when patients pursue oncological and cardiovascular care at different institutions. In addition, the screening and management guidelines are not streamlined and contribute to confusion along with poor adherence to recommendations leading to mismanagement of early asymptomatic cardiomyopathy [78]. The outcomes can be drastically improved by collaborative efforts between the oncologists and cardiologists in management of these disease processes [79].

The other major issue in cardiac-oncology is to maintain a fine balance between management of malignancy and cardiovascular outcomes. The aim is to provide adequate anti-cancer therapy with minimal cardiovascular risks. However, due to lack of data and absence of clear guidelines, the decision to continue or withhold chemotherapeutic agent has to be individualized and requires communication between the patient, the oncologist and the cardiologist.

There is an urgent need for development and widespread use of cardiac-oncology centers. These centers can result in better communication, better decision-making and hopefully, better outcomes. Cardiac-oncology centers may provide specialized care in the future and will aim to provide the best quality oncological care, as well as, early detection and management of cardiac dysfunction.

References

1. Siegel R, DeSantis C, Virgo K, et al. Cancer treatment and survivorship statistics, 2012. CA Cancer J Clin. 2012;62:220–41.
2. Ning Y, Shen Q, Herrick K, et al. Cause of death in cancer survivors. Cancer Res. 2012;72:LB-339.
3. Khawaja MZ, Cafferkey C, Rajani R, et al. Cardiac complications and manifestations of chemotherapy for cancer. Heart. 2014;100:1133–40.
4. Seidman A, Hudis C, Pierri MK, et al. Cardiac dysfunction in the trastuzumab clinical trials experience. J Clin Oncol. 2002;20(5):1215–21.
5. Van Hoff DD, Layard MW, Basa P, et al. Risk factors for doxorubicin-induced congestive heart failure. Ann Intern Med. 1979;91:710–7.
6. Lefrak EA, Pitha J, Rosenheim S, et al. A clinicopathologic analysis of adriamycin cardiotoxicity. Cancer. 1973;32:302–14.

7. Steinherz LJ, Steinherz PG, Tan CT, et al. Cardiac toxicity 4 to 20 years after completing anthracycline therapy. JAMA. 1991;266:1672–7.
8. Swain SM, Whaley FS, Ewer MS. Congestive heart failure in patients treated with doxorubicin: a retrospective analysis of three trials. Cancer. 2003;97:2869–79.
9. Mulrooney DA, Yeazel MW, Kawashima T, et al. Cardiac outcomes in a cohort of adult survivors of childhood and adolescent cancer: retrospective analysis of Childhood Cancer Survivor Study Cohort. Br Med Journal. 2009;339:b4606.
10. Yeh ET, Bickford CL. Cardiovascular complications of cancer therapy: incidence, pathogenesis, diagnosis and management. J Am Coll Cardiol. 2009;53(24):2231–47.
11. Raj S, Franco VI, Lipshultz SE. Anthracycline-induced cardiotoxicity: a review of pathophysiology, diagnosis and treatment. Curr Treat Options Cardio Med. 2014;16:315.
12. Billingham M, Bristow M. Evaluation of anthracycline cardiotoxicity: predictive ability and functional correlation of endomyocardial biopsy. Cancer Treat Symp. 1984;3:71–6.
13. Octavia Y, Tocchetti CG, Gabrielson KL, et al. Doxorubicin-induced cardiomyopathy: from molecular mechanisms to therapeutic strategies. J Mol Cell Cardiol. 2012;52:1213–25.
14. Ryberg D, Nielsen D, Skovsgaard T, et al. Epirubicin cardiotoxicity: an analysis of 469 patients with metastatic breast cancer. J Clin Oncol. 1998;16:3502–8.
15. Robert NJ, Vogel CL, Henderson IC, et al. The role of the liposomal anthracyclines and other systemic therapies in the management of advanced breast cancer. Semin Oncol. 2004;31(6 Suppl 13):106–46.
16. Van Dalen EC, Van Der Pal HJ, Caron HN, et al. Different dosage schedules for reducing cardiotoxicity in cancer patients receiving anthracycline chemotherapy. Cochrane Database Syst Rev 2006;(4):CD005008.
17. Bria E, Cuppone F, Fornier M, et al. Cardiotoxicity and incidence of brain metastases after adjuvant trastuzumab for early breast cancer: the dark side of the moon? A meta-analysis of the randomized trials. Breast Cancer Res Treat. 2008;109:231–9.
18. Slamon DJ, Leyland-Jones B, Shak S, et al. Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. N Engl J Med. 2001;344:783–92.
19. Chen J, Long JB, Hurria A, et al. Incidence of heart failure or cardiomyopathy after adjuvant trastuzumab therapy for breast cancer. J Am Coll Cardiol. 2012;60:2504–12.
20. Suter TM, Procter M, Van Veldhuisen DJ, et al. Trastuzumab-associated cardiac adverse effects in herceptin adjuvant trial. J Clin Oncol. 2007;25:3859–65.
21. Guarneri V, Lenihan DJ, Valero V, et al. Long-term cardiac tolerability of trastuzumab in metastatic breast cancer: the M.D. Anderson Cancer Center Experience. J Clin Oncol. 2006;24:4107–15.
22. Procter M, Suter TM, de Azambuja E, et al. Longer-term assessment of trastuzumab-related cardiac adverse events in the Herceptin Adjuvant (HERA) trial. J Clin Oncol. 2010;28:3422–8.
23. Walker J, Bhullar N, Fallah-Rad N, et al. Role of three-dimensional echocardiography in breast cancer: comparison with two-dimensional echocardiography, multiple-gated acquisition scans and cardiac magnetic resonance imaging. J Clin Oncol. 2010;28(21):3429–36.
24. Force T, Krause DS, Van Etten RA. Molecular mechanisms of cardiotoxicity of tyrosine kinase inhibition. Nat Rev Cancer. 2007;7:332–44.
25. Tocchetti CG, Ragone G, Coppola C, et al. Detection, monitoring and management of trastuzumab-induced left ventricular dysfunction: an actual challenge. Eur J Heart Fail. 2012;14:130–7.
26. Geyer CE, Forster J, Lindquist D, et al. Lapatinib plus capecitabine for HER2-positive advanced breast cancer. N Engl J Med. 2006;355:2733–43.
27. Slamon DJ, Eiermann W, Robert N, et al. Adjuvant trastuzumab in HER2-positive breast cancer. N Engl J Med. 2011;365(14):1273–83.
28. Castrellon AB, Gluck S. Adjuvant therapy for HER2 positive breast cancer: are anthracyclines still necessary? Clin Adv Hematol Oncol. 2008;6:666–72.

29. Joensuu H, Kellokumpu-Lehtinen PL, Bono P, et al. Adjuvant docetaxel or vinorelbine with or without trastuzumab for breast cancer. N Engl J Med. 2006;354:1260–6.
30. Dow E, Schulman H, Agura E. Cyclophosphamide cardiac injury mimicking acute myocardial infarction. Bone Marrow Transplant. 1993;12(2):169–72.
31. Quezado ZM, Wilson WH, Cunnion RE, et al. High-dose ifosfamide is associated with severe, reversible cardiac dysfunction. Ann Intern Med. 1993;118(1):31–6.
32. Biganzoli L, Cufer T, Bruning P, et al. Doxorubicin-paclitaxel: a safe regimen in terms of cardiac toxicity in metastatic breast carcinoma patients. Results from a European organization for research and treatment of cancer multicenter trial. Cancer. 2003;97:40–5.
33. Rowinsky EK, Donehower RC. Paclitaxel (taxol). N Engl J Med. 1995;332:1004–14.
34. Kosmas C, Kallistratos MS, Kopterides P, et al. Cardiotoxicity of flouropyrimidines in different schedules of administration: a prospective study. J Cancer Res Clin Oncol. 2008;134:75–82.
35. Sorrentino MF, Kim J, Foderaro AE, et al. 5-Flourouracil induced cardiotoxicity: review of the literature. Cartogr J. 2012;19(5):453–8.
36. Hawkes EA, Okines AFC, Plummer C, et al. Cardiotoxicity in patients treated with bevacizumab is potentially reversible. J Clin Oncol. 2011;29:e560–2.
37. Di Lorenzo G, Autorino R, Bruni G, et al. Cardiovascular toxicity follow sunitinib therapy in metastatic renal cell carcinoma: a multicenter analysis. Ann Oncol. 2009;20:1535–42.
38. Kerkela R, Grazette L, Yacobi R, et al. Cardiotoxicity of the cancer therapeutic agent imatinib mesylate. Nat Med. 2006;12(8):908–16.
39. Skrypniuk JV, Bailey D, Cosgriff PS, et al. UK audit of left ventricular ejection fraction estimation from equilibrium ECG gated blood pool images. Nucl Med Commun. 2005;26:205–15.
40. Mettler FA, Huda W, Yoshizumi TT, et al. Effective doses in radiology and diagnostic nuclear medicine: a catalog 1. Radiol. 248(1):254–63.
41. Sugeng L, Mor-Avi V, Weinert L, et al. Quantitative assessment of left ventricular size and function: side-by-side comparison of real-time three-dimensional echocardiography and computed tomography with magnetic resonance reference. Circulation. 2006;114:654–61.
42. Hoffman R, von Bardeleben S, Ten Cate F, et al. Assessment of systolic left ventricular function: a multi-center comparison of cineventriculography, cardiac magnetic resonance imaging, unenhanced and contrast-enhanced echocardiography. Eur Heart J. 2005;26:607–16.
43. Tjeerdsma G, Meinardi MT, WT v DG, et al. Early detection of anthracycline induced cardiotoxicity in asymptomatic patients with normal left ventricular systolic function: autonomic versus echocardiographic variables. Heart. 1999;81:419–23.
44. Radulescu D, Pripon S, Parv A, et al. Altered left ventricular diastolic performance in oncologic patients treated with epirubicin. Congest Heart Fail. 2007;13:215–20.
45. Civelli M, Cardinale D, Martinoni A, et al. Early reduction in left ventricular contractile reserve detected by dobutamine stress echo predicts high-dose chemotherapy-induced cardiac toxicity. Int J Cardiol. 2006;111:120–6.
46. Jurcut R, Wildiers H, Ganame J, et al. Strain rate imaging detects early cardiac effects of pegylated liposomal doxorubicin as adjuvant therapy in elderly patients with breast cancer. J Am Soc Echocardiogr. 2008;21:1283–9.
47. Sawaya H, Sebag I, Plana JC, et al. Early detection and prediction of cardiotoxicity in chemotherapy-treated patients. Am J Cardiol. 2011;107(9):1375–80.
48. Grothues F, Braun-Dullaeus R. Serial assessment of ventricular morphology and function. Heart Fail Clin. 2009;5(3):301–14.
49. Ky B, Carver JR. Biomarker approach to the detection and cardioprotective strategies during anthracycline chemotherapy. Heart Failure Clin. 2011;7:323–31.
50. Kilickap S, Barista I, Akgul E, et al. cTnT can be useful marker for early detection of anthracycline cardiotoxicity. Ann Oncol. 2005;16:798–804.
51. Cardinale D, Sandri MT, Colombo A, et al. Prognostic value of troponin I in cardiac risk stratification of cancer patients undergoing high-dose chemotherapy. Circulation. 2004;109:2749–54.

52. Horacek JM, Pudil R, Jebavy L, et al. Assessment of anthracycline-induced cardiotoxicity with biochemical markers. Exp Oncol. 2007;29(4):309–13.
53. Knobloch K, Tepe J, Lichtinghagen R, et al. Monitoring of cardiotoxicity during immunotherapy with Herceptin using simultaneous continuous wave Doppler depending on N-terminal pro-brain natriuretic peptide. Clio Med. 2007;7(1):88–9.
54. ElGhandour AH, ElSorady M, Azab S, et al. Human heart-type fatty acid-binding protein as an early diagnostic marker of doxorubicin cardiac toxicity. Hematology Rev. 2009;1:29–32.
55. Horacek JM, Tichy M, Pudil R, et al. Glycogen phosphorylase BB could be a new circulating biomarker for detection of anthracycline cardiotoxicity. Ann Oncol. 2008;19:1656–7.
56. Schwartz RG, McKenzie WB, Alexander I, et al. Congestive heart failure and left ventricular dysfunction complicating doxorubicin therapy: a seven year experience using serial radionuclide angiocardiography. Am J Med. 1987;82:1109–18.
57. Children's Oncology Group. Long-term follow-up guidelines for survivors of childhood, adolescent, and young adult cancers. 2009, www.survivorshipguidelines.com.
58. National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology. Breast Cancer version 1. 2012.
59. Jones AL, Barlow M, Barrett-Lee PJ, et al. Management of cardiac health in trastuzumab treated patients with breast cancer: updated United Kingdom Nationa95l Cancer Research Institute recommendations for monitoring. Br J Cancer. 2009;100(5):684–92.
60. Lipshultz SE, Rifai N, Dalton VM, et al. The effect of dexrazoxane on myocardial injury in doxorubicin-treated children with acute lymphoblastic leukemia. N Engl J Med. 2004;351:145–53.
61. Van Dalen EC, Caron HN, Dickinson HO, et al. Cardioprotective interventions for cancer patients receiving anthracyclines. Cochrane Database Syst Rev 2008;(2):CD003917.
62. Kalay N, Basar E, Ozdogru I, et al. Protective effects of carvedilol against anthracycline-induced cardiomyopathy. J Am Coll Cardiol. 2006;48:2258–62.
63. Nakamae H, Tsumura K, Terada Y, et al. Notable effects of angiotension II receptor blocker, valsartan, on acute cardiotoxic changes after standard chemotherapy with cyclophosphamide, doxorubicin, vincristine, and prednisolone. Cancer. 2005;104:2492–8.
64. Cardinale D, Colombo A, Sandri MT, et al. Prevention of high-dose chemotherapy-induced cardiotoxicity in high-risk patients by angiotensin-converting enzyme inhibition. Circulation. 2006;114:2474–81.
65. Bosch X, Rovira M, Sitges M, et al. Enalapril and carvedilol for preventing chemotherapy-induced left ventricular systolic dysfunction in patients with malignant hemopathies. J Am Coll Cardiol. 2013;61:2355–62.
66. Felker GM, Thompson RE, Hare JM, et al. Underlying causes and long-term survival in patients with initially unexplained cardiomyopathy. N Engl J Med. 2000;342:1077–84.
67. Cardinale D, Colombo A, Lamantia G, et al. Anthracycline-induced cardiomyopathy. Clinical relevance and response to pharmacological therapy. J Am Coll Cardiol. 2010;55:213–20.
68. Rickard J, Kumbhani DJ, Baranowski B, et al. Usefulness of cardiac resynchronization therapy in patients with adriamycin-induced cardiomyopathy. Am J Cardiol. 2010;105(4):522–6.
69. Moss AJ. Multicenter Automated Defibrillator Implantation Trial- Chemotherapy Induced Cardiomyopathy (MADIT-CHIC). Clinicaltrials.gov/show/NCT02164721
70. Lenneman AJ, Wang L, Wigger M, et al. Heart transplant survival outcomes for adriamycin dilated cardiomyopathy. Am J Cardiol. 2013;111(4):609–12.
71. Oliveira GH, Hardaway BW, Kucheryavaya AY, et al. Characteristics and survival of patients with chemotherapy-induced cardiomyopathy undergoing heart transplantation. J Heart Lung Transplant. 2012;31:805–10.
72. Smith SA, Auseon AJ. Chemotherapy-induced Takotsubo cardiomyopathy. Heart Failure Clin. 2013;9:233–42.
73. Kanamori H, Tsutsumi Y, Mori A, et al. Delayed reduction in left ventricular function following treatment of non-Hodgkin's lymphoma with chemotherapy and rituximab, unrelated to acute infusion reaction. Cardiology. 2006;105(3):184–7.

74. Grunwald MR, Howie L, Diaz Jr LA. Takotsubo cardiomyopathy and fluorouracil: case report and review of literature. J Clin Oncol. 2012;30(2):e11–4.
75. Franco TH, Khan A, Joshi V, et al. Takotsubo cardiomyopathy in two men receiving bevacizumab for metastatic cancer. Ther Clin Risk Manag. 2008;4(6):1367–70.
76. Bhakta S, Flick SM, Cooney MM, et al. Myocardial stunning following combined modality combrestatin-based chemotherapy: two case reports and review of literature. Clin Cardiol. 2009;32(12):e80–4.
77. Chen CL, Steingart R. Cardiac disease and heart failure in cancer patients: is our training adequate to provide optimal care? Heart Failure Clin. 2011;7:357–62.
78. Yoon GJ, Telli ML, Kao DP, et al. Left ventricular dysfunction in patients receiving cardiotoxic cancer therapies: are clinicans responding optimally? J Am Coll Cardiol. 2010;56:1644–50.
79. Albini A, Pennesi G, Donatelli F, et al. Cardiotoxicity of anticancer drugs: the need for cardio-oncology and cardio-oncological prevention. J Natl Cancer Inst. 2010;102(1):14–25.

Chapter 14
Atrial Arrhythmias and Heart Failure

S. Luke Kusmirek

Introduction

Congestive heart failure and atrial arrhythmias, in particular atrial fibrillation are the two major cardiovascular epidemics of the current era with a major impact on the healthcare economics [1]. Incidence of both atrial fibrillation (AF) and congestive heart failure (CHF) is rapidly increasing [2]. These two conditions frequently coexist; onset of one often predates and predicts the occurrence of the other [3, 4]. In a prospective study that examined the temporal relations of AF and CHF, the incidence of CHF among AF patients was 33 per 1000 person-years, and the incidence of AF among CHF subjects was 64 per 1000 person-years. In patients with AF or CHF, subsequent development of the other is associated with increased mortality [2]. Patients with CHF are at excess risk of developing AF and the more advanced CHF is the more often AF occurs [4–8]. In the CONSENSUS trial, AF prevalence as high as 50 % was observed in NYHA class IV CHF population [8]. Conversely, presence of AF with uncontrolled ventricular response may lead to tachycardia-induced cardiomyopathy and precipitate CHF symptoms.

Pathophysiology

Failing heart undergoes mechanical and electrical remodeling that promotes proarrhythmic changes at the cellular and organ level. All major arrhythmia mechanisms are promoted and facilitated by the typical progression of the myocardial injury from the time of the acute insult, through the compensated phase of recovery to the

S.L. Kusmirek, MD
Drexel Atrial Arrhythmia Center, Hahnemann University Hospital, Drexel University College of Medicine, Division of Cardiology, 245 North 15th Street, Suite 6122, Philadelphia, PA 19102, USA
e-mail: skusmire@drexelmed.edu

H. Eisen (ed.), *Heart Failure*, DOI 10.1007/978-1-4471-4219-5_14

long-term myocardial dysfunction and progressive loss of the cellular integrity and organ function. The increased levels of the serum and tissue norepinephrine, beta-receptor down regulation and unopposed activation of the sympathetic autonomic nervous system with the associated loss of the vagal input promote enhanced normal and pathological automaticity of the atrial pacemaker cells. Similarly, intracellular calcium perturbations, increased catecholamines levels, ischemia and proarrhythmic effects of the medications and electrolyte disorders facilitate triggered activity. Reentry, both functional as well as based on the presence of a fixed anatomical obstacle is also more likely to occur in CHF. The substrate necessary for reentry is created by the diffuse or focal cardiac tissue fibrosis leading to the loss of the gap junction function and enhancement in the anisotropic conduction properties. While the cellular changes are potentially reversible if addressed early, the loss of electrical and mechanical function of the atrium is generally irreversible once extensive tissue necrosis and fibrosis has occurred [9, 10].

Classification

Atrial arrhythmias are usually classified on the basis of the anatomical structures involved in their initiation and propagation. Supraventricular tachycardias including atrioventricular node re-entrant tachycardia, atrioventricular re-entrant tachycardia and focal automatic atrial tachycardia are typically seen in younger patients without structural heart disease. Their prevalence is approximately 0.22 % in general population [11]. Diagnosis is usually established when a 12 lead electrocardiogram or a rhythm strip is recorded during the symptomatic episode of arrhythmia. There are only sporadically associated with the development of structural heart disease and carry overall benign prognosis. In rare cases of the rapid incessant arrhythmia, tachycardia-induced cardiomyopathy may develop. Cardiomyopathy is usually reversible once the tachycardia is controlled. Options of the therapy include rate control with atrioventricular node blocking agents (β-blockers, calcium channel blockers, digoxin), antiarrhythmic drugs (sotalol, amiodarone) or catheter ablation. Catheter ablation of all types of supraventricular tachycardia is very effective and carries a very low risk of the periprocedural complications. Thus, it is the therapy of choice for the majority of patients regardless of the status of the underlying cardiac disease. Moreover, in the cases of supraventricular tachycardia occurring in patients with the preexisting structural heart disease, CHF and tachycardia-induced cardiomyopathy catheter ablation should be used preferentially to maximize the likelihood of the arrhythmia cure and avoid the long-term risks and complications of drug therapy.

Conversely, micro and macro reentrant atrial tachycardias, atrial flutters and atrial fibrillation are the typical atrial arrhythmias associated with structural heart disease and CHF. Despite the occasional differences in the underlying basic arrhythmia mechanism, atrial rates and the anatomical substrates involved, they are all producing similar clinical symptoms and share the same long term impact on the

atrial transport mechanics and overall cardiac performance. They also create similar increased risk of thromboembolic complications and respond to similar therapies. They will collectively be addressed as atrial fibrillation (AF) and as such will be the focus of this chapter. AF is often classified as first detected or recurrent as well as paroxysmal (when it terminates spontaneously), persistent (when it lasts more than 7 days or requires some form of cardioversion for termination) or permanent (when it no longer responds to any therapeutic intervention). These categories are not mutually exclusive as the dominant pattern of AF may change over time depending on the patient's clinical status and the therapies used for arrhythmia control.

Epidemiology

AF is the most common heart rhythm abnormality. It is uncommon in young healthy individuals but rapidly increases in prevalence after the age of 50 up to approximately 10 % of patients over the age of 80 years old. Men are affected earlier in life but women catch up rapidly when in their 70s and 80s with the slight overall higher prevalence in women. Lifetime risk of AF development in the Western countries is about 1 in 4. The AF association with structural heart disease is well established. The most common associated conditions are hypertensive heart disease, coronary artery disease, and congestive heart failure [2]. The AF epidemiology in the non-Caucasian populations is not well studied but the available data reveals risk factors pattern similar to Caucasian patients but overall lower AF age-adjusted incidence and prevalence.

Diagnosis

Atrial fibrillation is diagnosed with a combination of clinical history, physical examination findings and electrocardiographic recordings. Patient's usually report palpitations, sensation of irregular pulse, dizziness, fatigue, shortness of breath and decreased exercise capacity. On physical examination pulse and heart rate are irregularly irregular and excessive resting or exercional tachycardia or bradycardia may be present. Findings of associated decompensated heart failure including low peripheral pulses, cool extremities, peripheral or pulmonary congestion and S3 gallop often coexist. Recording of at least single lead electrocardiographic rhythm strip is necessary to confirm the diagnosis. AF may also be asymptomatic and the diagnosis is made solely on the basis of abnormal physical examination and/or electrocardiographic recordings. There is a wide spectrum of the ECG recording methods useful in AF diagnosis including "spot check" 12-lead ECG, ambulatory 24 h Holter monitors, extended use ECG loop recorders as well as implantable loop recorders. The accuracy of AF detection varies substantially between the methods but generally improves with the length of the monitoring and the patient compliance. The

implantable loop recorders provide the best compliance and their overall accuracy for AF detection was reported at 98.5 % in the XPECT trial [12]. The ECG monitoring is also useful in the long term rate control assessment, monitoring the symptoms and evaluation of the efficacy of the therapy.

Once the diagnosis of AF is established, basic ancillary testing is recommended including blood tests (CBC, serum electrolytes, hepatic, renal and thyroid function tests) transthoracic echocardiography and in selected patients chest x-ray, transesophageal echocardiography, 6-min walk test, stress testing and electrophysiological study.

Many of these tests are also routinely used for evaluation of congestive heart failure status and if available may not need to be repeated [13].

Therapy

Therapy of atrial arrhythmias in CHF is focused on preventing thromboembolic complications and controlling the arrhythmia associated symptoms. Successful restoration and maintenance of normal sinus rhythm should bring about the theoretical benefits of restoring the atriventricular synchrony, improvement in the atrial transport, reduction in the long-term thromboembolic risk and return of the normal chronotropic competency. However these potential advantages were thus far not demonstrated to provide survival benefit in the clinical trials comparing diverse rhythm controlling strategies to rate control only.

Prevention of the Thromboembolic Complications

CHF is a prothrombotic state. The neurohormonal changes triggered by CHF lead to increased risk of intracardiac thrombus formation leading to systemic thromboembolism. In the WARCEF study, patients with CHF in normal sinus rhythm were treated with either oral aspirin or warfarin. The risk of the ischemic stroke in the anticoagulated patient was 2.5 % in warfarin group and 4.7 % in aspirin group, significantly exceeding the stroke risk in general population [14]. However, the association of CHF and stroke in patients with preexisting AF is not as robust although the data is largely from older trials with variable CHF definitions [15]. AF is known to substantially increase the risk of stroke and systemic embolization in all patients with the possible exception of young patients with no structural heart disease and no associated risk factors who have paroxysmal AF only. No single risk assessment scale is proven to predict the individual occurrence of stroke with a high accuracy. In clinical practice CHADS2 and CHA2DS2-VASc scores serve as a convenient while imperfect tool for a rapid stroke risk assessment. Other scales like HAS-BLED are helpful in assessing the risk of anticoagulation related complications [16]. Coincidentally, CHF patients often have additional stroke risk factors and

generally should be considered for chronic anticoagulation with warfarin with the international normalized ratio (INR) target of 2.0 to 3.0. Currently approved and available oral anticoagulant alternatives to warfarin include direct thrombin inhibitor dabigatran and oral factor Xa inhibitors rivaroxiban and apixaban. The pivotal trials of the newer anticoagulants included a significant number of patients with clinical CHF and systolic LV dysfunction. In all these trials, the outcomes in the CHF subgroup were similar to the overall positive results of the general study population without excess risk of complications thus, the newer anticoagulants are considered safe and effective in CHF patients [17–19]. Given their decreased level of bleeding complications and excellent efficacy, novel oral anticoagulants are a valuable option for most of the patients with existing stroke risk factors including CHF population. Individuals who are intolerant to oral anticoagulants may be treated with aspirin or aspirin and clopidogrel combination. However, the antiplatelet therapy is less effective than warfarin while the risk of bleeding complications is as high as with the oral anticoagulants [20, 21]. The alternative strategies of the thromboembolic risk reduction in AF in a form of a percutaneous left atrial appendage occlusion device, percutaneous left atrial appendage ligation or surgical ligation may be considered in selected patient even if no outcomes data for their use in CHF patients is yet available.

Rate Control Versus Rhythm Control in CHF

Rate control and rhythm control strategies result in similar outcomes in both mildly symptomatic patients as well as patients with more advanced CHF. AFFIRM trial of rate versus rhythm control in mildly symptomatic AF patients included over 4000 patients. 23 % of patients had a history of mild CHF. No advantage of restoration of normal sinus rhythm over rate control was seen [22]. AF-CHF trial studied 1376 AF patients with more advanced CHF. Sinus rhythm restoration and maintenance primarily with amiodarone resulted in the same outcomes for mortality, stroke and CHF hospitalization as rate control only [23]. Interestingly, the ability to maintain normal sinus rhythm with the antiarrhythmic drug therapy is associated with improved prognosis both in patients with mild and advanced CHF. It is not clear whether this phenomenon represents a true causative effect or is simply a marker of a lower risk patient.

Rate Control

Rate control of AF is an accepted goal of therapy and an alternative to the restoration and maintenance of normal sinus rhythm. Effective rate control of AF can be accomplished with medications as well as atrioventricular node ablation and permanent pacemaker implantation. Pharmacological approach is usually the initial

strategy given its less invasive nature and reasonable efficacy. Pace and ablate strategy is reserved for situations where medications are ineffective or are not tolerated. β-blockers are the drugs of choice in AF rate control and are particularly valuable in CHF patients. In general, β-blockers that have proven outcomes benefit in CHF including carvedilol, metoprolol succinate and bisoprolol should be use preferentially. However, unstable patient may not be able to tolerate the higher doses needed for effective rate control. In addition, CHF patients with AF naive to β-blocker therapy are more likely to be β-blocker intolerant and have a lesser chance to respond to the therapy including less reduction in mortality as compared to their non-AF counterparts. Digoxin maybe added to β-blocker for an improved rate control efficacy and to allow for a lower dose of either drug to be used. Digoxin alone or in combination is less effective rate controlling agent during acute CHF decompensation. In refractory cases, intravenous or oral amiodarone may also be utilized but this strategy increases bradycardic complications and the need for a pacemaker implantation. Calcium channel antagonist especially nondihydropyridines should be avoided in patients with depressed left ventricular function. Dronaderone was evaluated as a rate control strategy in patients with persistent AF. In PALLAS trial, active therapy with dronaderone resulted in increased cardiovascular events including mortality. Moreover, the use of dronaderone in patients with moderate to severe heart failure resulted in significant increase in mortality and worsening of heart failure status. Thus, dronaderone should not be used in patients with active CHF symptoms and AF [24, 25]. The targets of strict rate control (<80/min at rest, <110/min with moderate exercise) were historically based on the values adopted from the AFFIRM trial [22]. The same targets were used in AF-CHF trial [23]. More recently, the strategy of strict versus lenient rate control (< 110/min at rest) was evaluated in RACE II study. Both approaches were found to have equivalent results however; patients with CHF and left ventricular dysfunction were underrepresented [26]. Periodic monitoring of left ventricular function is recommended for patients who are treated with lenient rate control to avoid the insidious onset of tachycardia-induced cardiomyopathy.

Pace and ablate approach to permanent AF rate control in CHF has significant benefits but also carries a risk of short and long term complications. The benefits are related to the immediate complete rate control, rhythm regularization and reversal of the tachycardia mediated left ventricular dysfunction. Poorly tolerated rate controlling drugs can be discontinued. On the other hand, patient is rendered pacemaker dependent and faces the inherent risk of a random device failure or infection as well as hemodynamic consequences of the permanent pacing including progressive left ventricular failure and mitral regurgitation. Studies of pace and ablate strategy in unselected general population conducted prior to the era of cardiac resynchronization suggested net positive effect on symptoms control, improvement in left ventricular systolic performance and decreased rate of hospitalizations. However the same strategy studied in patients with low ejection fraction (EF) and CHF revealed more diverse outcomes with significant improvement in some patients but progressive deterioration associated with a very high early mortality rates in majority of patients. The PAVE study examined the effect of right ventricular versus biventricular

pacing after AV node ablation in patients with permanent AF. Biventricular pacing protected from LV systolic function deterioration and improved quality of life and functional measures. The effect was particularly apparent in the population of patients with preexisting CHF and reduced EF [27]. Similar improved outcomes were subsequently reported in pace and ablate patients with initial RV pacing only after the upgrade to biventricular system was performed and patients with de novo biventricular pacing [28, 29]. Recent systematic review of the AV node ablation in the cardiac resynchronization therapy recipients with CHF and AF suggested not only improvement in symptoms but also mortality benefit [30]. Therefore, pace and ablate strategy utilizing isolated RV pacing should not be used in heart failure patients while cardiac resynchronization therapy should be strongly considered in all patients with LV dysfunction and anticipated high rate of ventricular pacing or pacemaker dependency.

Rhythm Control

Dofetilide and amiodarone are the only two antiarrhythmic drugs recommended for the pharmacological rhythm control of AF in CHF patients [31, 32]. The recommendation is based on their lack of negative inotropic effect on myocardial contractility and neutral effect on survival in patients with CHF. Dofetilide is usually well tolerated and moderately effective for the sinus rhythm maintenance in patients with CHF or ischemic heart disease as reported in the DIAMOND study. The risk of drug-induced proarrhythmia, most commonly in a form of torsades de pointes is acceptably low as long as the renal function and serum electrolytes are stable and excessive QTc interval prolongation is avoided. Dofetilide should only be initiated in the hospital settings. Amiodarone is also safe and more effective than placebo for normal sinus rhythm maintenance in variety of clinical setting including CHF patients. Frequent occurrence of intolerance and potential for serious organ toxicity limits the utility of amiodarone in long-term AF therapy. In DIONYSOS trial, amiodarone had to be stopped prematurely in 13.3 % of patients while 44.5 % of patients reported drug side effects at 12 months of its use [33]. It should be noted that the use of all other antiarrhythmic drugs including class I drugs, D-sotalol and dronaderone is associated with increased mortality in CHF patients and should be avoided.

Pacing Therapy

Cardiac pacing therapy outside of the pace and ablate situation is often necessary in CHF population with and without AF. The need for pacing is triggered by the increased frequency of sinus and atrioventricular node dysfunction as well as degenerative His-Purkinje conduction system disease driven by the cardiomyopathic process and frequent iatrogenic bradyarrhythmic complications

of medical therapy with βblockers, digoxin and amiodarone. In addition, biventricular pacing is indicated in patients with decreased left ventricular systolic function, widened QRS and at least mild heart failure. Atrial pacing in patients with sinus node dysfunction may reduce occurrences of AF precipitated by severe bradycardia. Overdrive atrial pacing, multisite pacing and unconventional site pacing for AF prevention or AF burden reduction is controversial and the benefit is not clearly documented. High frequency conventional right ventricular pacing is known to increase incidence of both AF and CHF regardless of the baseline LV systolic function [34]. Optimal pacemaker programming set to minimize right ventricular pacing should be utilized in all pacemaker recipients when appropriate. Cardiac resynchronization therapy is reasonable in the setting of the coexisting AF. Despite the improvements in the left ventricular systolic performance and CHF functional status associated with biventricular pacing the effect on AF is not as favorable. In CARE-HF study, biventricular pacing was not protective against the future development of AF. In the MADIT-CRT the subgroup of clinical responders to resynchronization therapy defined as reduction in left atrial volume had lower incidence of new onset atrial fibrillation [35]. Presence of AF at the time of the biventricular pacemaker implantation is associated with decreases likelihood of clinical response and predicts increased risk of cardiac mortality particularly if the pacing therapy is not delivered at all times. Atrioventricular node ablation assures complete rate control and near 100 % delivery of cardiac resynchronization therapy and should be considered under these circumstances [36].

Atrial Fibrillation Ablation

Catheter ablation of AF is an accepted therapy for symptomatic patients intolerant or unresponsive to medical management. It is postulated that ablation therapy in CHF patients would offer superior arrhythmia control translating into improvement in symptoms, myocardial systolic function parameters and potential mortality benefit. Some observational or non-randomized studies in AF ablation suggest that CHF patients may be effectively treated by ablation and often have significant improvement in left ventricular function when arrhythmia is controlled [37–40]. These observations from non-randomized trials were corroborated by meta-analysis that reviewed outcomes of 1851 patients undergoing catheter ablation of AF. Subgroup of CHF patients required more redo procedures but experienced an average EF improvement of 11 % [41]. Randomized catheter ablation trial data in patients with LV dysfunction remains sparse. PABA-CHF randomized trial compared AF ablation to AV node ablation and biventricular pacing in patients with LV dysfunction and found the AF ablation to be more effective resulting in improvement in left ventricular EF, 6-min walk test and quality of life [42]. Another randomized trial compared ablation to medical management in patients with symptomatic CHF and EF <35 % and found that the improvements in EF were

restricted to the ablation patients who were able to maintain sinus rhythm [43]. ARC HF trial randomized persistent AF patients with stable moderate to severe CHF and EF <35 % to extensive biatrial AF ablation versus rate control. Sinus rhythm was restored in 92 % of patients. At 12 months of follow up the ablation group had significant improvement in peak oxygen consumption as well as significant improvement in quality of life, decreased B-type naturetic peptide levels and regression of left atrial dilatation. A trend towards improved left ventricular EF was observed as well [44]. Large scale randomized trials enrolling CHF patients with EF 35 % or less and assigning them to either AF ablation or conventional medical therapy are ongoing and should provide more definitive data for the role of AF ablation in CHF population [45–47]. Accordingly, 2011 ACCF/AHA/HRS Focused Update on the Management of Patients With Atrial Fibrillation positions AF catheter ablation in patients with CHF in a " may be considered" category where more studies are needed before a definitive assessment and recommendation for the therapy can be made [13].

Summary

Atrial arrhythmias and CHF are common and often coexisting cardiac conditions. When present in the same patient, they tend to signify more advanced stage of cardiac disease and lower probability of the successful control of either problem. All patients with AF and CHF should receive β-blockers and angiotensin receptor inhibitors in addition to arrhythmia directed therapy. Therapeutic options for arrhythmia control are sparser when CHF is present. Traditional pharmacological therapies offer modest success while more contemporary therapies are more promising but not extensively studied yet. The current approach to the therapy of AF is based on stroke prevention with systemic anticoagulation and adequate heart rate control. Atrioventricular node ablation and biventricular pacing is appropriate for patient who fail to achieve rate control targets with medications or are unable to tolerate medical therapy. Aggressive rhythm control with increasingly important role of the catheter ablation is reserved for patients who remain symptomatic despite successful rate control.

References

1. Braunwald E. Shattuck Lecture – cardiovascular medicine at the turn of the millennium: triumphs, concerns, and opportunities. N Engl J Med. 1997;337:1360–9.
2. Wang TJ, Larson MG, Levy D, et al. Temporal relations of atrial fibrillation and congestive heart failure and their joint influence on mortality: the Framingham Heart Study. Circulation. 2003;107:2920–5.
3. Stevenson WG, Stevenson LW. Atrial fibrillation in heart failure. N Engl J Med. 1999;341:910–1.

4. Ehrlich JR, Nattel S, Hohnloser SH. Atrial fibrillation and congestive heart failure: specific considerations at the intersection of two common and important cardiac disease sets. J Cardiovasc Electrophysiol. 2002;13:399–405.
5. Carson PE, Johnson GR, Dunkman WB for the V-HeFT VA Cooperative Studies Group. The influence of atrial fibrillation on prognosis in mild to moderate heart failure. The V-HeFT studies. Circulation. 1993;87:VI-102–10.
6. Deedwania PC, Singh BN, Ellenbogen KA, et al. Spontaneous conversion and maintenance of sinus rhythm by amiodarone in patients with heart failure and atrial fibrillation. Observation from the Veterans Affairs Congestive Heart Failure Trial on Antiarrhythmic Therapy (CHF-STAT). Circulation. 1998;98:2574–9.
7. Middlekauff HR, Stevenson WG, Stevenson LW. Prognostic significance of atrial fibrillation in advanced heart failure. A study of 390 patients. Circulation. 1991;84:40–8.
8. The CONSENSUS Trial Study Group: effects of enalapril on mortality in severe congestive heart failure. Results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). N Engl J Med. 1987;316:1429–35.
9. Allessie MA, Boyden PA, Camm AJ, et al. Pathophysiology and Prevention of Atrial Fibrillation. Circulation. 2001;103:769–77.
10. Wakili R, Voigt N, Kääb S, et al. Recent advances in the molecular pathophysiology of atrial fibrillation. J Clin Invest. 2011;121(8):2955–68.
11. Orejarena L, Vidaillet H, DeStefano F, et al. Paroxysmal supraventricular tachycardia in the general population. J Am Coll Cardiol. 1998;31(1):150–7.
12. Hindricks G, Pokushalov E, Urban L, et al. Performance of a new leadless implantable cardiac monitor in detecting and quantifying atrial fibrillation: results of the XPECT trial. Circ Arrhythm Electrophysiol. 2010;3(2):141–7.
13. 2011 ACCF/AHA/HRS focused update on the management of patients with atrial fibrillation (Updating the 2006 Guideline): a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2011;57(2):223–42.
14. Homma S, Thompson JL, Pullicino PM. WARCEF Investigators Warfarin and aspirin in patients with heart failure and sinus rhythm. N Engl J Med. 2012;366(20):1859–69.
15. Stroke Prevention in Atrial Fibrillation Investigators. Stroke Prevention in Atrial Fibrillation Study: final results. Circulation. 1991;84:527–39.
16. Lane DA, Lip GYH. Use of the CHA2DS2-VASc and HAS-BLED scores to aid decision making for thromboprophylaxis in non-valvular atrial fibrillation. Circulation. 2012;126:860–5.
17. Connolly SJ, Ezekowitz MD, Yusuf S, et al. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med. 2009;361:1139–51.
18. Patel MR, Mahaffey KW, Garg J, et al. Rivaroxaban vs. warfarin in nonvalvular atrial fibrillation. N Engl J Med. 2011;365:883–91.
19. Granger CB, Alexander JH, McMurray JJ, et al. Apixaban vs. warfarin in patients with atrial fibrillation. N Engl J Med. 2011;365:981–92.
20. Connolly SJ, Pogue J, Hart RG, et al. Effect of clopidogrel added to aspirin in patients with atrial fibrillation. N Engl J Med. 2009;360:2066–78.
21. Connolly SJ, Pogue J, Hart R, et al. Clopidogrel plus aspirin versus oral anticoagulation for atrial fibrillation in the Atrial fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events (ACTIVE W): a randomised controlled trial. Lancet. 2006;367:1903–12.
22. Olshansky B, Rosenfeld LE, Warner AL, et al. The Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) study: approaches to control rate in atrial fibrillation. J Am Coll Cardiol. 2004;43:1201–8.
23. Roy D, Talajic M, Nattel S, et al. Rhythm control versus rate control for atrial fibrillation and heart failure. N Engl J Med. 2008;358:2667–77.
24. Kober L, Torp-Pedersen C, McMurray JJ, et al. Increased mortality after dronedarone therapy for severe heart failure. N Engl J Med. 2008;358:2678–87.

25. Connolly SJ, Camm AJ, Halperin JL, et al. Dronedarone in high-risk permanent atrial fibrillation. N Engl J Med. 2011;365:2268–76.
26. Van Gelder IC, Groenveld HF, Crijns HJ, et al. Lenient versus strict rate control in patients with atrial fibrillation. N Engl J Med. 2010;362:1363–73.
27. Doshi RN, Daoud EG, Fellows C, et al. Left ventricular-based cardiac stimulation post AV nodal ablation evaluation (the PAVE study). J Cardiovasc Electrophysiol. 2005;16:1160–5.
28. Leon AR, Greenberg JM, Kanuru N, et al. Cardiac resynchronization in patients with congestive heart failure and chronic atrial fibrillation: effect of upgrading to biventricular pacing after chronic right ventricular pacing. J Am Coll Cardiol. 2002;39:1258–63.
29. Valls-Bertault V, Fatemi M, Gilard M, et al. Assessment of upgrading to biventricular pacing in patients with right ventricular pacing and congestive heart failure after atrioventricular junctional ablation for chronic atrial fibrillation. Europace. 2004;6:438–43.
30. Ganesan AN, Brooks AG, Roberts-Thomson KC, et al. Role of AV nodal ablation in cardiac resynchronization in patients with coexistent atrial fibrillation and heart failure a systematic review. J Am Coll Cardiol. 2012;59:719–26.
31. Torp-Pedersen C, Moller M, Bloch-Thomsen PE, et al. Dofetilide in patients with congestive heart failure and left ventricular dysfunction. Danish Investigations of Arrhythmia and Mortality on Dofetilide Study Group. N Engl J Med. 1999;341:857–65.
32. Singh SN, Fletcher RD, Fisher SG, et al. Amiodarone in patients with congestive heart failure and asymptomatic ventricular arrhythmia. Survival trial of antiarrhythmic therapy in congestive heart failure. N Engl J Med. 1995;333:77–82.
33. Le Heuzey JY, De Ferrari GM, Radzik D, et al. A short-term, randomized, double-blind, Parallel-Group Study to evaluate the efficacy and safety of dronedarone versus amiodarone in patients with persistent atrial fibrillation: the DIONYSOS Study. J Cardiovasc Electrophysiol. 2010;21(6):597–605.
34. Sweeney MO, Bank AJ, Nsah E, et al. Minimizing ventricular pacing to reduce atrial fibrillation in sinus-node disease. N Engl J Med. 2007;357(10):1000–8.
35. Brenyo A, Link MS, Barsheshet A, et al. Cardiac resynchronization therapy reduces left atrial volume and the risk of atrial tachyarrhythmias in MADIT-CRT. J Am Coll Cardiol. 2011;58:1682–9.
36. Gasparini M, Auricchio A, Regoli F, et al. Four-year efficacy of cardiac resynchronization therapy on exercise tolerance and disease progression: the importance of performing atrioventricular junction ablation in patients with atrial fibrillation. J Am Coll Cardiol. 2006;48:734–43.
37. Haissaguerre M, Jais P, Shah DC, et al. Electrophysiological end point for catheter ablation of atrial fibrillation initiated from multiple pulmonary venous foci. Circulation. 2000;101:1409–17.
38. Pappone C, Oreto G, Rosanio S, et al. Atrial electroanatomic remodeling after circumferential radiofrequency pulmonary vein ablation: efficacy of an anatomic approach in a large cohort of patients with atrial fibrillation. Circulation. 2001;104:2539–44.
39. Oral H, Knight BP, Tada H, et al. Pulmonary vein isolation for paroxysmal and persistent atrial fibrillation. Circulation. 2002;105:1077–81.
40. Hsu L-F, Jaïs P, Sanders P, et al. Catheter ablation for atrial fibrillation in congestive heart failure. N Engl J Med. 2004;351:2373–83.
41. Wilton SB, Fundytus A, WA G, et al. Meta-analysis of the effectiveness and safety of catheter ablation of atrial fibrillation in patients with versus without left ventricular systolic dysfunction. Am J Cardiol. 2010;106(9):1284–91.
42. Khan MN, Jaïs P, Cummings J, et al. Pulmonary-vein isolation for atrial fibrillation in patients with heart failure. N Engl J Med. 2008;359(17):1778–85.
43. MacDonald MR, Connelly DT, Hawkins NM, et al. Radiofrequency ablation for persistent atrial fibrillation in patients with advanced heart failure and severe left ventricular systolic dysfunction: a randomised controlled trial. Heart. 2011;97(9):740–7.

44. Jones DG, Haldar SK, Hussain W, et al. A randomized trial to assess catheter ablation versus rate control in the management of persistent atrial fibrillation in heart failure. J Am Coll Cardiol. 2013;61:1894–1903.
45. Marrouche NF, Brachmann J. Catheter ablation versus standard conventional treatment in patients with left ventricular dysfunction and atrial fibrillation (CASTLE-AF) – Study design. PACE. 2009;32:987–94.
46. Rate versus catheter ablation rhythm control in patients with heart failure and high burden atrial fibrillation (RAFT-AF). US National Library of Medicine. NCT01420393. ClinicalTrials.gov; 2016.
47. Atrial fibrillation management in congestive heart failure with ablation (AMICA). US National Library of Medicine. NCT00652522. ClinicalTrials.gov; 2016.

Chapter 15
Ventricular Arrhythmias and Heart Failure

Ethan R. Ellis and Mark E. Josephson

Abbreviations

AAD	Antiarrhythmic drug
ARB	Angiotensin receptor blocker
ARVC	Arrhythmogenic right ventricular cardiomyopathy
BBRVT	Bundle branch reentrant ventricular tachycardia
CMR	Cardiovascular magnetic resonance
DAD	Delayed after-depolarization
EAD	Early after-depolarization
ECG	Electrocardiogram
HCM	Hypertrophic cardiomyopathy
HPS	His-Purkinje system
ICD	Implantable cardioverter-defibrillator
LCSD	Left cardiac sympathetic denervation
LGE	Late gadolinium enhancement
LVEF	Left ventricular ejection fraction
MI	Myocardial infarction
NSVT	Nonsustained ventricular tachycardia
RAAS	Renin-angiotensin-aldosterone system
RFA	Radiofrequency ablation

E.R. Ellis, MD
Cardiac Electrophysiologist, University of Colorado Health,
2121 East Harmony Road, Suite 100, Fort Collins, CO 80528, USA
e-mail: ethan.ellis@uchealth.org

M.E. Josephson, MD (✉)
Harvard Medical School, Cardiovascular Division, Beth Israel Deaconess Medical Center
Harvard-Thorndike Electrophysiology Institute and Arrhythmia Service,
330 Brookline Avenue, Boston, MA 02215, USA
e-mail: mjoseph2@bidmc.harvard.edu

H. Eisen (ed.), *Heart Failure*, DOI 10.1007/978-1-4471-4219-5_15

SCD	Sudden cardiac death
SR	Sarcoplasmic reticulum
VAD	Ventricular assist device
VF	Ventricular fibrillation
VNS	Vagal nerve stimulation
VPDs	Ventricular premature depolarizations
VT	Ventricular tachycardia

Introduction

Sudden death accounts for a significant number of deaths in heart failure patients. A majority of sudden deaths in heart failure are from ventricular tachyarrhythmias [1, 2]. Ventricular tachycardia (VT) is common in heart failure patients and the approach to its evaluation and treatment requires special attention. Unique pathophysiologic changes in cardiomyopathy and heart failure predispose these patients to the development of ventricular arrhythmias. Specifically targeting these changes can be beneficial when developing treatment strategies for VT in heart failure. In this chapter, we will review the mechanisms of arrhythmogenesis as they relate to the heart failure syndrome, the different clinical manifestations of ventricular arrhythmias in heart failure, as well as the most appropriate methods for treating ventricular arrhythmias in heart failure patients to prevent recurrent arrhythmias and sudden cardiac death (SCD).

Mechanisms of Arrhythmogenesis

There are two primary mechanisms of arrhythmogenesis in general: abnormal impulse generation and abnormal impulse conduction leading to reentry. The two basic mechanisms of impulse generation in this context include automaticity, which refers to spontaneous depolarization based on pacemaker membrane currents, and triggered activity, which is dependent on after-depolarizations. Reentry is usually dependent on slow conduction but can also result from repolarization heterogeneity. Although every heart failure etiology has a predilection for a specific mechanism of arrhythmogenesis, all mechanisms of arrhythmogenesis may exist in all forms of heart failure (Table 15.1).

Automaticity

Automaticity in cardiac myocytes may be normal or abnormal. Normal automaticity originates in cells with intrinsic pacemaker properties at baseline whereas abnormal automaticity occurs in cells that do not normally have automaticity but express

Table 15.1 Structural heart disease and ventricular tachycardia mechanisms

Structural heart disease	Reentry	Triggered activity	Automaticity
Infarct-related cardiomyopathy			
Coronary artery disease/Myocardial infarction	++++	+	++
Non-ischemic cardiomyopathy			
Dilated cardiomyopathy	++++	+	++
Hypertrophic cardiomyopathy	++++	+	+
Arrhythmogenic RV cardiomyopathy	++++	+	+
Heart failure	++++	++	+

All three of the classic mechanisms of arrhythmogenesis (reentry, triggered activity, and automaticity) may contribute to the genesis of ventricular arrhythmias in heart failure regardless of the etiology. Here, the frequency of each mechanism based on heart failure etiology is shown. ++++ = very common, ++ = less common, + = rare. See text for discussion

it when membrane properties are altered by disease. Pathological environments lead to a reduction in resting membrane potential and when reduced sufficiently, spontaneous diastolic depolarization may occur and lead to impulse initiation [3]. Some cells, such as Purkinje system myocytes, can display normal and abnormal automaticity, expressing normal automaticity at high levels of membrane potential and abnormal automaticity when the membrane potential is reduced [3]. Ventricular myocytes on the other hand, only develop automaticity when they are partially depolarized due to underlying pathology and automaticity in ventricular myocytes is always abnormal. Under normal conditions, there is a hierarchy of intrinsic pacemaker rates with the sinus node being the most rapid, followed by the atria, the AV node, the His bundle, and the Purkinje fibers respectively. In this hierarchy slower latent pacemaker cells are depolarized by propagating wavefronts originating from faster pacemaker cells preventing them from reaching their own spontaneous depolarization threshold potential. These latent pacemaker cells are inhibited by repeated depolarization, a phenomenon known as overdrive suppression [3, 4]. For automatic VT to occur, the pacemaker rate in the Purkinje cells or ventricular myocytes must increase above that of the sinus node and higher pacemaker cells. The most important cause of this is sympathetic activation, which enhances the rate of spontaneous diastolic depolarization in latent ventricular pacemakers more than the sinus node. Catecholamine stimulation is generally required for the development of automatic ventricular arrhythmias.

Triggered Activity

Triggered activity describes impulse initiation dependent on after-depolarizations, which are oscillations in membrane potential that follow the upstroke of an action potential. There are two kinds of after-depolarizations. One occurs early during repolarization (early after-depolarizations (EADs)) and the other is delayed until repolarization is complete or nearly complete (delayed after-depolarizations

(DADs)) [5, 6]. A triggered impulse is initiated when an after-depolarization depolarizes a cell to its threshold potential leading to initiation of an action potential. A triggered action potential can then be followed by another after-depolarization that may or may not reach threshold. When it does reach threshold, a "train" of additional triggered action potentials can occur each arising from the after-potential caused by the previous action potential.

DADs occur when Ca^{2+} in the myoplasm and sarcoplasmic reticulum (SR) increases above normal levels ("calcium overload"). Abnormalities in the sequestration and release of Ca^{2+} by the SR may also contribute to their occurrence. When intracellular Ca^{2+} is elevated, Ca^{2+} in the SR may rise during repolarization to a critical level at which time a secondary, spontaneous release of Ca^{2+} occurs after the action potential generating a transient inward current (the DAD) [3, 5, 6]. This increase in intracellular Ca^{2+} may be a result of increase in heart rate or premature stimulation, digitalis inhibition of Na+/K+ pump, catecholamine enhanced L-type Ca^{2+} current, or other effects of pathology that increase Ca^{2+} loading such as heart failure or hypertrophy [3, 5, 6].

As opposed to DADs, EADs occur when repolarization of the action potential does not follow the normal smooth trajectory but suddenly shifts in a depolarizing direction. This occurs when outward current slows or inward current increases, at least transiently. When the relationship between inward and outward current is altered such that depolarization reaches threshold, inward current can be reactivated causing an action potential upstroke [5, 7, 8]. EADS occur under conditions that delay repolarization resulting in prolongation of the action potential duration, either by increasing inward current or decreasing outward current. They occur more readily in Purkinje fibers than in ventricular or atrial muscle. Antiarrhythmic drugs that prolong the duration of the action potential of Purkinje fibers (i.e. class III antiarrhythmic drugs (AADs) such as sotalol and dofetilide or class IA AADs such as quinidine) can cause EADs through inhibition of the I_{Kr} repolarizing current [9]. Hypoxia, the combination of hypoxia and acidosis with or without catecholamines, and stretch are other causes of EADs to name a few [3, 5]. All causes of EADs are manifest on the surface electrocardiogram (ECG) as QT prolongation. EADs are the trigger of functional reentrant excitation leading to polymorphic VT.

Slow Conduction and Reentry

Reentrant excitation requires a region of unidirectional block, at least transiently, allowing for propagation of an impulse in one direction while preventing excitation in the other direction over the return pathway, which the impulse eventually uses to reenter the region and re-excite. Transient block can occur after rapid repetitive activation or after premature excitation. Reentry also may occur when there is permanent unidirectional block. In addition, for reentry to recur, the impulse conducting through the reentrant pathway must find excitable tissue. This requires that

conduction time around the circuit is longer than the effective refractory period of the myocardium from which it originated. Slow conduction and/or short refractory periods permit reentry to occur and are often a consequence of underlying pathology. The reentrant circuit can have an anatomical component with a central obstacle or it may be functional with its size and shape determined by electrophysiologic properties of the involved tissue.

Myocardial fibrosis and scarring in a diseased heart affects conduction by several mechanisms. It increases the extracellular resistivity of myocyte bundles leading to slow conduction and block. Fibrosis can also distort the size and shape of myocardial bundles trapped in scar tissue leading to changes in their conductive properties. Changes in cell-to-cell connections caused by fibrosis can also lead to conduction abnormalities in the diseased heart. During normal conduction of an impulse, axial current flows from one myocardial cell to another through gap junctions [10]. Gap junctions are specialized regions of close interaction between neighboring myocytes in which clusters of transmembrane channels bridge the paired plasma membranes [11]. Gap junctions are mainly located at the ends of myocytes in the intercalated disks and provide low resistance pathways for current flow between cells, which is important for impulse propagation. The primary proteins making up the channels of gap junctions are called connexins. Connexin 43 is the primary connexin found in the ventricles [12, 13] whereas connexin 40 is primarily found in the His-Purkinje system (HPS). The orientation of gap junctions leads to more rapid conduction through the ventricular myocardium in the longitudinal direction, a property termed anisotropic conduction [14, 15]. This property can be altered by fibrosis and remodeling of gap junctions, which may predispose a diseased heart to slow conduction, unidirectional block, and reentry. An increased resistance to axial current flow caused by pathological structural alterations in gap junctions decreases the magnitude and spread of current along a myocardial bundle which can decrease conduction velocity and cause conduction block. The most important causes of slow conduction and reentry are connexin dysfunction and fibrosis, which often coexist (Fig. 15.1).

Heart Failure and Arrhythmogenesis

As previously mentioned, all of the classic mechanisms of arrhythmogenesis may play a role in the development of ventricular arrhythmias in heart failure. Fibrosis and scarring of the ventricles due to myocardial infarction (MI), pathologic hypertrophy, non-infarct related fibrosis, or myocardial dysplasia predispose patients with cardiomyopathy to reentrant ventricular arrhythmias. Heart failure is associated with changes in the cardiac ion channel currents that lead to abnormal depolarization and repolarization, predisposing to automatic and triggered activity. These changes are at least in part due to the neurohormonal activation and biomechanical abnormalities associated with the heart failure syndrome (Table 15.2).

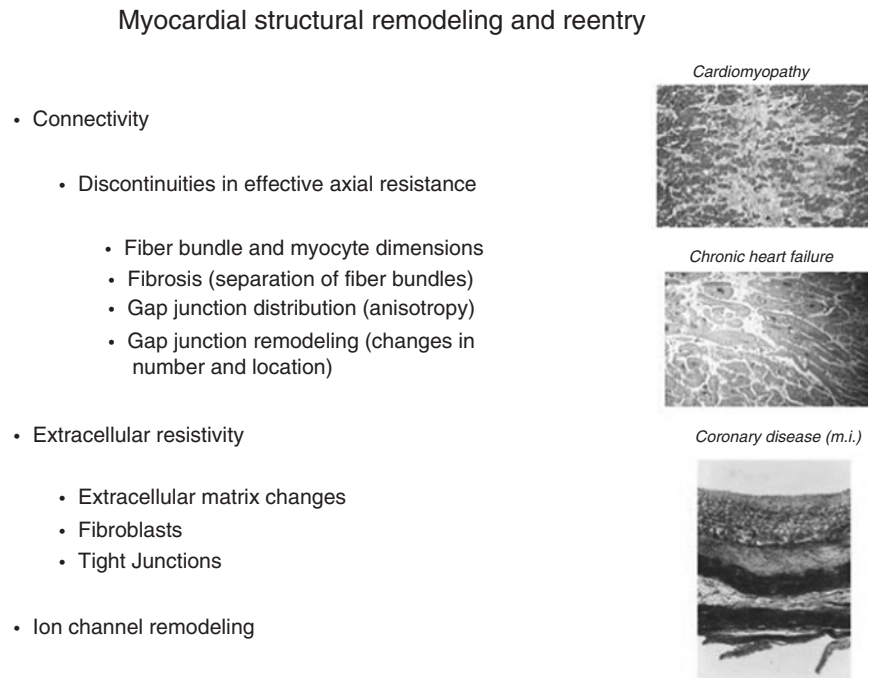


Fig. 15.1 Myocardial Structural Remodeling Promotes Conditions for Reentry**.** Structural heart disease in heart failure and cardiomyopathy leads to pathophysiologic changes which result in abnormal impulse formation and propagation setting the stage for reentrant excitation. Abnormalities in cell-to-cell connectivity, extracellular resistance, and ion channel remodeling all contribute to the increased likelihood of reentrant arrhythmias in heart failure and cardiomyopathy. See text for discussion

Fibrosis

Fibrosis is the most common cause of functional and anatomic block leading to slow conduction and reentry and occurs in both infarct-related and nonischemic cardiomyopathies. The pattern and extent of fibrosis may range from patchy areas in some forms of heart failure to extensive fibrotic scars in MI. In infarct-related cardiomyopathies, fibrosis replaces necrotic regions and may extend into non-infarcted bordering regions. The number of cell-to-cell contacts is reduced with side-to-side connections selectively affected [16, 17]. In healing infarct border zones, increased interstitial collagen disrupts the long transversely oriented gap junctions enhancing anisotropy by increasing the axial resistivity transverse to the long fiber axis [17]. Gap junctions at the ends of myocytes undergo fewer changes. Thus the normal property of uniform anisotropy is converted to non-uniform anisotropy [16, 17].

When there is a large scar such as in hearts with myocardial infarcts, “peninsulas” and bridges of intact myocytes can project into or completely across areas of

Table 15.2 Components of the arrhythmogenic substrate in structural heart disease

Structural heart disease	Fibrosis	Myocyte hypertrophy	Non-uniform anisotropy	Gap junction remodeling	Neural factors	Ion channel changes
Infarct-related cardiomyopathy						
Coronary artery disease/Myocardial infarction	+++	+++	+++	+++	+++	+++
Non-ischemic cardiomyopathy						
Dilated cardiomyopathy	+++	+++	? (likely)	+++	+++	??
Hypertrophic cardiomyopathy	+++	+++	? (likely)	+++	??	??
Arrhythmogenic RV cardiomyopathy	+++	+++	? (likely)	+++	??	??
Heart failure	+++	+++	? (likely)	+++	+++	+++

Multiple pathophysiologic changes occur in cardiomyopathy and heart failure that predispose patients to the development ventricular arrhythmias. The most common pathophysiologic changes are shown as is the frequency with which they are seen based on the type of underlying structural heart disease. +++ = common, ?(likely) = probable, ?? = unknown. See text for discussion

fibrosis termed "channels". Myocytes in these bridges sometimes link with normal myocytes on the outer borders of the infarct [18]. Slow conduction can result from circuitous, nonuniform propagation through these myocardial bundles trapped in scar tissue, so-called "zig-zag conduction" [19]. The effects of fibrosis on conduction is often detectable by low amplitude, long duration, fractionated electrograms with delayed activation, the basis for substrate mapping for ablation of VT [20]. The number of fractionated electrograms seen during endocardial substrate mapping has been shown to correlate with the likelihood of inducible monomorphic ventricular tachycardia at the time of electrophysiology study [21]. Fractionated electrograms are also more likely to be seen during endocardial mapping in patients with infarct-related and nonischemic cardiomyopathy who present with VT when compared to patients with no VT, nonsustained ventricular tachycardia (NSVT), or cardiac arrest [22].

Ischemia

Acute ischemia may result in abnormal automaticity or focal discharges from calcium overload and triggered activity in the form of delayed or early afterdepolarizations [23, 24]. Acute ischemia activates the ATP-sensitive potassium (K_{ATP}) channels, causing an increase in extracellular potassium in the cardiac muscle. Minor increases in extracellular potassium depolarize the myocyte's resting membrane potential, which can increase tissue excitability in early phases of ischemia [25]. Further hyperkalemia causes greater resting depolarization, decreased

conduction velocity and tissue excitability, and shortening of the action potential duration, but prolongs the effective refractory period due to post-repolarization refractoriness [25]. These changes provide a substrate for injury current to flow between ischemic and nonischemic cells located in border zones, which can promote focal abnormal automaticity and initiate VT [26, 27].

Action Potential Prolongation and Abnormal Calcium Handling

Prolongation of the action potential has been repeatedly demonstrated in isolated myocytes [28] and intact ventricular preparations [29] from failing hearts independent of the cause. Downregulation of the transient outward current (I_{to}) is the most consistent ionic current change observed in heart failure [30–32] but downregulation of other potassium channel currents including $I_{K1,}$ I_{Kr}, and I_{Ks} have also been reported in several models of heart failure [30, 33–37]. Another mechanism for altered repolarization is a late sodium current, found in high density in myocytes of animals with chronic heart failure [38].

Alterations in Ca^{2+} handling are also involved in action potential prolongation and a predisposition to ventricular arrhythmias in heart failure. Abnormal intracellular calcium handling is a prominent feature of myocytes from failing hearts [39, 40]. Variable changes in the Na^+/Ca^+ exchanger have been reported with the majority of studies reporting an increase in function [41]. Downregulation of SERCA is also a consistent finding across studies [42–44] as is an increased open probability of the ryanodine receptor (the calcium release channel of the SR) [45, 46]. The basis for delayed afterdepolarizations is spontaneous calcium release from the SR which is facilitated by the presence of beta-adrenergic stimulation and the increased open probability of the ryanodine receptor [47]. Several studies have shown that adrenergic stimulation is necessary for the eliciting spontaneous calcium release from the SR and delayed afterdepolarizations [47, 48]. The calcium released is removed from the cell by the electrogenic Na^+/Ca^{2+} exchanger whose function is upregulated in heart failure. This leads to a transient inward Na^+ current that causes the delayed after-depolarization [49]. This is facilitated by the higher resting membrane potential created by a decrease in outward potassium current.

As previously mentioned, Purkinje myocytes are commonly the sources of afterdepolarizations associated with triggered arrhythmias and these cells undergo substantial remodeling of both K^+ and Ca^{2+} currents, prolonging the action potential and leading to labile repolarization in these cells [50]. Prolongation of the action potential duration associated with down regulation of repolarizing currents and an increase in depolarizing currents lead to spatially and temporally labile repolarization that can predispose to after-depolarization-mediated triggered activity and functional reentry. The existence of after-depolarizations and reentry are not mutually exclusive. After-depolarizations that are of sufficient amplitude to illicit an action potential may serve to initiate an arrhythmia while reentry may sustain such arrhythmias [2].

Mechanical Factors

Mechanical abnormalities in patients with heart failure such as increased wall stress and cavitary dilatation can alter the electrophysiologic properties of myocardial tissue, termed mechanoelectric feedback [51, 52]. In the normal heart, acute myocardial stretch exaggerates the normal rate-dependent shortening of refractoriness but does not influence transverse or longitudinal conduction velocity [53]. In contrast, an animal model found that the development of dilated cardiomyopathy resulted in significant prolongation of refractoriness and repolarization that increased further by volume augmentation and was not reversed by pharmacologic load reduction [54]. Stretch has also been shown to cause a reduction of connexin 43 as well as its redistribution to the lateral sarcolemmal membranes resulting in slowing of conduction in the transverse direction, predisposing these cells to reentry [55]. In human studies, direct correlations between left ventricular end-diastolic volume and the prevalence of ventricular arrhythmia have been seen [56]. It has also been reported that the typical QT prolongation seen in patients with advanced heart failure can be significantly reversed by mechanically unloading the left ventricle with a left ventricular assist device [57].

Altered Neurohormonal Signaling

Activation of the adrenergic and renin-angiotensin-aldosterone system (RAAS) is known to be important in the progression of heart failure. Inhibition of these pathways in randomized clinical trials has been associated with reduction in overall mortality as well as SCD mortality [58–64]. Heart failure is associated with enhancement in sympathetic activity and a reduction in parasympathetic activity [65, 66]. This neurohormonal activation likely influences the substrate and triggers for ventricular arrhythmias in heart failure. In ventricular biopsies and autopsy specimens, an increased density and exaggerated spatial heterogeneity of sympathetic nerves have been associated with a previous history of ventricular arrhythmias in cardiomyopathies [67]. In the normal ventricle, sympathetic stimulation shortens the action potential duration and reduces the dispersion of repolarization, both associated with a decrease in arrhythmia potential [68]. However, in heart failure, sympathetic stimulation is a potent stimulus for the generation of arrhythmias perhaps by enhancing the dispersion of repolarization. Beta-adrenergic stimulation is known to have significant effects on calcium handling as noted above [2]. Elevated levels of sympathetic stimulation enhance the rate of spontaneous diastolic depolarization in latent ventricular pacemakers more than the sinus node which can lead to the development of automatic arrhythmias. Increases in intrinsic heart rate in the setting of sympathetic stimulation can also increase the likelihood of occurrence of triggered arrhythmias [6]. Furthermore, catecholamines can alter conduction and refractoriness, which may promote functional block and facilitate reentry.

RAAS signaling has numerous effects on the cardiovascular system that increase heart failure patients' propensity to develop ventricular arrhythmias. The two major effectors of the RAAS axis, angiotensin II and aldosterone, are upregulated in heart failure and have prominent effects on properties of myocardial cells [2]. Angiotensin II can indirectly promote arrhythmia formation via potassium and magnesium loss in the urine resulting in prolongation of repolarization. It can also potentiate the effects of the sympathetic nervous system. Vasoconstriction caused by RAAS activation alters loading conditions, affecting wall stress and mechanical factors. Angiotensin II and aldosterone also promote generation of fibrosis in the myocardium by myofibroblasts [69]. Angiotensin II has also been shown to influence gap junction coupling in cardiac cells [70] possibly related to abnormal phosphorylation of connexin 43 [71] leading to nonuniform anisotropy and promoting reentry. Angiotensin II can also inhibit a number of K^+ currents including the transient outward K^+ current (I_{to}) and delayed rectifier K^+ currents (I_{Kr}) in the myocardium [72–75].

Conduction System Disease and Bundle Branch Reentry

The QRS prolongation that often accompanies progression of myocardial disease can predispose patients to a unique arrhythmia called bundle branch reentrant ventricular tachycardia (BBRVT) [76, 77]. The unique properties of the HPS allow for rapid conduction and long refractory periods ordinarily preventing sustained reentry. However, conditions that result in prolongation of conduction in the HPS such as cardiomyopathy can facilitate sustained reentry [78]. Three circuits have been described in BBRVT. The first utilizes anterograde conduction over the right bundle branch and retrograde conduction over the left bundle branch with the His bundle adjacent to but separate from the circuit. The second form utilizes the left bundle as its anterograde limb and the right bundle for retrograde conduction. In more rare circumstances, intrafasicular reentry can also occur with the separate fascicles of the left bundle branch being used for the reentrant circuit [79]. Most patients that develop BBRVT tend to have advanced structural heart disease and QRS prolongation in the form of bundle branch block or nonspecific conduction delay. Although most have a baseline bundle branch block, the QRS prolongation in these patients is generally due to delayed conduction in one or both of the bundle branches rather than true block as complete block would not allow propagation of wavefronts retrogradely, which is required to facilitate reentry. This delay tends to be a result of the severity of the underlying heart disease with cardiac enlargement and heart failure being common.

Ventricular Arrhythmias and Heart Failure Etiology

The management and prognosis of ventricular arrhythmias vary based on the etiology of the underlying cardiomyopathy as well as the characteristics of the clinical arrhythmia. Although certain types of cardiomyopathy may predispose patients to

the development of certain types of arrhythmias, all mechanisms of arrhythmogenesis can exist in all forms of heart failure. For example, sustained monomorphic VT due to reentry is common in infarct-related cardiomyopathy. However, such patients may also have tachycardias due to triggered activity from sites more classically associated with idiopathic VT such as the outflow tracts, fascicles, and coronary cusps. Similarly, certain cardiomyopathies may have a predisposition towards the development of arrhythmias originating in certain anatomic areas, such as the right ventricular inflow and outflow tracts in arrhythmogenic right ventricular cardiomyopathy. However, arrhythmias may originate from areas outside of these more classic sites in the same patients.

Infarct-Related Cardiomyopathy

Sustained monomorphic VT occurs most frequently in the setting of a healed MI and may occur in the subacute phase or long after the acute ischemic injury [80]. The extent of myocardial necrosis and subsequent fibrosis as well as the degree of left ventricular dysfunction are important determinants of arrhythmia risk following an MI. The overall incidence of sustained VT following an MI was classically reported to be between 3 and 5 percent but has been estimated to have declined to 1 % in recent years due to advances in revascularization resulting in smaller infarct scars [80]. Although most VTs in infarct-related cardiomyopathy are sustained through a reentrant mechanism, focal activation by abnormal automaticity or triggered activity from the ischemic border zone may serve to initiate the tachycardia, especially in the setting of ischemia. Reentry is the mechanism underlying VT associated with healed or healing MIs in more than 95 % of cases [80].

The 12-lead ECG during VT can provide important information regarding the presence or absence of prior myocardial infarction and localization of the VT origin. In the setting of prior MI, VT tends to arise subendocardially in the region of myocardial scarring. This results in qR or QR patterns of the QRS complexes overlying areas of infarction reflecting terminal activation of the subepicardium. A QS pattern can also occur in the setting of a prior full thickness MI. However, in this setting, the QS pattern represents a cavity potential and is of no value in localizing the VT origin. In the absence of a prior MI, such as in nonischemic cardiomyopathy, a QS pattern of the QRS complex may suggest an epicardial origin of the VT (Fig. 15.2).

Although several possible anatomic abnormalities allowing for reentry in the setting of MI have been postulated, it is now accepted that reentry in the presence of MI utilizes surviving bundles of myocardium within the scar, separated by connective tissue, fibrosis, and disordered intercellular coupling [81] (Fig. 15.3). Evidence for this hypothesis includes the fact that fixed areas of slow conduction can be mapped during sinus rhythm in patients with VT and ablation at these sites can effectively eliminate VT [80]. The triggers for initiation of VT in this setting are increased in situations such as acute heart failure decompensation, which lead to surges in autonomic tone, electrolyte imbalances, and acute ischemia [24, 80].

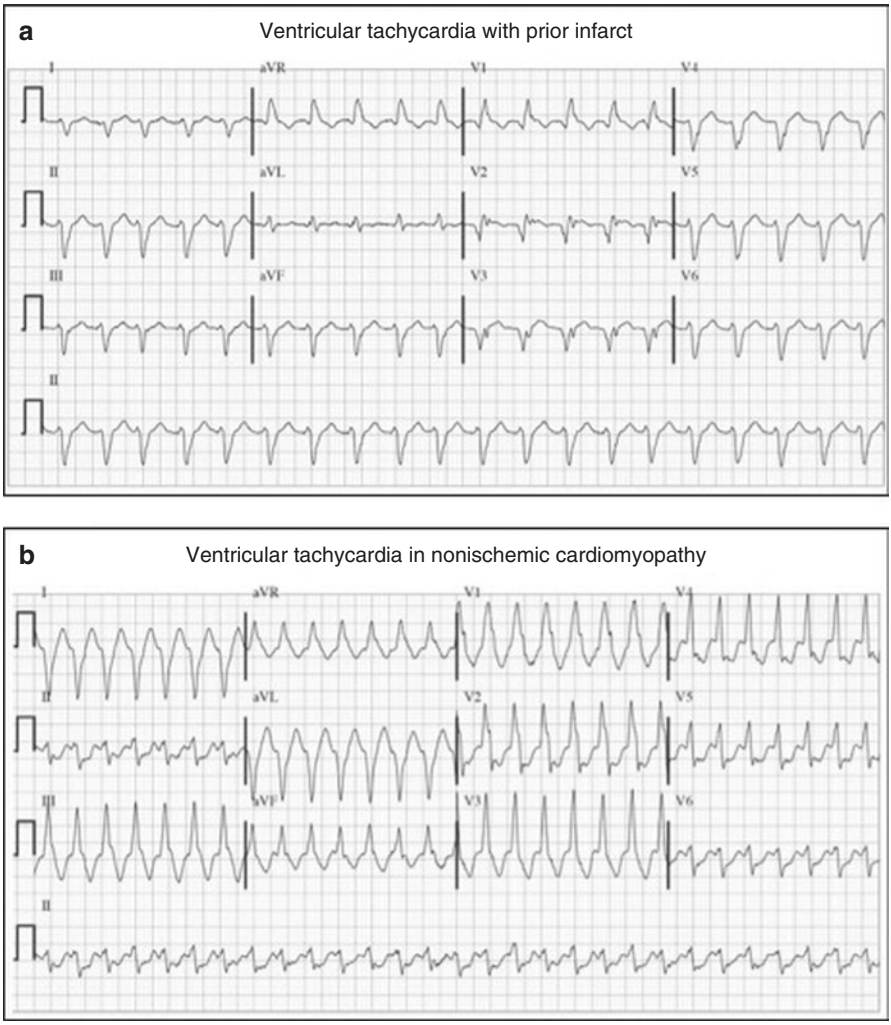


Fig. 15.2 The 12-lead ECG of VT in the presence and absence of prior myocardial infarction. Panel (**a**) is the ECG of a monomorphic VT in a patient with a prior anteroseptal MI. The QRS complexes in the anterior precordial leads demonstrate a qR pattern in a distribution consistent with the previous anteroseptal MI representing terminal activation of the subepicardium in this region. Panel (**b**) is the ECG of a monomorphic ventricular tachycardia in a patient with nonischemic cardiomyopathy and no history of prior MI. None of the QRS complexes demonstrate a qR pattern consistent with the nonischemic substrate. The QS pattern seen in the lateral leads suggests an epicardial origin of the VT given the absence of prior infarction. See text for discussion

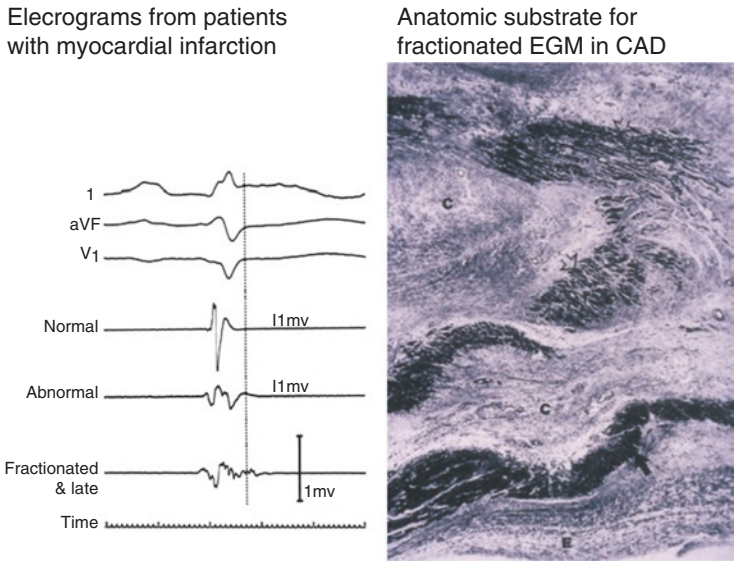


Fig. 15.3 The Anatomic substrate for fractionated electrograms in coronary artery disease (CAD). Most ventricular tachycardias in the setting of prior myocardial infarction are sustained through a reentrant mechanism. Reentry is facilitated by slow conduction through surviving myocardial bundles trapped inside fibrotic myocardium. This slow conduction is detectable by low amplitude fractionated and late potentials with delayed activation represented above, *left*. Above *right*, fibrosis and scar from a prior myocardial infarction is pictured at the microscopic level. See text for discussion

Dilated Cardiomyopathy

The pathophysiologic basis for ventricular arrhythmias in dilated cardiomyopathies is not well understood although several possible mechanisms have been postulated [80]. Extensive myocardial abnormalities, fibrosis, and the loss of cell-to-cell coupling in patients with dilated cardiomyopathy may provide the substrate for reentry. Increased levels of fibrosis in the endocardium as well as the epicardium lead to increase in tissue anisotropy, particularly from epicardium to endocardium [82]. Most endocardial scars in dilated cardiomyopathy tend to be adjacent to the valve annulus while epicardial scars in these patients are often greater in extent than on the endocardium [83]. These epicardial scars may facilitate reentry due to development of conduction block in lines parallel to the epicardial fiber orientation between the epicardium and endocardium [82]. Focal mechanisms may also contribute to the genesis of ventricular arrhythmias in these patients. Spontaneous and induced VT in patients with dilated cardiomyopathy have been found to arise in the subendocardium

through triggered activity from early or delayed after-depolarizations without evidence of reentry [84]. Patients with dilated cardiomyopathy have been shown to have nonhomogeneous distribution of sympathetic fibers. Regions with dense fibrosis show myocardial denervation similar to what is seen in a scar due to MI while other regions may show an increase in sympathetic innervations [85]. It is postulated that denervation hypersensitivity could lead to a regional increase in sensitivity to catecholamines. Patients with severe heart failure requiring transplantation have been shown to have regional increases in sympathetic nerves around diseased myocardium and blood vessels and this was shown to be more pronounced in patients with a history of VT [67]. Autoantibodies against beta-1 adrenergic receptors have also been detected in up to 50 percent of patients with dilated cardiomyopathy, some subgroups of which can exert sympathomimetic activity [86]. These autoantibodies have been associated with increased rates of ventricular arrhythmias in heart failure patients as well [86, 87]. It is important to note that patients with dilated cardiomyopathy are ten times more likely to develop cardiac arrest associated with polymorphic VT or ventricular fibrillation (VF) than to develop hemodynamically tolerated sustained monomorphic VT and this is likely an underestimate as this experience only includes survivors or cardiac arrest [80].

Hypertrophic Cardiomyopathy

Multiple variations of hypertrophic cardiomyopathy (HCM) exist with different clinical manifestations depending on the site and extent of hypertrophy. The hemodynamic consequences of myocardial hypertrophy in these patients include left ventricular outflow tract obstruction, mitral regurgitation, diastolic dysfunction, and myocardial ischemia. These patients have an increased likelihood of developing ventricular arrhythmias. Similar to all other etiologies of heart failure, it is thought that myocardial fibrosis, potentially related to ischemic damage, plays an important role in the arrhythmogenic substrate of HCM [88]. Late gadolinium enhancement (LGE) on cardiovascular magnetic resonance (CMR) imaging is a common finding in HCM patients, likely reflecting collagen deposition and fibrosis [89–91]. The extent of LGE in HCM patients has been correlated with SCD risk factors [90] as well as frequency of ventricular premature depolarizations (VPDs) and NSVT on ambulatory monitoring [92]. Although sustained monomorphic VT may occur in the presence of HCM, similar to dilated cardiomyopathies, these patients more commonly have cardiac arrest due to polymorphic VT or VF [80].

Arrhythmogenic Right Ventricular Cardiomyopathy

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is characterized by fibrous or fibro-fatty replacement of the right ventricular myocardium in the inflow tract, outflow tract, or apex of the right ventricle. The right ventricular myocardial

scarring initially produces regional wall motion abnormalities but as the disease progresses, it may involve the free wall and become global with right ventricular dilatation [93]. In some cases the left ventricle may also be involved [94]. These areas of scarring tend to be the focus of ventricular arrhythmias in patients with ARVC who often present with sustained or nonsustained monomorphic VT originating in the right ventricle. VTs originate from areas where scarring develops, most commonly the inflow tract, apex, or outflow tract of the right ventricle. As in the case with dilated cardiomyopathy, the fibrosis and scarring in this setting tends to be more pronounced in the epicardium than the endocardium. For individuals with advanced fibrosis, VT tends to be due to macroreentry in areas of epicardial scar. However, in patients with earlier stages of disease, VT may be due to triggered or automatic activity in the diseased myocardium, often related to adrenergic stimulation. In such instances, VT and SCD are often exercise-induced [95]. Exercise is thought to increase the risk of sudden death in ARVC patients, potentially due to catecholamine effects on triggered or automatic activity or due to the increased stress placed on the right ventricle during exercise [96]. Animal models of ARVC have suggested that exercise increases right ventricular dilatation and worsens manifestations of the disease [97]. In regards to the relationship of catecholamines and VT in patients with ARVC, a higher frequency of induced ventricular arrhythmias in patients with ARVC on isoproterenol infusion has been reported when compared to control patients [98]. Onset of VT has also been shown to be associated with gradual rises in sinus rates and shortening of coupling intervals prior to initiation suggesting an increase in sympathetic tone may play a role in initiation [99].

Ventricular Arrhythmias and Risk of Sudden Death

Ventricular arrhythmias in heart failure patients may range from VPDs to VF leading to SCD. VPDs occur in 70 to 95 percent of patients with heart failure [100–102]. The significance of these beats varies according to the etiology of the cardiomyopathy. VPDs in a patient with prior MI are associated with an increased risk of death. However, in patients with non-infarct-related cardiomyopathy, VPDs have not been uniformly shown to be associated with a worse prognosis [103]. The use of AADs to suppress VPDs has been shown to be harmful regardless of the etiology of heart failure due to their proarrhythmic effects [104, 105]. On the other hand, beta-blockers can often suppress VPDs and are indicated for most forms of heart failure regardless of the presence or absence of arrhythmias. In rare cases, very frequent VPDs may cause or worsen left ventricular dysfunction or patients may be highly symptomatic despite beta blockade. In such circumstances, treatment with AADs and catheter ablation is often necessary and can improve left ventricular function [106, 107]. When AADs are necessary, amiodarone has been shown to be safe in heart failure patients but it is not used for the routine suppression of ventricular arrhythmias as it has not been shown to provide any survival benefit [108, 109].

NSVT has been reported in 50 to 80 percent of heart failure patients on ambulatory monitoring [101, 110, 111]. The significance of NSVT in heart failure is similar

to that of VPDs. In patients with infarct-related cardiomyopathy [112, 113] and hypertrophic cardiomyopathy [114–116], NSVT has been associated with increased mortality. However, this has not been reliably shown in other forms of heart failure such as dilated cardiomyopathy [101, 111, 117] and heart failure related to valvular disease [118]. As is the case with VPDs, there is no clear role for pharmacologic suppression of NSVT to reduce the risk of SCD, but NSVT can be an indication for electrophysiology study in order to better risk stratify heart failure patients with the hopes of determining who may benefit from implantable cardioverter-defibrillator (ICD) therapy [119, 120]. Like VPDs, in rare cases, very frequent NSVT can contribute to or exacerbate left ventricular dysfunction and may require more aggressive therapies such as AADs or catheter ablation.

Sustained VT is far less frequent than VPDs and NSVT in heart failure patients. Several studies have reported an incidence of sustained VT in patients with heart failure or cardiomyopathy of 5 % or less [101, 110, 111]. However, VT and VF cause the majority of sudden deaths in heart failure patients [1]. It is notable that all types of ventricular arrhythmias, including VPDs, NSVT, and sustained VT have been associated with increased mortality for most groups of heart failure patients. Despite the increased mortality associated with ventricular arrhythmias in heart failure, the rates of sudden cardiac death are not increased. Even as total mortality rises, the percentage of patients dying suddenly remains the same across groups. Approximately half of all deaths in heart failure patients are sudden, regardless of the amount of ventricular ectopy. For any given patient, the greater the severity of the heart failure, the more likely they are to die suddenly, irrespective to their history of ventricular arrhythmias.

Effect of Heart Failure Medications

Multiple classes of medications have been shown to improve mortality in heart failure patients due to systolic dysfunction. Standard therapy includes beta-blockers, ace inhibitors, angiotensin receptor blockers (ARBs), and aldosterone antagonists. Beta-blockers have been shown in multiple trials to impart a survival benefit to heart failure patients, mainly due to a significant reduction in SCD [61, 63, 121]. As previously discussed, heart failure is associated with enhancement of sympathetic activity and a reduction in parasympathetic activity [65, 66]. An increase in sinus rates in heart failure patients may be associated with an increased risk of sudden death, most likely due to an excess of sympathetic activity [2]. This may be because rapid rates increase the likelihood of triggered arrhythmias [6]. Although heart rate reduction has been associated with a survival benefit in heart failure patients, for any given reduction in heart rate and any baseline heart rate, beta blockade has been shown to further improve survival compared to placebo. This suggests that heart rate reduction is not the only mechanism responsible for the beneficial effects of beta blocker therapy [61].

Ace inhibitors and ARBs have been shown to improve all cause mortality in heart failure. However, their effects on SCD are less clear. Several major trials found that the survival benefit was primarily due to slowed progression of heart failure with little or no reduction in sudden death [60, 122, 123]. However, other large trials have found ace inhibitors and ARBs to be associated with significant reductions in sudden death [124–126]. Less controversial is the effect of aldosterone antagonists on sudden death. Both spironolactone and eplerenone have been shown to significantly reduce overall mortality and sudden death in patients with advanced heart failure [59, 127]. Spironolactone has also been shown to reduce the frequency of VPDs and NSVT [128]. The mechanisms by which modulation of the RAAS axis might decrease the risk of sudden death is not well understood. However, possible effects may include reverse remodeling of the arrhythmogenic substrate, decreased proliferation of fibrosis, and fewer effects of angiotensin II and aldosterone on active membrane properties [2]. Ace inhibitors and ARBs have been shown to prevent myocyte uncoupling and improve gap junction conductance through modulation of connexin 43 which may decrease the likelihood of sustained reentrant arrhythmias [55, 71]. Ace inhibitors, ARBs, and aldosterone antagonists may also decrease risk of ventricular arrhythmias through maintenance of a higher serum potassium concentration and decreased prolongation of action potential duration.

Therapies for Ventricular Arrhythmias

Ventricular arrhythmias are of greatest concern in heart failure patients because of the risks of developing a fatal arrhythmia leading to SCD. Although heart failure patients represent a high-risk group of patients for SCD, only a minority of patients with heart failure develops fatal ventricular arrhythmias. Knowing this, antiarrhythmic medications and ICDs that prevent or abort SCD will benefit some patients but most high-risk patients will never require these interventions [129]. Interventions that prevent or abort SCD carry risks. Multiple large randomized controlled trials have demonstrated that antiarrhythmic drugs have significant and often fatal proarrhythmic effects [104, 130]. ICDs have risks as well including infectious complications, inappropriate ICD discharges, and device malfunctions [131]. Furthermore, ICDs may have proarrhythmic effects [132]. Further advances in risk stratification of heart failure patients will be an important role of future research.

Antiarrhythmic Drug Therapy

The role of AADs for ventricular arrhythmias in patients with heart failure is limited. The use of AADs for suppression of ventricular arrhythmias fell out of favor after the CAST trial demonstrated that AADs had significant, often proarrhythmic

effects [104]. This was later confirmed in large randomized trials, suggesting AADs might harm more patients than they benefit. Beyond their proarrhythmic effects, most antiarrhythmic drugs also have some negative inotropic activity, which can produce heart failure in patients with ventricular dysfunction [133]. Low cardiac output and the associated renal dysfunction that is common in heart failure can impair elimination of these drugs, increasing the risk of drug toxicity. Some of the AADs, particularly the class I and class III agents exert a strong proarrhythmic effect. Heart failure is a risk factor for the development of torsades de pointes in patients receiving the class III agents ibutilide, sotalol, and dofetilide. Amiodarone is generally considered to be less proarrhythmic than other AADs and is often the preferred drug for treatment of ventricular arrhythmias in heart failure. Amiodarone trials have shown mixed results on mortality and SCD [120, 134–136]. The 2005 ACC/AHA guidelines on the management of chronic heart failure do not recommend amiodarone for the prevention of SCD but concluded that the evidence was in favor of efficacy for its use for reducing the frequency of ICD shocks in patients with recurrent ventricular arrhythmias [137].

Catheter Ablation

Radiofrequency ablation (RFA) can be an effective treatment for VT, particularly in patients with prior MI. In such patients the endocardial border zones of scar are frequently the sites of reentrant circuits, which tend to be amenable to ablation. Ventricular arrhythmias in patients with nonischemic cardiomyopathy are more challenging to treat with catheter ablation as they often have more diffuse myocardial disease and may have multiple reentrant circuits on the endocardium as well as epicardium [83]. Due to this more complex substrate, RFA tends to be less effective in such patients. Catheter ablation can be used as an alternative treatment strategy in patients who do not want an ICD or who are not considered candidates for ICD implantation. RFA can also be a useful adjunct to an ICD in patients who have frequent arrhythmias and ICD shocks to reduce subsequent ICD therapies. Catheter ablation has also been shown to be effective at reducing the incidence of ICD shocks prophylactically in patients with a history of MI who received ICDs for secondary prevention of sudden death [138]. For patients with bundle branch reentrant VT (BBRVT), RFA is front line therapy where catheter ablation of the right bundle branch can eliminates the arrhythmia. The 2006 ACC/AHA/ESC guidelines recommend patients with BBRVT undergo electrophysiology study and ablation [139].

Surgical Treatment

Map-guided surgical ablative therapy is an effective treatment for VT in patients with a prior MI and scar-related reentrant VT [140, 141] although it has little role in patients with more diffuse cardiomyopathy. Surgery for VT was more common

prior to the advent of catheter ablation and ICD therapy and the successes of these therapies have made VT surgery relatively uncommon. Despite its current infrequent use, the results of VT surgery were excellent in appropriately selected patients with experienced centers achieving over 90 % freedom from recurrent clinical VT in patients surviving surgery. Among those patients, more than half did not need adjuvant antiarrhythmic therapy [142]. VT surgery is particularly effective for patients whose VT is associated with a discrete aneurysm. ICDs, while responding to an episode of VT by pacing or shocking the heart to a stable rhythm, effectively prevent fatal consequences, but do not prevent further episodes of VT. Surgery for VT can offer a cure to appropriate patients at higher rates than would be expected with catheter ablation due to the amount of tissue damage achieved in surgery as compared to catheter ablation [142]. Advances in revascularization techniques and improvement in medical therapy for heart failure has led to a large reduction in patients presenting with large aneurysms and sustained monomorphic VT. A decline in the number of surgeons and electrophysiologists who are experienced in surgical techniques for VT due to coronary disease has limited the development of further refinements in VT surgery. However, given its high success rates for patients with heart failure and VT related to prior MI and aneurysm, we hope its utilization increases so that it does not become obsolete [142].

Implantable Cardioverter-Defibrillators

ICD therapy has been shown to be effective in aborting sudden arrhythmic death and is primarily employed for patients with cardiomyopathy and heart failure. In this section we will focus on the utility of ICDs for the secondary prevention of sudden death in heart failure patients with ventricular arrhythmias. In regards to ICD implantation for primary prevention of sudden death, it is important to note that no randomized controlled trials have demonstrated a statistically significant mortality benefit in patients with nonischemic cardiomyopathy although a mortality benefit has been demonstrated in infarct-related cardiomyopathy [143].

The indications for ICDs for secondary prevention in heart failure patients with a history of ventricular arrhythmias have rapidly expanded over the past 15 years. The results of several clinical trials have quickly been implemented into guidelines and subsequently routine clinical practice. However, ICD implantation carries risks including infection, inappropriate or unnecessary shocks, potential for proarrhythmia, device malfunctions, and procedural complications [131, 132]. Furthermore, not all patients who meet criteria for a secondary prevention ICD will have a recurrent arrhythmia as their cause of death. Thus, there is a need for better risk stratification strategies and a reappraisal of the strengths and limitations of evidence supporting ICD implantation [143].

Most patients with heart failure and cardiomyopathy who have had serious ventricular arrhythmias in the absence of a clearly reversible cause are candidates for ICD implantation based on current guidelines [144]. These recommendations are based mainly on the results of three randomized clinical trials and a pooled analysis

of these studies, which compared ICDs to antiarrhythmic drug therapy in survivors of SCD as well as high-risk patients with sustained VT. These studies found that ICD therapy was associated with a decrease in arrhythmic death as compared to antiarrhythmic therapy and a mortality benefit was seen in the largest of the three studies [145–150]. Although these trials were not limited to patients with heart failure or cardiomyopathy, a significant percentage had a reduced left ventricular ejection fraction (LVEF). A more detailed analysis of the results of these studies is imperative before applying the overall results to determine ICD indications in heart failure patients with ventricular arrhythmias. In the AVID trial, the largest and best-designed secondary prevention trial and the only one to demonstrate a statistically significant total mortality reduction with ICD therapy, the magnitude of benefit for ICD therapy may have been influenced by an imbalance in beta blocker usage between groups (38.1 % in the ICD arm vs. 11.0 % in the antiarrhythmic arm at 12 months of follow up). There was also a lower incidence of congestive heart failure in the ICD group and a higher incidence of NYHA functional class III heart failure in the antiarrhythmic group [143]. Similar to the AVID trial, the CIDS trial had more frequent use of beta-blockers in the ICD arm although the difference was less pronounced than in the AVID trial [151]. In the pooled analysis of AVID, CIDS, and CASH, over a follow up period of 6 years, prolongation of life in patients with ICDs was 4.4 months and the advantages of ICD therapy seemed to be present only in the first 3–4 years of follow-up. A subgroup analysis showed that in patients with EF>35 %, ICD therapy did not improve survival [148]. One could argue that in patients with LVEF>35 %, an ICD confers a relatively small and transient survival benefit for secondary prevention of SCD, which might be minimized in the current era of routine beta-blocker therapy and other highly effective heart failure therapies [151]. The benefits of an ICD in patients with severe left ventricular dysfunction have also been brought into question given the increased likelihood of nonarrhythmic death in these patients. However, current guidelines do not stratify recommendations for secondary prevention based upon LVEF. Although there are certain patients that will clearly benefit from ICD implantation to prevent recurrent malignant ventricular arrhythmias and sudden death, applying simplified guidelines to a complex patient population poses clear risks to patients without guaranteed benefits and an individualized approach to these patients is vital.

Left Ventricular Assist Devices and Cardiac Transplantation

Sustained ventricular tachycardia in patients with advanced heart failure can be a potentially life-threatening arrhythmia, especially when associated with hemodynamic embarrassment. This becomes of particular concern when such patients are refractory to antiarrhythmic drugs and hemodynamic stability limits the safety of catheter or surgical ablation strategies. Percutaneous circulatory assist devices are now being used to provide hemodynamic support during VT ablation allowing for entrainment mapping of sustained VT as well as prolonged substrate mapping and

ablation [152, 153]. Unfortunately, durable cure of sustained recurrent VT with catheter ablation in the setting of advanced heart failure can be difficult to achieve. For patients with a high burden of ventricular arrhythmias, ventricular assist devices (VADs) can provide circulatory support to the failing ventricle even if a patient is in ventricular tachycardia for a substantial amount of time. Surgical implantation of a VAD has been used to hemodynamically stabilize patients with VT storm and advanced cardiomyopathy [154, 155]. Such an intervention may prevent further episodes of VT by unloading the left ventricle and can also provide a bridge to cardiac transplantation [156]. If VT does recur after VAD implant, the device will provide hemodynamic support for potential mapping and successful ablation has been reported in VAD patients [157, 158]. Should patients continue to have recurrent symptomatic ventricular tachycardia refractory to medical therapy, ICD implantation, catheter ablation, and VT surgery, consideration of cardiac transplant evaluation could be recommended [159].

Autonomic Nervous System Modulation

As has been described, heart failure is associated with dysfunction of the autonomic nervous system, which plays a role in heart failure patients increased susceptibility to ventricular arrhythmias. Beyond regulation of the autonomic nervous system with medications, surgical and device-based therapies have also been employed for the treatment of ventricular arrhythmias. Left cardiac sympathetic denervation (LCSD) is a well-established treatment for patients with refractory ventricular arrhythmias in long QT syndrome and arrhythmogenic channelopathies and has recently been shown to be effective in patients with cardiomyopathy [160–162]. The procedure involves resection of the lower half of the left stellate ganglion and thoracic ganglia 2–4, which diminishes noradrenergic input to the left ventricular myocardium. The result is an adequate denervation without a significant Horner's syndrome, since most sympathetic innervation to the eye arises from the upper ganglion. Early studies have also shown that LCSD may have beneficial effects in heart failure patients irrespective of its effects on ventricular arrhythmias [163]. Percutaneous stellate ganglia and thoracic sympathetic blocks or ablation have also been utilized for refractory ventricular tachycardia and have the benefit of being less invasive [164–166].

Vagal nerve stimulation (VNS) has also been shown to provide a protective effect against ventricular arrhythmias and preclinical studies have suggested that VNS will be effective at improving heart failure as well [167, 168]. Multiple studies have demonstrated a reduced incidence of ventricular arrhythmias with VNS in animals with cardiomyopathy and heart failure [169, 170]. Early human trials have suggested that VNS is safe and feasible in chronic heart failure patients and may improve quality of life and left ventricular function [171]. Two large-scale clinical trials are currently underway to assess the efficacy of VNS for management of chronic heart failure [172, 173].

Further data from these and future trials will likely aid in our understanding of the effects of VNS on ventricular arrhythmias in chronic heart failure.

Conclusion

Understanding the mechanisms of arrhythmogenesis and the pathophysiologic changes in heart failure that predispose patients to ventricular tachycardia is important in the overall management of these complex cardiovascular patients. Through advances in medical knowledge and technologies, treatment strategies continue to target the underlying arrhythmia substrate and the pathologic changes of the heart failure syndrome, which will remain the cornerstone of VT treatment in cardiomyopathy.

References

1. Janse MJ. Electrophysiological changes in heart failure and their relationship to arrhythmogenesis. Cardiovasc Res. 2004;61(2):208–17.
2. Tomaselli GF, Zipes DP. What causes sudden death in heart failure? Circ Res. 2004;95(8):754–63. doi:10.1161/01.Res.0000145047.14691.Db.
3. Wit A. The ventricular arrhythmias of ischemia and infarction: electrophysiological mechanisms. Mt Kisco: Futura; 1980.
4. Mangoni ME, Nargeot J. Genesis and regulation of the heart automaticity. Physiol Rev. 2008;88(3):919–82. doi:10.1152/Physrev.00018.2007.
5. Cranefield P, Aronson R. Cardiac arrhythmias: the role of triggered activity and other mechanisms. Mt Kisco: Futura; 1988.
6. Wit A, Rosen M. Afterdepolarizations and triggered activity: distinction from automaticity as an arrhythmogenic mechanism. In: The heart and cardiovascular system. New York: Raven Press Ltd.; 1992.
7. Luo CH, Rudy Y. A dynamic model of the cardiac ventricular action potential. Ii. Afterdepolarizations, triggered activity, and potentiation. Circ Res. 1994;74(6):1097–113.
8. Szabo B, Sweidan R, Rajagopalan CV, Lazzara R. Role of Na+:Ca2+ exchange current in Cs(+)-induced early afterdepolarizations in Purkinje fibers. J Cardiovasc Electrophysiol. 1994;5(11):933–44.
9. Kannankeril PJ, Roden DM. Drug-induced long Qt and Torsade De Pointes: recent advances. Curr Opin Cardiol. 2007;22(1):39–43.
10. Kleber AG, Rudy Y. Basic mechanisms of cardiac impulse propagation and associated arrhythmias. Physiol Rev. 2004;84(2):431–88. doi:10.1152/Physrev.00025.2003.
11. Page E. Cardiac gap junctions. In: Fozzard H, Haber E, Jennings R, Katz A, Morgan H, editors. The heart and cardiovascular system. New York: Raven Press; 1992.
12. Severs NJ, Bruce AF, Dupont E, Rothery S. Remodelling of gap junctions and connexin expression in diseased myocardium. Cardiovasc Res. 2008;80(1):9–19. doi:10.1093/Cvr/Cvn133 .Epub 2008 Jun 2
13. Sohl G, Willecke K. Gap junctions and the connexin protein family. Cardiovasc Res. 2004;62(2):228–32. doi:10.1016/J.Cardiores.2003.11.013.
14. Roberts DE, Hersh LT, Scher AM. Influence of cardiac fiber orientation on wavefront voltage, conduction velocity, and tissue resistivity in the dog. Circ Res. 1979;44(5):701–12.
15. Saffitz JE, Davis LM, Darrow BJ, Kanter HL, Laing JG, Beyer EC. The molecular basis of anisotropy: role of gap junctions. J Cardiovasc Electrophysiol. 1995;6(6):498–510.

16. Spach MS, Dolber PC. Relating extracellular potentials and their derivatives to anisotropic propagation at a microscopic level in human cardiac muscle. Evidence for electrical uncoupling of side-to-side fiber connections with increasing age. Circ Res. 1986;58(3):356–71.
17. Luke RA, Saffitz JE. Remodeling of ventricular conduction pathways in healed canine infarct border zones. J Clin Invest. 1991;87(5):1594–602. doi:10.1172/Jci115173.
18. Smith JH, Green CR, Peters NS, Rothery S, Severs NJ. Altered patterns of gap junction distribution in ischemic heart disease. An Immunohistochemical Study of human myocardium using laser scanning confocal microscopy. Am J Pathol. 1991;139(4):801–21.
19. De Bakker JM, Wittkampf FH. The pathophysiologic basis of fractionated and complex electrograms and the impact of recording techniques on their detection and interpretation. Circ Arrhythm Electrophysiol. 2010;3(2):204–13. doi:10.1161/Circep.109.904763.
20. Gardner PI, Ursell PC, Fenoglio JJ, Jr., Wit AL. Electrophysiologic and anatomic basis for fractionated electrograms recorded from healed myocardial infarcts. Circulation 1985;72(3):596–611.
21. Miller JM, Vassallo JA, Kussmaul 3rd WG, Cassidy DM, Hargrove 3rd WC, Josephson ME. Anterior left ventricular aneurysm: factors associated with the development of sustained ventricular tachycardia. J Am Coll Cardiol. 1988;12(2):375–82.
22. Cassidy DM, Vassallo JA, Buxton AE, Doherty JU, Marchlinski FE, Josephson ME. The value of catheter mapping during sinus rhythm to localize site of origin of ventricular tachycardia. Circulation. 1984;69(6):1103–10.
23. Rubart M, Zipes DP. Mechanisms of sudden cardiac death. J Clin Invest. 2005;115(9):2305–15.
24. Benito B, Josephson ME. Ventricular tachycardia in coronary artery disease. Revista Espanola De Cardiologia. 2012;65(10):939–55. doi:10.1016/J.Recesp.2012.03.027.
25. Carmeliet E. Cardiac ionic currents and acute ischemia: from channels to arrhythmias. Physiol Rev. 1999;79(3):917–1017.
26. Coronel R, Wilms-Schopman FJ, Dekker LR, Janse MJ. Heterogeneities in [K+]O and Tq potential and the inducibility of ventricular fibrillation during acute regional ischemia in the isolated perfused porcine heart. Circulation. 1995;92(1):120–9.
27. Arnar DO, Bullinga JR, Martins JB. Role of the Purkinje system in spontaneous ventricular tachycardia during acute ischemia in a canine model. Circulation. 1997;96(7):2421–9.
28. Tomaselli GF, Marban E. Electrophysiological remodeling in hypertrophy and heart failure. Cardiovasc Res. 1999;42(2):270–83.
29. Akar FG, Rosenbaum DS. Transmural electrophysiological heterogeneities underlying arrhythmogenesis in heart failure. Circ Res. 2003;93(7):638–45. doi:10.1161/01.Res.0000092248.59479.Ae.
30. Beuckelmann DJ, Nabauer M, Erdmann E. Alterations of K+ currents in isolated human ventricular myocytes from patients with terminal heart failure. Circ Res. 1993;73(2):379–85.
31. Nabauer M, Beuckelmann DJ, Erdmann E. Characteristics of transient outward current in human ventricular myocytes from patients with terminal heart failure. Circ Res. 1993;73(2):386–94.
32. Wettwer E, Amos GJ, Posival H, Ravens U. Transient outward current in human ventricular myocytes of subepicardial and subendocardial origin. Circ Res. 1994;75(3):473–82.
33. Kaab S, Nuss HB, Chiamvimonvat N, O'rourke B, Pak PH, Kass DA, Marban E, Tomaselli GF. Ionic mechanism of action potential prolongation in ventricular myocytes from dogs with pacing-induced heart failure. Circ Res. 1996;78(2):262–73.
34. Tsuji Y, Opthof T, Kamiya K, Yasui K, Liu W, et al. Pacing-induced heart failure causes a reduction of delayed rectifier potassium currents along with decreases in calcium and transient outward currents in rabbit ventricle. Cardiovasc Res. 2000;48(2):300–9.
35. Li GR, Lau CP, Ducharme A, Tardif JC, Nattel S. Transmural action potential and ionic current remodeling in ventricles of failing canine hearts. Am J Physiol Heart Circ Physiol. 2002;283(3):H1031–41.
36. Koumi S, Backer CL, Arentzen CE. Characterization of inwardly rectifying K+ channel in human cardiac myocytes. Alterations in channel behavior in myocytes isolated from patients with idiopathic dilated cardiomyopathy. Circulation. 1995;92(2):164–74.

37. Furukawa T, Bassett AL, Furukawa N, Kimura S, Myerburg RJ. The ionic mechanism of reperfusion-induced early afterdepolarizations in feline left ventricular hypertrophy. J Clin Invest. 1993;91(4):1521–31. doi:10.1172/Jci116358.
38. Maltsev VA, Sabbah HN, Higgins RS, Silverman N, Lesch M, Undrovinas AI. Novel, ultraslow inactivating sodium current in human ventricular cardiomyocytes. Circulation. 1998;98(23):2545–52.
39. Gwathmey JK, Copelas L, Mackinnon R, Schoen FJ, Feldman MD, Grossman W, Morgan JP. Abnormal intracellular calcium handling in myocardium from patients with end-stage heart failure. Circ Res. 1987;61(1):70–6.
40. Beuckelmann DJ, Nabauer M, Erdmann E. Intracellular calcium handling in isolated ventricular myocytes from patients with terminal heart failure. Circulation. 1992;85(3):1046–55.
41. Sipido KR, Volders PG, Vos MA, Verdonck F. Altered Na/Ca exchange activity in cardiac hypertrophy and heart failure: a new target for therapy? Cardiovasc Res. 2002;53(4):782–805.
42. Mercadier JJ, Lompre AM, Duc P, Boheler KR, Fraysse JB, Wisnewsky C, et al. Altered sarcoplasmic reticulum Ca2(+)-Atpase gene expression in the human ventricle during end-stage heart failure. J Clin Invest. 1990;85(1):305–9. doi:10.1172/Jci114429.
43. Arai M, Alpert NR, Maclennan DH, Barton P, Periasamy M. Alterations in sarcoplasmic reticulum gene expression in human heart failure. A possible mechanism for alterations in systolic and diastolic properties of the failing myocardium. Circ Res. 1993;72(2):463–9.
44. O'rourke B, Kass DA, Tomaselli GF, Kaab S, Tunin R, Marban E. Mechanisms of altered excitation-contraction coupling in canine tachycardia-induced heart failure, I: experimental studies. Circ Res. 1999;84(5):562–70.
45. Marx SO, Reiken S, Hisamatsu Y, Jayaraman T, Burkhoff D, et al. Pka phosphorylation dissociates Fkbp12.6 from the calcium release channel (ryanodine receptor): defective regulation in failing hearts. Cell. 2000;101(4):365–76.
46. Yano M, Ono K, Ohkusa T, Suetsugu M, Kohno M, Hisaoka T, et al. Altered stoichiometry of Fkbp12.6 versus ryanodine receptor as a cause of abnormal Ca(2+) leak through ryanodine receptor in heart failure. Circulation. 2000;102(17):2131–6.
47. Baartscheer A, Schumacher CA, Belterman CN, Coronel R, Fiolet JW. Sr calcium handling and calcium after-transients in a rabbit model of heart failure. Cardiovasc Res. 2003;58(1):99–108.
48. Vermeulen JT, Mcguire MA, Opthof T, Coronel R, DE Bakker JM, et al. Triggered activity and automaticity in ventricular trabeculae of failing human and rabbit hearts. Cardiovasc Res. 1994;28(10):1547–54.
49. Pogwizd SM, Sipido KR, Verdonck F, Bers DM. Intracellular Na in animal models of hypertrophy and heart failure: contractile function and arrhythmogenesis. Cardiovasc Res. 2003;57(4):887–96.
50. Han W, Chartier D, Li D, Nattel S. Ionic remodeling of cardiac purkinje cells by congestive heart failure. Circulation. 2001;104(17):2095–100.
51. Dean JW, Lab MJ. Arrhythmia in heart failure: role of mechanically induced changes in electrophysiology. Lancet. 1989;1(8650):1309–12.
52. White CW, Mirro MJ, Lund DD, Skorton DJ, Pandian NG, Kerber RE. Alterations in ventricular excitability in conscious dogs during development of chronic heart failure. Am J Physiol. 1986;250(6 Pt 2):H1022–9.
53. Reiter MJ, Landers M, Zetelaki Z, Kirchhof CJ, Allessie MA. Electrophysiological effects of acute dilatation in the isolated rabbit heart: cycle length-dependent effects on ventricular refractoriness and conduction velocity. Circulation. 1997;96(11):4050–6.
54. Zhu WX, Johnson SB, Brandt R, Burnett J, Packer DL. Impact of volume loading and load reduction on ventricular refractoriness and conduction properties in canine congestive heart failure. J Am Coll Cardiol. 1997;30(3):825–33.
55. Hussain W, Patel PM, Chowdhury RA, Cabo C, Ciaccio EJ, Lab MJ, et al. The renin-angiotensin system mediates the effects of stretch on conduction velocity, connexin43 expression, and redistribution in intact ventricle. J Cardiovasc Electrophysiol. 2010;21(11):1276–83. doi:10.1111/J.1540-8167.2010.01802.X.

56. Koilpillai C, Quinones MA, Greenberg B, Limacher MC, Shindler D, Pratt CM, et al. Relation of ventricular size and function to heart failure status and ventricular dysrhythmia in patients with severe left ventricular dysfunction. Am J Cardiol. 1996;77(8):606–11.
57. Xydas S, Rosen RS, Ng C, Mercando M, Cohen J, Ditullio M, et al. Mechanical unloading leads to echocardiographic, electrocardiographic, neurohormonal, and histologic recovery. J Heart Lung Transplant. 2006;25(1):7–15 Epub 2005 Nov 10. doi:10.1016/J.Healun.2005.08.001.
58. Yusuf S, Sleight P, Pogue J, Bosch J, Davies R, Dagenais G. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. The Heart Outcomes Prevention Evaluation Study Investigators. New Engl J Med. 2000;342(3):145–53. doi:10.1056/Nejm200001203420301.
59. Pitt B, Zannad F, Remme WJ, Cody R, Castaigne A, Perez A, et al. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators. New Engl J Med. 1999;341(10):709–17. doi:10.1056/Nejm199909023411001.
60. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. The Solvd Investigators. N Engl J Med. 1991;325(5):293–302. doi:10.1056/Nejm199108013250501.
61. The cardiac insufficiency bisoprolol study Ii (Cibis-Ii): a randomised trial. Lancet. 1999;353(9146):9–13.
62. A trial of the beta-blocker bucindolol in patients with advanced chronic heart failure. N Engl J Med. 2001;344(22):1659–67. doi:10.1056/Nejm200105313442202.
63. Effect of metoprolol Cr/Xl in chronic heart failure: metoprolol Cr/Xl randomised intervention trial in congestive heart failure (Merit-Hf) (1999). Lancet. 1999;353(9169):2001–7.
64. Kober L, Torp-Pedersen C, Carlsen JE, Bagger H, Eliasen P, Lyngborg K, et al. A clinical trial of the angiotensin-converting-enzyme inhibitor trandolapril in patients with left ventricular dysfunction after myocardial infarction. Trandolapril Cardiac Evaluation (Trace) Study Group. N Engl J Med. 1995;333(25):1670–6. doi:10.1056/Nejm199512213332503.
65. Porter TR, Eckberg DL, Fritsch JM, Rea RF, Beightol LA, et al. Autonomic pathophysiology in heart failure patients. Sympathetic-Cholinergic Interrelations. J Clin Inv. 1990;85(5):1362–71. doi:10.1172/Jci114580.
66. Binkley PF, Nunziata E, Haas GJ, Nelson SD, Cody RJ. Parasympathetic withdrawal is an integral component of autonomic imbalance in congestive heart failure: demonstration in human subjects and verification in a paced canine model of ventricular failure. J Am Coll Cardiol. 1991;18(2):464–72.
67. Cao JM, Fishbein MC, Han JB, Lai WW, Lai AC, Wu TJ, et al. Relationship between regional cardiac hyperinnervation and ventricular arrhythmia. Circulation. 2000;101(16):1960–9.
68. Takei M, Sasaki Y, Yonezawa T, Lakhe M, Aruga M, Kiyosawa K. The autonomic control of the transmural dispersion of ventricular repolarization in anesthetized dogs. J Cardiovasc Electrophysiol. 1999;10(7):981–9.
69. Kim S, Iwao H. Molecular and cellular mechanisms of angiotensin Ii-mediated cardiovascular and renal diseases. Pharmacol Rev. 2000;52(1):11–34.
70. Dhein S. Pharmacology of gap junctions in the cardiovascular system. Cardiovasc Res. 2004;62(2):287–98. doi:10.1016/J.Cardiores.2004.01.019.
71. Iravanian S, Sovari AA, Lardin HA, Liu H, Xiao HD, Dolmatova E, et al. Inhibition of renin-angiotensin system (Ras) reduces ventricular tachycardia risk by altering connexin43. J Mol Med (Berl). 2011;89(7):677–87. doi:10.1007/S00109-011-0761-3.
72. Yu H, Gao J, Wang H, Wymore R, Steinberg S, Mckinnon D, et al. Effects of the renin-angiotensin system on the current I(To) in epicardial and endocardial ventricular myocytes from the canine heart. Circ Res. 2000;86(10):1062–8.
73. Daleau P, Turgeon J. Angiotensin Ii modulates the delayed rectifier potassium current of guinea pig ventricular myocytes. Pflugers Archiv Eur J Physiol. 1994;427(5–6):553–5.
74. Clement-Chomienne O, Walsh MP, Cole WC. Angiotensin Ii activation of protein kinase C decreases delayed rectifier K+ current in rabbit vascular myocytes. J Physiol. 1996;495(Pt 3):689–700.

75. Caballero R, Delpon E, Valenzuela C, Longobardo M, Tamargo J. Losartan and its metabolite E3174 modify cardiac delayed rectifier K(+) currents. Circulation. 2000;101(10):1199–205.
76. Lloyd EA, Zipes DP, Heger JJ, Prystowsky EN. Sustained ventricular tachycardia due to bundle branch reentry. Am Heart J. 1982;104(5 Pt 1):1095–7.
77. Caceres J, Jazayeri M, Mckinnie J, Avitall B, Denker S, et al. Sustained bundle branch reentry as a mechanism of clinical tachycardia. Circulation. 1989;79(2):256–70.
78. Balasundaram R, Rao HB, Kalavakolanu S, Narasimhan C. Catheter ablation of bundle branch reentrant ventricular tachycardia. Heart Rhythm. 2008;5(6 Suppl):S68–72. doi:10.1016/J.Hrthm.2008.02.036.Epub 2008 Mar 4.
79. Tchou P, Mehdirad AA. Bundle branch reentry ventricular tachycardia. Pacing Clin Electrophysiol PACE. 1995;18(7):1427–37.
80. Josephson ME. Recurrent ventricular tachycardia. In: Clinical cardiac electrophysiology. 4th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2008. p. 446–642.
81. Lazzara R, Scherlag BJ. Mechanisms of monomorphic ventricular tachycardia in coronary artery disease. J Interv Card Electrophysiol. 2003;8(2):87–92.
82. Wu TJ, Ong JJ, Hwang C, Lee JJ, Fishbein MC, Czer L, et al. Characteristics of wave fronts during ventricular fibrillation in human hearts with dilated cardiomyopathy: role of increased fibrosis in the generation of reentry. J Am Coll Cardiol. 1998;32(1):187–96.
83. Soejima K, Stevenson WG, Sapp JL, Selwyn AP, Couper G, Epstein LM. Endocardial and epicardial radiofrequency ablation of ventricular tachycardia associated with dilated cardiomyopathy: the importance of low-voltage scars. J Am Coll Cardiol. 2004;43(10):1834–42. doi:10.1016/J.Jacc.2004.01.029.
84. Pogwizd SM, Mckenzie JP, Cain ME. Mechanisms underlying spontaneous and induced ventricular arrhythmias in patients with idiopathic dilated cardiomyopathy. Circulation. 1998;98(22):2404–14.
85. Schofer J, Spielmann R, Schuchert A, Weber K, Schluter M. Iodine-123 meta-iodobenzylguanidine scintigraphy: a noninvasive method to demonstrate myocardial adrenergic nervous system disintegrity in patients with idiopathic dilated cardiomyopathy. J Am Coll Cardiol. 1988;12(5):1252–8.
86. Chiale PA, Ferrari I, Mahler E, Vallazza MA, Elizari MV, et al. Differential profile and biochemical effects of antiautonomic membrane receptor antibodies in ventricular arrhythmias and sinus node dysfunction. Circulation. 2001;103(13):1765–71.
87. Iwata M, Yoshikawa T, Baba A, Anzai T, Mitamura H, Ogawa S. Autoantibodies against the second extracellular loop of beta1-adrenergic receptors predict ventricular tachycardia and sudden death in patients with idiopathic dilated cardiomyopathy. J Am Coll Cardiol. 2001;37(2):418–24.
88. Basso C, Thiene G, Corrado D, Buja G, Melacini P, Nava A. Hypertrophic cardiomyopathy and sudden death in the young: pathologic evidence of myocardial ischemia. Hum Pathol. 2000;31(8):988–98. doi:10.1053/Hupa.2000.16659.
89. Choudhury L, Mahrholdt H, Wagner A, Choi KM, Elliott MD, Klocke FJ, et al. Myocardial scarring in asymptomatic or mildly symptomatic patients with hypertrophic cardiomyopathy. J Am Coll Cardiol. 2002;40(12):2156–64.
90. Moon JC, Mckenna WJ, Mccrohon JA, Elliott PM, Smith GC, Pennell DJ. Toward clinical risk assessment in hypertrophic cardiomyopathy with gadolinium cardiovascular magnetic resonance. J Am Coll Cardiol. 2003;41(9):1561–7.
91. Moon JC, Reed E, Sheppard MN, Elkington AG, Ho SY, Burke M, et al. The histologic basis of late gadolinium enhancement cardiovascular magnetic resonance in hypertrophic cardiomyopathy. J Am Coll Cardiol. 2004;43(12):2260–4. doi:10.1016/J.Jacc.2004.03.035.
92. Adabag AS, Maron BJ, Appelbaum E, Harrigan CJ, Buros JL, Gibson CM, et al. Occurrence and frequency of arrhythmias in hypertrophic cardiomyopathy in relation to delayed enhancement on cardiovascular magnetic resonance. J Am Coll Cardiol. 2008;51(14):1369–74. doi:10.1016/J.Jacc.2007.11.071.
93. Richardson P, Mckenna W, Bristow M, Maisch B, Mautner B, O'connell J, et al. Report of the 1995 World Health Organization/International Society And Federation Of Cardiology Task Force on the definition and classification of cardiomyopathies. Circulation. 1996;93(5):841–2.

94. Pinamonti B, Sinagra G, Salvi A, Di Lenarda A, Morgera T, Silvestri F, et al. Left ventricular involvement in right ventricular dysplasia. Am Heart J. 1992;123(3):711–24.
95. Corrado D, Basso C, Schiavon M, Thiene G. Screening for hypertrophic cardiomyopathy in young athletes. New Engl J Med. 1998;339(6):364–9. doi:10.1056/Nejm199808063390602.
96. Douglas PS, O'toole ML, Hiller WD, Reichek N. Different effects of prolonged exercise on the right and left ventricles. J Am Coll Cardiol. 1990;15(1):64–9.
97. Kirchhof P, Fabritz L, Zwiener M, Witt H, Schafers M, Zellerhoff S, et al. Age- and training-dependent development of arrhythmogenic right ventricular cardiomyopathy in heterozygous plakoglobin-deficient mice. Circulation. 2006;114(17):1799–806. doi:10.1161/Circulationaha.106.624502.
98. Haissaguerre M, Le Metayer P, D'ivernois C, Barat JL, Montserrat P, Warin JF. Distinctive response of arrhythmogenic right ventricular disease to high dose isoproterenol. Pacing Clin Electrophysiol PACE. 1990;13(12 Pt 2):2119–26.
99. Leclercq JF, Potenza S, Maison-Blanche P, Chastang C, Coumel P. Determinants of spontaneous occurrence of sustained monomorphic ventricular tachycardia in right ventricular dysplasia. J Am Coll Cardiol. 1996;28(3):720–4.
100. Francis GS. Development of arrhythmias in the patient with congestive heart failure: pathophysiology, prevalence and prognosis. Am J Cardiol. 1986;57(3):3b–7b.
101. Teerlink JR, Jalaluddin M, Anderson S, Kukin ML, Eichhorn EJ, Francis G, et al. Ambulatory ventricular arrhythmias in patients with heart failure do not specifically predict an increased risk of sudden death. Promise (Prospective Randomized Milrinone Survival Evaluation) Investigators. Circulation. 2000;101(1):40–6.
102. Podrid PJ, Fogel RI, Fuchs TT. Ventricular arrhythmia in congestive heart failure. Am J Cardiol 1992;69 (18):82g–95g; discussion 95g–6g
103. Packer M. Lack of relation between ventricular arrhythmias and sudden death in patients with chronic heart failure. Circulation. 1992;85(1 Suppl):I50–6.
104. Echt DS, Liebson PR, Mitchell LB, Peters RW, Obias-Manno D, Barker AH, et al. Mortality and morbidity in patients receiving encainide, flecainide, or placebo. The Cardiac Arrhythmia Suppression Trial. N Engl J Med. 1991;324(12):781–8. doi:10.1056/Nejm199103213241201.
105. Teo KK, Yusuf S, Furberg CD. Effects of prophylactic antiarrhythmic drug therapy in acute myocardial infarction. An overview of results from Randomized Controlled Trials. JAMA. 1993;270(13):1589–95.
106. Duffee DF, Shen WK, Smith HC. Suppression of frequent premature ventricular contractions and improvement of left ventricular function in patients with presumed idiopathic dilated cardiomyopathy. Mayo Clinic Proc Mayo Clinic. 1998;73(5):430–3. doi:10.1016/S0025-6196(11)63724-5.
107. Bogun F, Crawford T, Reich S, Koelling TM, Armstrong W, Good E, et al. Radiofrequency ablation of frequent, idiopathic premature ventricular complexes: comparison with a control group without intervention. Heart Rhythm. 2007;4(7):863–7. doi:10.1016/J.Hrthm.2007.03.003.
108. Cairns JA, Connolly SJ, Roberts R, Gent M. Randomised trial of outcome after myocardial infarction in patients with frequent or repetitive ventricular premature depolarisations: Camiat. Canadian Amiodarone Myocardial Infarction Arrhythmia Trial Investigators. Lancet. 1997;349(9053):675–82.
109. Julian DG, Camm AJ, Frangin G, Janse MJ, Munoz A, et al. Randomised trial of effect of amiodarone on mortality in patients with left-ventricular dysfunction after recent myocardial infarction: Emiat. European Myocardial Infarct Amiodarone Trial Investigators. Lancet. 1997;349(9053):667–74.
110. Meinertz T, Hofmann T, Kasper W, Treese N, Bechtold H, Stienen U, et al. Significance of ventricular arrhythmias in idiopathic dilated cardiomyopathy. Am J Cardiol. 1984;53(7):902–7.
111. Singh SN, Fisher SG, Carson PE, Fletcher RD. Prevalence and significance of nonsustained ventricular tachycardia in patients with premature ventricular contractions and heart failure treated with vasodilator therapy. Department Of Veterans Affairs Chf Stat Investigators. J Am Coll Cardiol. 1998;32(4):942–7.

112. Bigger JT, Jr., Fleiss JL, Rolnitzky LM. Prevalence, characteristics and significance of ventricular tachycardia detected by 24-hour continuous electrocardiographic recordings in the late hospital phase of acute myocardial infarction. Am J Cardiol 1986;58(13):1151–60.
113. Mukharji J, Rude RE, Poole WK, Gustafson N, Thomas LJ, Jr., Strauss HW, Et Al. Risk factors for sudden death after acute myocardial infarction: two-year follow-up. Am J Cardiol 1984;54 (1):31–36
114. Mckenna WJ, England D, Doi YL, Deanfield JE, Oakley C, Goodwin JF. Arrhythmia in hypertrophic cardiomyopathy. I: influence on prognosis. Br Heart J. 1981;46(2):168–72.
115. Elliott PM, Poloniecki J, Dickie S, Sharma S, Monserrat L, Varnava A, et al. Sudden death in hypertrophic cardiomyopathy: identification of high risk patients. J Am Coll Cardiol. 2000;36(7):2212–8.
116. Monserrat L, Elliott PM, Gimeno JR, Sharma S, Penas-Lado M, Mckenna WJ. Non-sustained ventricular tachycardia in hypertrophic cardiomyopathy: an independent marker of sudden death risk in young patients. J Am Coll Cardiol. 2003;42(5):873–9.
117. Larsen L, Markham J, Haffajee CI. Sudden death in idiopathic dilated cardiomyopathy: role of ventricular arrhythmias. Pacing Clin Electrophysiol PACE. 1993;16(5 Pt 1):1051–9.
118. Kligfield P, Hochreiter C, Niles N, Devereux RB, Borer JS. Relation of sudden death in pure mitral regurgitation, with and without mitral valve prolapse, to repetitive ventricular arrhythmias and right and left ventricular ejection fractions. Am J Cardiol. 1987;60(4):397–9.
119. Buxton AE, Lee KL, Fisher JD, Josephson ME, Prystowsky EN, Hafley G. A randomized study of the prevention of sudden death in patients with coronary artery disease. Multicenter Unsustained Tachycardia Trial Investigators. New Engl J Med. 1999;341(25):1882–90. doi:10.1056/Nejm199912163412503.
120. Moss AJ, Hall WJ, Cannom DS, Daubert JP, Higgins SL, Klein H, et al. Improved survival with an implanted defibrillator in patients with coronary disease at high risk for ventricular arrhythmia. Multicenter Automatic Defibrillator Implantation Trial Investigators. New Engl J Med. 1996;335(26):1933–40. doi:10.1056/Nejm199612263352601.
121. Packer M, Bristow MR, Cohn JN, Colucci WS, Fowler MB, et al. The effect of carvedilol on morbidity and mortality in patients with chronic heart failure. U.S. Carvedilol Heart Failure Study Group. New Engl J Med. 1996;334(21):1349–55. doi:10.1056/Nejm199605233342101.
122. Pratt CM, Gardner M, Pepine C, Kohn R, Young JB, Greenberg B, et al. Lack of long-term ventricular arrhythmia reduction by enalapril in heart failure. Solvd Investigators. Am J Cardiol. 1995;75(17):1244–9.
123. Effects of enalapril on mortality in severe congestive heart failure. Results of the Cooperative North Scandinavian Enalapril Survival Study (Consensus). The Consensus Trial Study Group. New Engl J Med. 1987;316(23):1429–35. doi:10.1056/Nejm198706043162301.
124. Cleland JG, Erhardt L, Murray G, Hall AS, Ball SG. Effect of ramipril on morbidity and mode of death among survivors of acute myocardial infarction with clinical evidence of heart failure. A report from The Aire Study Investigators. Eur Heart J. 1997;18(1):41–51.
125. Fletcher RD, Cintron GB, Johnson G, Orndorff J, Carson P, Cohn JN. Enalapril decreases prevalence of ventricular tachycardia in patients with chronic congestive heart failure. The V-Heft Ii Va Cooperative Studies Group. Circulation. 1993;87(6 Suppl):Vi49–55.
126. Cohn JN, Johnson G, Ziesche S, Cobb F, Francis G, Tristani F, et al. A comparison of enalapril with hydralazine-isosorbide dinitrate in the treatment of chronic congestive heart failure. New Engl J Med. 1991;325(5):303–10. doi:10.1056/Nejm199108013250502.
127. Pitt B, Remme W, Zannad F, Neaton J, Martinez F, Roniker B, et al. Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. New Engl J Med. 2003;348(14):1309–21. doi:10.1056/Nejmoa030207.
128. Ramires FJ, Mansur A, Coelho O, Maranhao M, Gruppi CJ, et al. Effect of spironolactone on ventricular arrhythmias in congestive heart failure secondary to idiopathic dilated or to ischemic cardiomyopathy. Am J Cardiol. 2000;85(10):1207–11.
129. Thomas KE, Josephson ME. The role of electrophysiology study in risk stratification of sudden cardiac death. Prog Cardiovasc Dis. 2008;51(2):97–105. doi:10.1016/J.Pcad.2008.05.001.

130. Waldo AL, Camm AJ, Deruyter H, Friedman PL, Macneil DJ, Pauls JF, et al. Effect of D-Sotalol on mortality in patients with left ventricular dysfunction after recent and remote myocardial infarction. The Sword Investigators. Survival With Oral D-Sotalol. Lancet. 1996;348(9019):7–12.
131. Reynolds MR, Cohen DJ, Kugelmass AD, Brown PP, Becker ER, et al. The frequency and incremental cost of major complications among medicare beneficiaries receiving implantable cardioverter-defibrillators. J Am Coll Cardiol. 2006;47(12):2493–7. doi:10.1016/J.Jacc.2006.02.049.
132. Germano JJ, Reynolds M, Essebag V, Josephson ME. Frequency and causes of implantable cardioverter-defibrillator therapies: is device therapy proarrhythmic? Am J Cardiol. 2006;97(8):1255–61. doi:10.1016/J.Amjcard.2005.11.048.
133. Amabile CM, Spencer AP. Keeping your patient with heart failure safe: a review of potentially dangerous medications. Arch Intern Med. 2004;164(7):709–20. doi:10.1001/Archinte.164.7.709.
134. Doval HC, Nul DR, Grancelli HO, Perrone SV, Bortman GR, Curiel R. Randomised trial of low-dose amiodarone in severe congestive heart failure. Grupo De Estudio De La Sobrevida En La Insuficiencia Cardiaca En Argentina (Gesica). Lancet. 1994;344(8921):493–8.
135. Effect of prophylactic amiodarone on mortality after acute myocardial infarction and in congestive heart failure: meta-analysis of individual data from 6500 patients in randomised trials. Amiodarone Trials Meta-Analysis Investigators. Lancet. 1997;350(9089):1417–24.
136. Singh SN, Fletcher RD, Fisher SG, Singh BN, Lewis HD, Deedwania PC, et al. Amiodarone in patients with congestive heart failure and asymptomatic ventricular arrhythmia. Survival trial of antiarrhythmic therapy in congestive heart failure. New Engl J Med. 1995;333(2):77–82. doi:10.1056/Nejm199507133330201.
137. Hunt SA, Abraham WT, Chin MH, Feldman AM, Francis GS, Ganiats TG, et al. 2009 focused update incorporated into the Acc/Aha 2005 guidelines for the diagnosis and management of heart failure in adults: a report of the American College Of Cardiology Foundation/American Heart Association Task Force On Practice Guidelines: Developed In Collaboration With The International Society For Heart And Lung Transplantation. Circulation. 2009;119(14):E391–479. doi:10.1161/Circulationaha.109.192065.
138. Reddy VY, Reynolds MR, Neuzil P, Richardson AW, Taborsky M, Jongnarangsin K, et al. Prophylactic catheter ablation for the prevention of defibrillator therapy. N Engl J Med. 2007;357(26):2657–65. doi:10.1056/Nejmoa065457.
139. Zipes DP, Camm AJ, Borggrefe M, Buxton AE, Chaitman B, Fromer M, et al. Acc/Aha/Esc 2006 guidelines for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: a report of the American College Of Cardiology/American Heart Association Task Force And The European Society Of Cardiology Committee For Practice Guidelines (Writing Committee To Develop Guidelines For Management Of Patients With Ventricular Arrhythmias And The Prevention Of Sudden Cardiac Death). J Am Coll Cardiol. 2006;48(5):E247–346. doi:10.1016/J.Jacc.2006.07.010.
140. Josephson ME, Harken AH, Horowitz LN. Endocardial excision: a new surgical technique for the treatment of recurrent ventricular tachycardia. Circulation. 1979;60(7):1430–9.
141. Swerdlow CD, Mason JW, Stinson EB, Oyer PE, Winkle RA, Derby GC. Results of operations for ventricular tachycardia in 105 patients. J Thorac Cardiovasc Surg. 1986;92(1):105–13.
142. Krishnan SC, Josephson ME. Surgery for postinfarction ventricular tachycardia: is it obsolete? Pacing Clin Electrophysiol PACE. 2000;23(8):1295–301.
143. Tung R, Zimetbaum P, Josephson ME. A critical appraisal of implantable cardioverter-defibrillator therapy for the prevention of sudden cardiac death. J Am Coll Cardiol. 2008;52(14):1111–21. doi:10.1016/J.Jacc.2008.05.058.
144. Epstein AE, Dimarco JP, Ellenbogen KA, Estes NA, 3rd, Freedman RA, Gettes LS, et al. Acc/Aha/Hrs 2008 guidelines for device-based therapy of cardiac rhythm abnormalities: a report of the American College Of Cardiology/American Heart Association Task Force On Practice Guidelines (Writing Committee To Revise The Acc/Aha/Naspe 2002 Guideline Update

For Implantation Of Cardiac Pacemakers And Antiarrhythmia Devices): Developed In Collaboration With The American Association For Thoracic Surgery And Society Of Thoracic Surgeons. Circulation 2008;117(21):E350–408. doi:10.1161/Circualtionaha.108.189742.
145. Kuck KH, Cappato R, Siebels J, Ruppel R. Randomized comparison of antiarrhythmic drug therapy with implantable defibrillators in patients resuscitated from cardiac arrest: The Cardiac Arrest Study Hamburg (Cash). Circulation. 2000;102(7):748–54.
146. Connolly SJ, Gent M, Roberts RS, Dorian P, Roy D, Sheldon RS, et al. Canadian Implantable Defibrillator Study (Cids): a randomized trial of the implantable cardioverter defibrillator against amiodarone. Circulation. 2000;101(11):1297–302.
147. A comparison of antiarrhythmic-drug therapy with implantable defibrillators in patients resuscitated from near-fatal ventricular arrhythmias. The Antiarrhythmics Versus Implantable Defibrillators (Avid) Investigators. N Engl J Med. 1997;337(22):1576–83. doi:10.1056/Nejm199711273372202.
148. Connolly SJ, Hallstrom AP, Cappato R, Schron EB, Kuck KH, Zipes DP, et al. Meta-analysis of the implantable cardioverter defibrillator secondary prevention trials. Avid, Cash And Cids Studies. Antiarrhythmics Vs Implantable Defibrillator Study. Cardiac Arrest Study Hamburg. Canadian Implantable Defibrillator Study. Eur Heart J. 2000;21(24):2071–8. doi:10.1053/Euhj.2000.2476.
149. Desai AS, Fang JC, Maisel WH, Baughman KL. Implantable defibrillators for the prevention of mortality in patients with nonischemic cardiomyopathy: a Meta-analysis of Randomized Controlled Trials. JAMA. 2004;292(23):2874–9.
150. Lee DS, Green LD, Liu PP, Dorian P, Newman DM, Grant FC, et al. Effectiveness of implantable defibrillators for preventing arrhythmic events and death: a meta-analysis. J Am Coll Cardiol. 2003;41(9):1573–82.
151. Katritsis DG, Josephson ME. Sudden cardiac death and implantable cardioverter defibrillators: two modern epidemics? Europace. 2012;14(6):787–94. doi:10.1093/Europace/Eus001.
152. Abuissa H, Roshan J, Lim B, Asirvatham SJ. Use of the impella microaxial blood pump for ablation of hemodynamically unstable ventricular tachycardia. J Cardiovasc Electrophysiol. 2010;21(4):458–61. doi:10.1111/J.1540-8167.2009.01673.X.
153. Friedman PA, Munger TM, Torres N, Rihal C. Percutaneous endocardial and epicardial ablation of hypotensive ventricular tachycardia with percutaneous left ventricular assist in the electrophysiology laboratory. J Cardiovasc Electrophysiol. 2007;18(1):106–9. doi:10.1111/J.1540-8167.2006.00619.X.
154. Maile S, Kunz M, Oechslin E, Zund G, Rahn M, et al. Intractable ventricular tachycardia and bridging to heart transplantation with a non-pulsatile flow assist device in a patient with isolated left-ventricular non-compaction. J Heart Lung Transplant. 2004;23(1):147–9.
155. Kulick DM, Bolman 3rd RM, Salerno CT, Bank AJ, Park SJ. Management of recurrent ventricular tachycardia with ventricular assist device placement. Ann Surg. 1998;66(2):571–3.
156. Cesario DA, Saxon LA, Cao MK, Bowdish M, Cunningham M. Ventricular tachycardia in the era of ventricular assist devices. J Cardiovasc Electrophysiol. 2011;22(3):359–63. doi:10.1111/J.1540-8167.2010.01911.X.
157. Osaki S, Alberte C, Murray MA, Brahmbhatt RD, Johnson MR, et al. Successful radiofrequency ablation therapy for intractable ventricular tachycardia with a ventricular assist device. J Heart Lung Transplant. 2008;27(3):353–6. doi:10.1016/J.Healun.2007.11.572.
158. Dandamudi G, Ghumman WS, Das MK, Miller JM. Endocardial catheter ablation of ventricular tachycardia in patients with ventricular assist devices. Heart Rhythm. 2007;4(9):1165–9. doi:10.1016/J.Hrthm.2007.05.029.
159. Lindenfeld J, Albert NM, Boehmer JP, Collins SP, Ezekowitz JA, Givertz MM, et al. Hfsa 2010 comprehensive heart failure practice guideline. J Card Fail. 2010;16(6):E1–194. doi:10.1016/J.Cardfail.2010.04.004.
160. Coleman MA, Bos JM, Johnson JN, Owen HJ, Deschamps C, et al. Videoscopic left cardiac sympathetic denervation for patients with recurrent ventricular fibrillation/malignant ventricular arrhythmia syndromes besides congenital long-Qt syndrome. Circ Arrhythm Electrophysiol. 2012;5(4):782–8. doi:10.1161/Circep.112.971754.

161. Zipes DP, Festoff B, Schaal SF, Cox C, Sealy WC, Wallace Ag. Treatment of ventricular arrhythmia by permanent atrial pacemaker and cardiac sympathectomy. Ann Intern Med. 1968;68(3):591–7.
162. Collura CA, Johnson JN, Moir C, Ackerman MJ. Left cardiac sympathetic denervation for the treatment of long Qt syndrome and catecholaminergic polymorphic ventricular tachycardia using video-assisted thoracic surgery. Heart Rhythm. 2009;6(6):752–9. doi:10.1016/J.Hrthm.2009.03.024.
163. Conceicao-Souza GE, Pego-Fernandes PM, Cruz F, Guimaraes GV, Bacal F, Vieira ML, et al. Left cardiac sympathetic denervation for treatment of symptomatic systolic heart failure patients: a Pilot Study. Eur J Heart Fail. 2012;14(12):1366–73. doi:10.1093/Eurjhf/Hfs132.
164. Tan AY, Abdi S, Buxton AE, Anter E. Percutaneous stellate ganglia block for acute control of refractory ventricular tachycardia. Heart Rhythm. 2012;9(12):2063–7. doi:10.1016/J.Hrthm.2012.07.030.
165. Allen F, Weaver B, Burkey A. Bilateral thoracic sympathetic block for refractory polymorphic tachycardia. Can J Anaesth. 2011;58(12):1110–4. doi:10.1007/S12630-011-9588-1.
166. Patel RA, Priore DL, Szeto WY, Slevin KA. Left stellate ganglion blockade for the management of drug-resistant electrical storm. Pain Med. 2011;12(8):1196–8. doi:10.1111/J.1526-4637.2011.01167.X.
167. Zhang Y, Mazgalev TN. Arrhythmias and vagus nerve stimulation. Heart Fail Rev. 2011;16(2):147–61. doi:10.1007/S10741-010-9178-2.
168. Lopshire JC, Zipes DP. Device therapy to modulate the autonomic nervous system to treat heart failure. Curr Cardiol Rep. 2012;14(5):593–600. doi:10.1007/S11886-012-0292-8.
169. Vanoli E, De Ferrari GM, Stramba-Badiale M, Hull SS, Jr., Foreman RD, Schwartz PJ. Vagal stimulation and prevention of sudden death in conscious dogs with a healed myocardial infarction. Circ Res 1991;68(5):1471–81.
170. Zheng C, Li M, Inagaki M, Kawada T, Sunagawa K, Sugimachi M. Vagal stimulation markedly suppresses arrhythmias in conscious rats with chronic heart failure after myocardial infarction. Conference proceedings: annual international conference of the Ieee Engineering In Medicine And Biology Society Ieee Engineering In Medicine And Biology Society conference. 2005;7:7072–5. Doi:10.1109/Iembs.2005.1616135
171. De Ferrari GM, Crijns HJ, Borggrefe M, Milasinovic G, Smid J, Zabel M, et al. Chronic vagus nerve stimulation: a new and promising therapeutic approach for chronic heart failure. Eur Heart J. 2011;32(7):847–55. doi:10.1093/Eurheartj/Ehq391.
172. Increase Of Vagal Tone In Chf (Inovate-Hf). http://Clinicaltrials.Gov/Ct2/Show/Nct01303718.
173. Neural Cardiac Therapy For Heart Failure Study (Nectar-Hf). http://Clinicaltrials.Gov/Ct2/Show/Nct01385176.

Chapter 16
Cardiac Defibrillators and Heart Failure

Michael L. Bernard and Michael R. Gold

Introduction

Sudden Cardiac Death (SCD) is the leading cause of mortality in the United States and annually claims over 500,000 lives [1]. Initial efforts to prevent SCD were focused on patients who had survived SCD or who had sustained ventricular arrhythmias. However, given the low rate of survival of an out-of-hospital arrest (<5 %), there remained a substantial population at high risk for an initial SCD event [2]. Several landmark trials assessing the impact of Implantable Cardioverter-Defibrillators (ICDs) in addition to conventional medical therapy demonstrated significant reduction in mortality for patients in whom ICDs were implanted. Currently, over 250,000 ICDs are implanted annually in the US with primary prevention serving as the most common indication [3]. The majority of patients undergoing ICD implantation suffer from congestive heart failure (CHF). A summary of indications for ICD implantation in heart failure patients is included in Table 16.1 [3, 4]. The standard of care for patients with persistent systolic dysfunction despite procedural and pharmacologic therapy includes implantation of ICDs in addition to conventional medical therapy. This review will address the role of ICDs in the heart failure population.

M.L. Bernard, MD, PhD
Department of Cardiology, Ochsner Medical Center,
1514 Jefferson Highway, New Orleans, LA 70121, USA
e-mail: mbernard@ochsner.org

M.R. Gold, MD, PhD (✉)
Division of Cardiology, Medical University of South Carolina,
114 Doughty Street, MSC 592, Charleston, SC 29425, USA
e-mail: goldmr@musc.edu

H. Eisen (ed.), *Heart Failure*, DOI 10.1007/978-1-4471-4219-5_16

Table 16.1 ICD guidelines for heart failure patients

Secondary prevention
Class I
ICD therapy is indicated in patients who are survivors of cardiac arrest due to VF or hemodynamically unstable sustained VT after evaluation to define the cause of the event and to exclude any completely reversible causes
ICD therapy is indicated in patients with structural heart disease and spontaneous sustained VT, whether hemodynamically stable or unstable
ICD therapy is indicated in patients with syncope of undetermined origin with clinically relevant, hemodynamically significant sustained VT or VF induced at electrophysiological study
ICD therapy is indicated in patients with nonsustained VT due to prior MI, LVEF less than or equal to 40 %, and inducible VF or sustained VT at electrophysiological study
Class IIa
ICD implantation is reasonable for patients with unexplained syncope, significant LV dysfunction, and nonischemic DCM
ICD implantation is reasonable for patients with sustained VT and normal or near-normal ventricular function
Primary prevention
Class I
ICD therapy is indicated in patients with LVEF less than or equal to 35 % due to prior MI who are at least 40 days post-MI and are in NYHA functional Class II or III
ICD therapy is indicated in patients with nonischemic DCM who have an LVEF less than or equal to 35 % and who are in NYHA functional Class II or III
ICD therapy is indicated in patients with LV dysfunction due to prior MI who are at least 40 days post
ICD in combination with biventricular pacing is indicated for patients who have LVEF less than or equal to 35 %, sinus rhythm, LBBB with a QRS duration greater than or equal to 150 ms, and NYHA class II, III, or ambulatory IV symptoms
Class IIa
ICD implantation is reasonable for non hospitalized patients awaiting transplantation
ICD in combination with biventricular pacing in patients with NYHA functional class II, III or IV, receiving optimal medical therapy, in sinus rhythm with a LBBB QRS 120–149 ms, and a reasonable survival expectation of >1 year
Patients who are at high risk of SCA due to genetic disorders, such as long QT syndrome, Brugada syndrome, hypertrophic cardiomyopathy and arrhythmogenic right ventricular cardiomyopathy (ARVC), and have reasonable expectation of survival with a good functional status at >1 year
ICD implantation is reasonable for patients with cardiac sarcoidosis, giant cell myocarditis, or Chagas disease
Class IIb
ICD therapy may be considered in patients with nonischemic heart disease who have an LVEF of less than or equal to 35 % and who are in NYHA functional Class I

Table 16.1 (continued)

ICD therapy may be considered in patients with syncope and advanced structural heart disease in whom thorough invasive and noninvasive investigations have failed to define a cause
ICD therapy may be considered in patients with a familial cardiomyopathy associated with sudden death
ICD therapy may be considered in patients with LV noncompaction

DMC dilated cardiomyopathy, *LBBB* left bundle branch block, *LV* left ventricular, *LVEF* left ventricular ejection fraction, *MI* myocardial infarction, *NYHA* New York Heart Association, *VF* ventricular fibrillation, *VT* ventricular tachycardia

Secondary Prevention Trials

ICDs were initially studied in patients who survived SCD or in those patients with sustained ventricular arrhythmias. From such secondary prevention trials, several findings suggested that patients with reduced systolic function had the greatest benefit from ICD implantation. In the AVID study, patients who survived SCD or had sustained ventricular arrhythmias were randomized to ICD or Class III antiarrhythmic drug therapy [5]. Left Ventricular Ejection Fraction (LVEF) was 0.31 and 0.32 in the ICD and medical treatment arms, respectively. Fifty-five percent of the ICD group and 60 % of the medical therapy group had clinical heart failure symptoms. The primary outcome was a significant reduction in mortality for patients in the ICD arm. The benefit of ICD therapy was more pronounced among patients with LVEF <0.35. CIDS (Canadian Implantable Defibrillator Study) randomized patients with ventricular arrhythmias to ICD implantation versus amiodarone therapy [6]. The mean LVEF was 0.33 and 0.34 in the ICD and amiodarone groups, respectively, with half of both groups diagnosed with clinical heart failure. Subanalysis of the CIDS population revealed that depressed LVEF (<0.35) and advanced NYHA (New York Heart Association) heart failure class were independent predictors of benefit from ICD therapy [7]. CASH evaluated the effect of metoprolol, propafenone, amiodarone or ICD therapy in survivors of SCD [8]. All patients had clinical heart failure with mean LVEF ranging from 0.44 to 0.47 in the treatment arms. Again, ICD implantation provided a significant reduction in mortality compared with AADs. Furthermore, propafenone increased mortality leading to early cessation of the treatment arm. A meta-analysis of the AVID, CIDS and CASH trials yielded a 28 % relative risk reduction in mortality with ICD therapy compared with amiodarone therapy [9]. Furthermore, the difference in mortality was attributed to a 50 % reduction to arrhythmic deaths in the ICD group. There was no statistical difference between mortality for patients with LVEF >0.35; however among patient(s) with LVEF <0.35, there was a 34 % reduction in mortality with ICD

therapy. Secondary prevention of SCD trials provided the basis for future studies investigating ICD implantation as a primary prevention therapy. Patients with reduced LVEF were identified from these studies as a sub-population with the potential for significant benefit from ICD implantation. Additionally, ICD therapy reduced mortality compared with AAD therapy supporting ICD implantation as first-line therapy for patients with history of SCD or ventricular arrhythmias.

Primary Prevention Trials

Due to the results of secondary prevention trials, the focus of ICD investigation switched to primary prevention of sudden death. Summaries of primary prevention ICD trials are included in Table 16.2. The MADIT and MUSTT trials were the first large primary prevention trials evaluating the impact ICD therapy on mortality. In both studies, the population included those with coronary artery disease, LV systolic dysfunction, non-sustained ventricular tachycardia and inducible sustained ventricular tachycardia. In the MADIT trial, ICD therapy resulted in a 54 % reduction in mortality compared with AAD therapy. The mean LVEF was ~0.25 in the study population and two-thirds of the patients had clinical heart failure. Amiodarone consisted of 74 % of the AAD group and was associated with increased mortality compared with beta blocker therapy. Although ICD was not a treatment arm of the MUSTT trial, the results suggested that patients with inducible ventricular tachycardia at the time of electrophysiology study were at high risk for SCD (MUSTT). Patients with coronary artery disease, LVEF <0.40, and non-sustained ventricular tachycardia underwent electrophysiology study. Patients with inducible sustained ventricular tachycardia were randomized to medical therapy or a strategy of antiarrhythmia guided therapy. In the latter arm, they received antiarrhythmic drugs and if unsuccessful for rendering VT/VF non-inducible then an ICD was implanted. Patients who were non-inducible at baseline were included in a registry. Fourteen percent (49/353) of patients randomized to no AAD therapy after inducible ventricular tachycardia had syncope, sustained ventricular tachycardia or SCD leading to ICD implantation. This was markedly greater than the 3 % (49/1397) of patients that were non-inducible and had similar events leading to ICD implantation. These results suggested that depressed LVEF and inducible ventricular tachycardia were associated with a high risk of SCD. Furthermore, ICD therapy significantly reduced mortality in this population compared with conventional AAD therapy. However, total mortality was less strongly affected by inducibility of VT [10].

Several trials explored the effect of primary prevention ICD implantation at the time of coronary artery revascularization or shortly after myocardial infarction. CABG-PATCH assessed the impact of ICD implantation at the time of coronary artery bypass graft (CABG) surgery for patients at high risk for SCD [11]. There were 900 patients with reduced LVEF and abnormal signal averaged ECG randomized to CABG with or without ICD implantation. The mean age was 62 years old, LVEF was 0.27, and greater than 70 % had NYHA Class II/III heart failure. At the

Table 16.2 Primary prevention ICD trials

Trial	No. of patients	Etiology	Major inclusion criteria	Hazard ratio for overall mortality (ICD)	P value
MADIT	196	ICM	EF ≤35 %, NSVT, inducible VT	0.46	0.009
MUSTT	704	ICM	EF ≤40 %, NSVT, inducible VT	0.45[a]	<0.001
MADIT II	1232	ICM	EF ≤30 %, prior MI	0.69	0.016
SCD-HeFT	2521	ICM & NICM	EF ≤35 %, CHF NYHA Class II or III	0.77	0.007
DEFINITE	458	NICM	EF ≤35 %, PVCs or NSVT	0.65	0.08
COMPANION	1520	ICM & NICM	EF ≤35 %, CHF NYHA Class II or III, QRS >120	0.64[b]	0.003
DINAMIT	676	ICM	EF ≤35 %, ¯HRV, recent MI (<40 days)	1.08	0.66
CABG-PATCH	900	ICM	EF ≤35 %, CABG, abnormal SAECG	1.07	0.64

MADIT Multicenter Automatic Defibrillator Implantation Trial, *MUSTT* Multicenter Unsustained Tachycardia Trial, *SCD-HeFT* Sudden Cardiac Death in Heart Failure Trial, *DEFINITE* Defibrillators in Non-Ischemic Cardiomyopathy Treatment Evaluation; *COMPANION* Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure Trial; *DINAMIT* Defibrillator in Acute Myocardial Infarction Trial, *CABG-PATCH* Coronary Artery Bypass Graft Patch, *ICM* ischemic cardiomyopathy, *EF* ejection fraction, *NSVT* nonsustained VT, *VT* ventricular tachycardia, *MI* myocardial infarction, *NICM* nonischemic cardiomyopathy, *CHF* congestive heart failure, *NYHA* New York Heart Association, *PVC* premature ventricular contraction, *HRV* heart rate variability, *SAECG* signal-averaged ECG

[a]COMPANION results listed are for CRT+ICD vs. medical therapy alone. The hazard ratio for overall mortality for CRT alone vs. medical therapy was 0.76 (P = 0.059)

[b]MUSTT results listed are the adjusted relative risk for overall mortality for patients receiving electrophysiologically guided therapy with an ICD compared with no antiarrhythmic therapy

end of 4 years there was no statistical difference in mortality among the two groups. Subsequent analysis demonstrated that ICD implantation significantly reduced arrhythmic deaths between groups by 45 % [12]. However, due to high percentages of non-arrhythmic death in the population the protective effect of ICD therapy was not effective in reducing all-cause mortality. Furthermore, revascularization may have lead to improvements in LVEF that protected from arrhythmic deaths. The DINAMIT trial evaluated ICD implantation in a high risk population at the time of acute myocardial infarction [13]. Patients with recent (6–40 days) myocardial infarction who had reduced LVEF and autonomic dysfunction (reduced heart rate variability or elevated 24 h average heart rate) were randomized to optimal medical therapy with and without ICD implantation. In 676 patients, the mean LVEF was 0.28, >85 % had NYHA Class II/III heart failure and >70 % of patients suffered a

new Q-wave myocardial infarction. All-cause mortality was not statistically different among the two groups; however, there was a statistically significant reduction in arrhythmic mortality in the ICD (HR 0.42). This was offset by an increase in non-arrhythmic deaths in the ICD group compared with control. The findings do not support implantation of primary prevention ICDs at the time of myocardial infarction. Furthermore this trial was the basis for the 40-day post-MI requirement for ICD implantation in the current guidelines. In a secondary analysis of DINAMIT, mortality in patients with ICD implantation differed greatly by whether they had received appropriate ICD shocks [14]. Patients in the ICD arm with appropriate ICD shocks had 15 % annual mortality compared with 6 % annual mortality in ICD patients with appropriate shocks. Effectively, the reduction in arrhythmic mortality observed in the ICD arm was negated by non-arrhythmic death in those ICD patients receiving appropriate ICD shocks. The DINAMIT results were supported by the IRIS trial where 898 patients with recent (5–31 days) myocardial infarction were randomized to conventional medical therapy with or without ICD implantation [15]. In the IRIS trial many more patients underwent PTCA (72 %) compared with the DINAMIT trial (27 %). There were similar rates of beta blocker and ACE/ARB use in both studies. All-cause mortality at an average of 37 months was not different in the ICD arm (HR 1.04) compared with control. Subgroup analysis demonstrated that patients with left main disease benefitted from ICD therapy whereas those with thrombolytic therapy fared better in the control group. There was a non-significant trend toward NYHA Class III/IV and smoking as predictors of ICD benefit. Similar to the DINAMIT trial, reduction in arrhythmic death in the ICD arm (HR 0.55) was offset by increase in non-arrhythmic death (HR 1.92). The results of the CABG-Patch, DINAMIT and IRIS trials found no mortality benefit of primary prevention ICD implantation in patients with reduced LVEF at the time of CABG or acute myocardial infarction.

MADIT II randomized 1232 patients with prior myocardial infarction and LVEF <0.30 to conventional medical therapy with and without ICD implantation [16]. Compared with MADIT, sustained VT or electrophysiology studies were not required for enrollment. The population was 85 % male with mean LVEF 0.23 in each group. Roughly two-thirds of the patient had at least NYHA Class II heart failure symptoms and 15 % were on AADs. There were 105/742 (14.2 %) and 97/490 (17.9 %) deaths in the ICD and conventional groups, respectively ($p = 0.016$), with a hazard ratio for ICD implantation of 0.69. The trial was stopped prematurely once superiority of ICD therapy was detected. The effect of ICD on survival was not affected by age, sex, LVEF or NYHA Class. These results supported ICD implantation for primary prevention of SCD in patients with reduced LVEF and ischemic cardiomyopathy, a majority of whom have symptomatic heart failure.

The next generation of primary prevention trials included patients with non-ischemic cardiomyopathy as well as ischemic cardiomyopathy. The CAT trial randomized 104 patients with reduced LVEF <0.30 and recent onset (<9 months) of dilated cardiomyopathy to conventional medical therapy with or without ICD implantation [17]. At a mean follow up of 5.5 years there was no statistical difference

in mortality with ICD implantation. Of note, the trial was stopped prematurely due to lower than expected SCD event rates in the control arm at 1 year. AMIOVERT randomized 103 patients with non-ischemic cardiomyopathy, LVEF >0.35 and asymptomatic non-sustained ventricular tachycardia to amiodarone versus ICD implantation [18]. There was no statistical difference in mortality at 1 and 3 years with a non-statistical trend toward reduced arrhythmic burden in the amiodarone arm. The DEFINITE trial [20] enrolled 458 patients with non-ischemic cardiomyopathy and ventricular ectopy to optimal medical therapy versus optimal medical therapy plus ICD. The mean LVEF was 0.21, roughly 80 % had NYHA Class II/III symptoms and clinical heart failure duration was 2.8 years. Beta blocker and ACE/ARB use was ~85 % in the population. ICD therapy reduced all-cause mortality by 35 %, although this was not statistically significant (HR 0.65, CI 0.4–1.06). ICD did significantly reduce arrhythmic deaths (HR 0.2) without changing deaths related to heart failure. Subgroup analysis demonstrated that men and patients with NYHA Class III symptoms benefitted the most from ICD implantation. Age, LVEF and QRS duration had no significant impact on the outcome. All of these studies were underpowered so it is difficult to make conclusions regarding the role of ICD therapy in this population based on these trials.

SCD-HeFT (Sudden Cardiac Death Heart Failure Trial) was the first large randomized trial to evaluate the efficacy of ICD therapy in systolic HF patients with reduced LVEF, regardless of etiology [19]. In contrast to the MADIT trials, patients with non-ischemic cardiomyopathy, in addition to those with ischemic cardiomyopathy, were included in the study. Over 2500 patients with NYHA Class II or III heart failure, LVEF <0.35 were randomized to placebo, amiodarone or ICD implantation. The mean ejection fraction of the population was 0.25 and there were roughly equal non-ischemic and ischemic cardiomyopathy patients. The use of evidence based medical therapy and other appropriate medications were strongly encouraged. ACE/ARBs and beta blockers were being used by 95 and 70 % of patients, respectively, at the time of last follow up. The primary finding was that single chamber ICD implantation imparted a 23 % relative risk reduction (HR 0.77) of all cause mortality that was statistically significant compared with placebo (Fig. 16.1).

The effect was similar in patients with either ischemic cardiomyopathy (HR 0.79) or non-ischemic cardiomyopathy (HR 0.73). The mortality benefit was markedly pronounced in patients with NYHA Class II heart failure (HR 0.54) compared with those with NYHA Class III (HR 1.16). Amiodarone did not significantly reduce mortality (HR 1.06) compared with placebo. There was a statistical trend toward worsened outcomes in NYHA Class III patients on amiodarone therapy (HR 1.44). SCD-HeFT demonstrated that regardless of etiology, patients with reduced LVEF benefited from ICD implantation. A meta-analysis of primary prevention ICD therapy versus conventional medical therapy in non-ischemic patients from SCD-HeFT, DEFINITE, CAT, AMIOVERT and COMPANION [21] trials studied over 1800 patients. The mean ejection fraction of the population was 0.28 with advanced heart failure (NYHA Class III/IV) present in roughly one third of the population. The analysis demonstrated a 31 % relative risk reduction in mortality in ICD recipients [22]. The results of primary prevention trials strongly supported ICD implantation

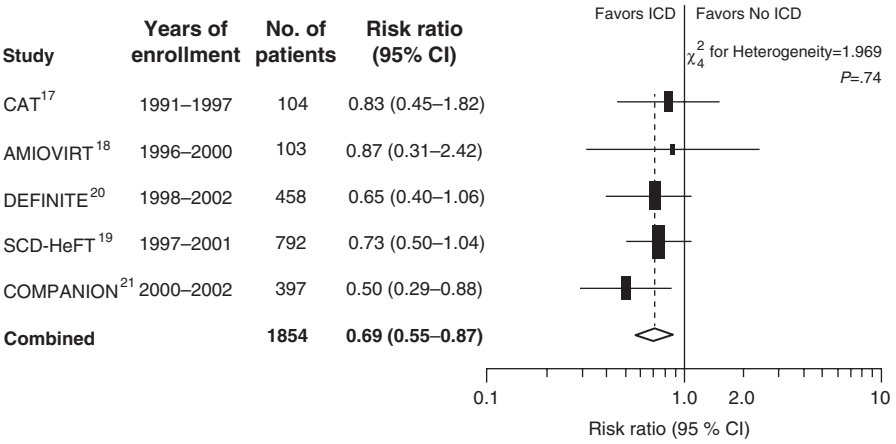


Fig. 16.1 All-cause mortality among patients with NICM randomized to ICD or CRT-D vs medical therapy in primary prevention. Number of patients with nonischemic cardiomyopathy (NICM) enrolled is reported. Size of the data marker corresponds to the relative weight assigned in the pooled analysis using fixed-effects models. *ICD* indicates implantable cardioverter defibrillator, *CRT-D* cardiac resynchronization plus defibrillator, *CI* confidence interval (Reprinted with permission *JAMA/American Medical Association*, from Desai et al. [22], ©2004 American Medical Association. All rights reserved)

in addition to optimal medical therapy for patients with reduced LVEF regardless of type of cardiomyopathy. Additionally, these trials placed less emphasis on the requirement of inducible ventricular arrhythmias for high risk patients prior to ICD implantation.

Cardiac Resynchronization Therapy (CRT)

Cardiac resynchronization therapy was developed based on observations that interventricular conduction disturbances, commonly observed in heart failure patients, were markers for poor ventricular function and increased mortality [23]. One of the most commonly observed conduction disturbances, LBBB, was associated with delayed activation of the left ventricular free wall. When early CRT investigators evaluated left ventricular pacing in concert with conventional right ventricular pacing, there were immediate improvements in hemodynamic performance as well as long term improvement in clinical symptoms [24, 25]. Based on these observations, larger clinical trials exploring CRT were performed demonstrating the benefit of CRT on mortality, left ventricular function, heart failure class and quality of life in symptomatic heart failure patients with depressed systolic function and wide (QRS >130 ms) LBBB [21, 26–32]. A full discussion of the effect of CRT on heart failure patients will be presented in a subsequent chapter; however, the decision to implant an ICD should include consideration of a left

ventricular lead where indicated. While the incremental benefit of CRT when added to ICD therapy has been reported [21, 31, 32], the benefit of a defibrillator lead with CRT (CRT-D) versus CRT without an ICD lead (CRT-P) is less well studied. The COMPANION trial randomized 1520 advanced heart failure (NYHA Class III/IV) patients with wide QRS morphologies to optimal medical therapy, CRT-P and CRT-D in a 1:2:2 ratios. Compared with optimal medical therapy, death and hospitalization were reduced by 36 and 40 % in the CRT-P and CRT-D groups, respectively, and all-cause mortality was reduced by 24 and 36 % in the CRT-P and CRT-D, respectively. A secondary analysis of mode of death in the COMPANION trial showed that CRT-D significantly reduced the number of cardiac deaths and, in particular, SCD compared with CRT-P [33]. Cardiac causes comprised 78 % of deaths in the COMPANION trial. CRT-D reduced all cardiac deaths by 38 % compared with optimal medical therapy whereas CRT-P reduced all cardiac deaths by 14.5 % which was not statistically different than optimal medical therapy (Fig. 16.2). The difference was due primarily to a significant reduction in SCD in the CRT-D arm of 56 %. Of note, both groups statistically reduced the rate of heart failure deaths by almost 30 % suggesting that CRT-D did not diminish the favorable hemodynamic effects of CRT-P. In an analysis of NYHA Class IV patients from COMPANION, CRT-D but not CRT-P significantly reduced sudden cardiac death compared with optimal medical therapy [34]. Since most patients with an indication for CRT also have an indication for an ICD and vise-versa, CRT-D is the usual choice for a biventricular implantable device for patients with heart failure and wide LBBB.

Left Ventricular Assist Devices and ICDS

Left ventricular assist device (LVAD) implantation has become an increasingly used method for both short and long term stabilization of severe heart failure. Technological improvements and advancements in operative experience have propelled LVAD numbers over the last decade. Since almost every patient with an LVAD meets criteria for an ICD, there are particular issues unique to LVAD/ICD recipients that need to be considered. Interference between LVAD and ICD electromagnetic properties have been reported which impaired ICD function, often due to inability to communicate with the device [35–37]. In some cases, the pulse generator was exchanged for an LVAD-compatible device. Current ICD systems have adapted to account for possible interference by LVAD implantation. The role of LVADs for reducing ventricular arrhythmias has yet to be comprehensively evaluated. In a retrospective analysis, LVAD implantation reduced the amount of ventricular arrhythmias but 21 % of patients had appropriate therapy for ventricular arrhythmias despite the beneficial effects of continuous mechanical support [38]. There remains controversy if patients without ICDs prior to LVAD implantation should receive an ICD for primary prevention [39]. More studies are required to definitively address this matter.

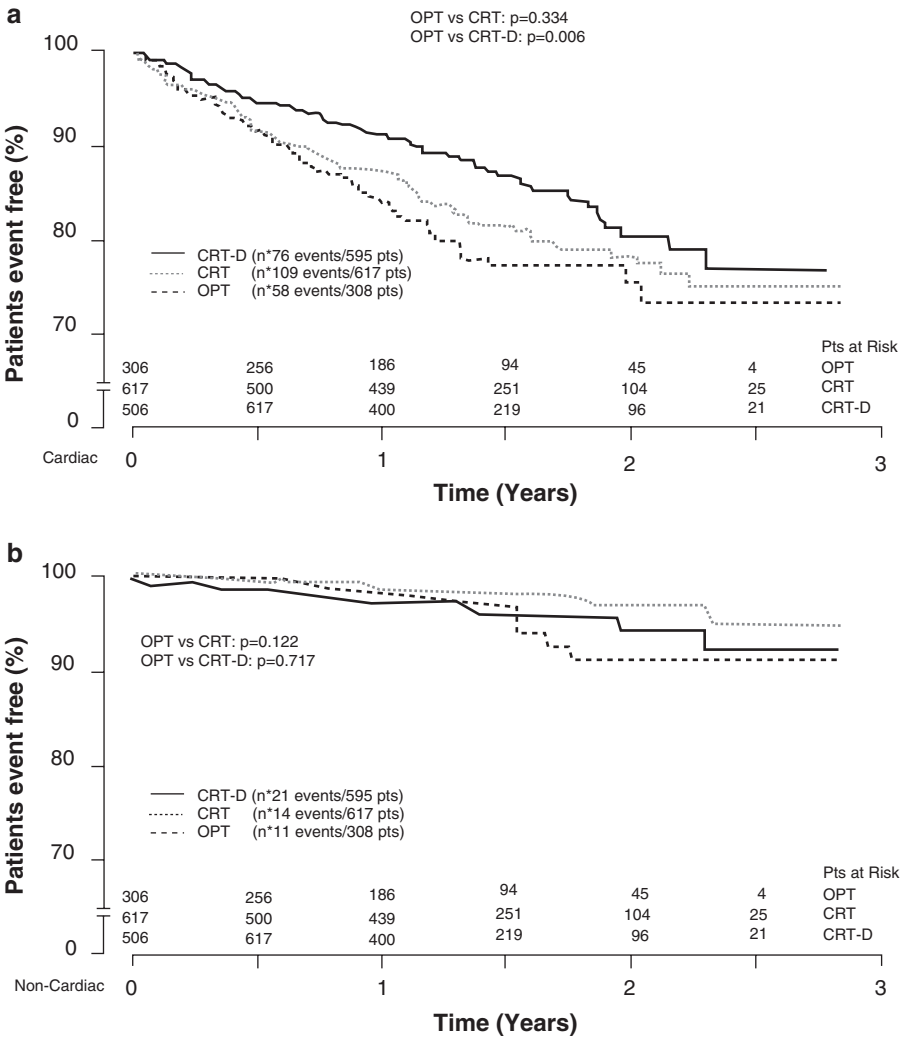


Fig. 16.2 (**a**) Kaplan-Meier estimates of the time to first cardiac death. (**b**) Kaplan-Meier estimates of the time to first non-cardiac death. *CRT* cardiac resynchronization therapy, *CRT-D* cardiac resynchronization therapy with defibrillation, *OPT* optimal pharmacologic therapy (Reprinted with permission from *Journal of the American College of Cardiology* [33], © 2005 with permission from Elsevier)

Subcutaneous ICDS

Subcutaneous leads have been used in conjunction with transvenous defibrillator systems for patients with abnormal defibrillation thresholds. An entirely subcutaneous ICD system, avoiding transvenous and intracardiac leads, has recently been

developed [40]. Initial studies showed that subcutaneous ICDs (S-ICDs) appropriately recognized and treated ventricular arrhythmias in 12 patients [41]. The S-ICD also performed as well or better than transvenous systems for SVT discrimination [42]. A major limitation of the S-ICD is the lack of antitachycardia or brady support pacing, except for a brief post-shock period. For patients requiring ICD implantation without a pacing indication, the subcutaneous ICD is an attractive option. The generator is placed in the left lateral costal margin and the lead courses subcutaneously to the xiphoid process and then along the left parasternal region. Avoiding the transvenous and intracardiac areas eliminates risk of intravascular infections, valvular damage, cardiac performation and pneumothorax. The S-ICD is also an alternative to traditional transvenous ICDs for patient with obstructive vascular access, prosthetic tricuspid valves and high risk of systemic infection such as dialysis or immunocompromised subjects.

Conclusion

In addition to survivors of sudden cardiac death, heart failure patients have a high risk of fatal ventricular arrhythmias. ICD implantation for secondary prevention of SCD is established. For either ischemic or non-ischemic heart failure patients with reduced LVEF <0.35 and NYHA Class II–III symptoms, primary prevention ICD implantation in addition to optimal medical therapy has become the standard of care. When combined with medical therapy, ICDs offer an additional 20–30 % mortality benefit that is most pronounced in those with the lowest LVEF. Mortality reduction is primarily driven by preventing sudden cardiac death rather than preventing heath failure deaths. CRT when combined with a defibrillator lead offers the greatest magnitude of mortality advantage as well as improving heart failure symptoms in the appropriate patient. Although LVAD interference has been reported, current ICDs are designed to accommodate LVAD implantation. New technologies such as subcutaneous ICDs offer an alternative to traditional transvenous systems. Finally, despite advancements in identifying high risk patients for SCD, over half of SCD victims do not meet current indications for ICD therapy [43, 44]. In addition to optimizing device based therapy, efforts to identify factors associated with SCD should be explored such as those with heart failure and ejection fraction >35 %.

References

1. Heron M. Deaths: leading causes for 2008. National Vital Statistics Reports. 2012;60(6):1–95.
2. Goldberger JJ, Cain ME, Hohnloser SH, Kadish AH, Knight BP, Lauer MS, et al. American Heart Association/American College of Cardiology Foundation/Heart Rhythm Society scientific statement on noninvasive risk stratification techniques for identifying patients at risk for sudden cardiac death: a scientific statement from the American Heart Association Council on

Clinical Cardiology Committee on Electrocardiography and Arrhythmias and Council on Epidemiology and Prevention. Circulation. 2008;118(14):1497–518.
3. Epstein AE, Dimarco JP, Ellenbogen KA, Estes 3rd NA, Freedman RA, Gettes LS, et al. ACC/AHA/HRS 2008 guidelines for device-based therapy of cardiac rhythm abnormalities. Heart Rhythm. 2008;5(6):e1–62.
4. Tracy CM, Epstein AE, Darbar D, Dimarco JP, Dunbar SB, Estes NA, 3rd, et al. ACCF/AHA/HRS focused update incorporated into the ACCF/AHA/HRS 2008 guidelines for device-based therapy of cardiac rhythm abnormalities: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. Circulation. 2012;126:1784–1800.
5. A comparison of antiarrhythmic-drug therapy with implantable defibrillators in patients resuscitated from near-fatal ventricular arrhythmias. The Antiarrhythmics versus Implantable Defibrillators (AVID) Investigators. N Engl J Med. 1997;337(22):1576–83.
6. Connolly SJ, Gent M, Roberts RS, Dorian P, Roy D, Sheldon RS, et al. Canadian implantable defibrillator study (CIDS): a randomized trial of the implantable cardioverter defibrillator against amiodarone. Circulation. 2000;101(11):1297–302.
7. Sheldon R, Connolly S, Krahn A, Roberts R, Gent M, Gardner M. Identification of patients most likely to benefit from implantable cardioverter-defibrillator therapy: the Canadian Implantable Defibrillator Study. Circulation. 2000;101(14):1660–4.
8. Kuck KH, Cappato R, Siebels J, Ruppel R. Randomized comparison of antiarrhythmic drug therapy with implantable defibrillators in patients resuscitated from cardiac arrest: the Cardiac Arrest Study Hamburg (CASH). Circulation. 2000;102(7):748–54.
9. Connolly SJ, Hallstrom AP, Cappato R, Schron EB, Kuck KH, Zipes DP, et al. Meta-analysis of the implantable cardioverter defibrillator secondary prevention trials. AVID, CASH and CIDS studies. Antiarrhythmics vs Implantable Defibrillator study. Cardiac Arrest Study Hamburg. Canadian Implantable Defibrillator Study. Eur Heart J. 2000;21(24):2071–8.
10. Buxton AE, Lee KL, DiCarlo L, Gold MR, Greer GS, Prystowsky EN, et al. Electrophysiologic testing to identify patients with coronary artery disease who are at risk for sudden death. Multicenter Unsustained Tachycardia Trial Investigators. N Engl J Med. 2000;342(26):1937–45.
11. Bigger Jr JT. Prophylactic use of implanted cardiac defibrillators in patients at high risk for ventricular arrhythmias after coronary-artery bypass graft surgery. Coronary Artery Bypass Graft (CABG) Patch Trial Investigators. N Engl J Med. 1997;337(22):1569–75.
12. Bigger Jr JT, Whang W, Rottman JN, Kleiger RE, Gottlieb CD, Namerow PB, et al. Mechanisms of death in the CABG Patch trial: a randomized trial of implantable cardiac defibrillator prophylaxis in patients at high risk of death after coronary artery bypass graft surgery. Circulation. 1999;99(11):1416–21.
13. Hohnloser SH, Kuck KH, Dorian P, Roberts RS, Hampton JR, Hatala R, et al. Prophylactic use of an implantable cardioverter-defibrillator after acute myocardial infarction. N Engl J Med. 2004;351(24):2481–8.
14. Dorian P, Hohnloser SH, Thorpe KE, Roberts RS, Kuck KH, Gent M, et al. Mechanisms underlying the lack of effect of implantable cardioverter-defibrillator therapy on mortality in high-risk patients with recent myocardial infarction: insights from the Defibrillation in Acute Myocardial Infarction Trial (DINAMIT). Circulation. 2010;122(25):2645–52.
15. Steinbeck G, Andresen D, Seidl K, Brachmann J, Hoffmann E, Wojciechowski D, et al. Defibrillator implantation early after myocardial infarction. N Engl J Med. 2009;361(15):1427–36.
16. Moss AJ, Zareba W, Hall WJ, Klein H, Wilber DJ, Cannom DS, et al. Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. N Engl J Med. 2002;346(12):877–83.
17. Bansch D, Antz M, Boczor S, Volkmer M, Tebbenjohanns J, Seidl K, et al. Primary prevention of sudden cardiac death in idiopathic dilated cardiomyopathy: the Cardiomyopathy Trial (CAT). Circulation. 2002;105(12):1453–8.

18. Strickberger SA, Hummel JD, Bartlett TG, Frumin HI, Schuger CD, Beau SL, et al. Amiodarone versus implantable cardioverter-defibrillator: randomized trial in patients with nonischemic dilated cardiomyopathy and asymptomatic nonsustained ventricular tachycardia – AMIOVIRT. J Am Coll Cardiol. 2003;41(10):1707–12.
19. Bardy GH, Lee KL, Mark DB, Poole JE, Packer DL, Boineau R, SCD-HeFT Investigators, et al. Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure. N Engl J Med. 2005;352(3):225–37.
20. Kadish A, Dyer A, Daubert JP, Quigg R, Estes NA, Anderson KP, et al. Defibrillators in Non-Ischemic Cardiomyopathy Treatment Evaluation (DEFINITE) Investigators. Prophylactic defibrillator implantation in patients with nonischemic dilated cardiomyopathy. N Engl J Med. 2004;350(21):2151–8.
21. Bristow MR, Saxon LA, Boehmer J, Krueger S, Kass DA, De Marco T, et al. Cardiac-resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure. N Engl J Med. 2004;350(21):2140–50.
22. Desai AS, Fang JC, Maisel WH, Baughman KL. Implantable defibrillators for the prevention of mortality in patients with nonischemic cardiomyopathy: a meta-analysis of randomized controlled trials. JAMA. 2004;292(23):2874–9.
23. Abraham WT. Cardiac resynchronization therapy for heart failure: biventricular pacing and beyond. Curr Opin Cardiol. 2002;17(4):346–52.
24. Cazeau S, Ritter P, Bakdach S, Lazarus A, Limousin M, Henao L, et al. Four chamber pacing in dilated cardiomyopathy. Pacing Clin Electrophysiol. 1994;17(11 Pt 2):1974–9.
25. Cazeau S, Ritter P, Lazarus A, Gras D, Backdach H, Mundler O, et al. Multisite pacing for end-stage heart failure: early experience. Pacing Clin Electrophysiol. 1996;19(11 Pt 2):1748–57.
26. Abraham WT, Fisher WG, Smith AL, Delurgio DB, Leon AR, Loh E, et al. Cardiac resynchronization in chronic heart failure. N Engl J Med. 2002;346(24):1845–53.
27. Gras D, Leclercq C, Tang AS, Bucknall C, Luttikhuis HO, Kirstein-Pedersen A. Cardiac resynchronization therapy in advanced heart failure the multicenter InSync clinical study. Eur J Heart Fail. 2002;4(3):311–20.
28. Higgins SL, Hummel JD, Niazi IK, Giudici MC, Worley SJ, Saxon LA, et al. Cardiac resynchronization therapy for the treatment of heart failure in patients with intraventricular conduction delay and malignant ventricular tachyarrhythmias. J Am Coll Cardiol. 2003;42(8):1454–9.
29. Cleland JG, Daubert JC, Erdmann E, Freemantle N, Gras D, Kappenberger L, et al. The effect of cardiac resynchronization on morbidity and mortality in heart failure. N Engl J Med. 2005;352(15):1539–49.
30. Linde C, Abraham WT, Gold MR, St John Sutton M, Ghio S, Daubert C. Randomized trial of cardiac resynchronization in mildly symptomatic heart failure patients and in asymptomatic patients with left ventricular dysfunction and previous heart failure symptoms. J Am Coll Cardiol. 2008;52(23):1834–43.
31. Moss AJ, Hall WJ, Cannom DS, Klein H, Brown MW, Daubert JP, et al. Cardiac-resynchronization therapy for the prevention of heart-failure events. N Engl J Med. 2009;361(14):1329–38.
32. Young JB, Abraham WT, Smith AL, Leon AR, Lieberman R, Wilkoff B, et al. Combined cardiac resynchronization and implantable cardioversion defibrillation in advanced chronic heart failure: the MIRACLE ICD trial. JAMA. 2003;289(20):2685–94.
33. Carson P, Anand I, O'Connor C, Jaski B, Steinberg J, Lwin A, et al. Mode of death in advanced heart failure: the Comparison of Medical, Pacing, and Defibrillation Therapies in Heart Failure (COMPANION) trial. J Am Coll Cardiol. 2005;46(12):2329–34.
34. Lindenfeld J, Feldman AM, Saxon L, Boehmer J, Carson P, Ghali JK, et al. Effects of cardiac resynchronization therapy with or without a defibrillator on survival and hospitalizations in patients with New York Heart Association class IV heart failure. Circulation. 2007;115(2):204–12.

35. Matthews JC, Betley D, Morady F, Pelosi Jr F. Adverse interaction between a left ventricular assist device and an implantable cardioverter defibrillator. J Cardiovasc Electrophysiol. 2007;18(10):1107–8.
36. Oswald H, Klein G, Struber M, Gardiwal A. Implantable defibrillator with left ventricular assist device compatibility. Interact Cardiovasc Thorac Surg. 2009;8(5):579–80.
37. Netzler PC, Vasuki N, Peura JL, Gold MR. Interactions between a left ventricular assist device and implantable cardioverter-defibrillator. Pacing Clin Electrophysiol. 2012;35(9):e272–3.
38. Refaat MM, Tanaka T, Kormos RL, McNamara D, Teuteberg J, Winowich S, et al. Survival benefit of implantable cardioverter-defibrillators in left ventricular assist device-supported heart failure patients. J Card Fail. 2012;18(2):140–5.
39. Pettit SJ, Petrie MC, Connelly DT, Japp AG, Payne JR, Haj-Yahia S, et al. Use of implantable cardioverter defibrillators in patients with left ventricular assist devices. Eur J Heart Fail. 2012;14(7):696–702.
40. Rowley CP, Lobodzinski SS, Gold MR. The subcutaneous defibrillator. Curr Treat Options Cardiovasc Med. 2012;14(5):550–7.
41. Bardy GH, Smith WM, Hood MA, Crozier IG, Melton IC, Jordaens L, et al. An entirely subcutaneous implantable cardioverter-defibrillator. N Engl J Med. 2010;363(1):36–44.
42. Gold MR, Theuns DA, Knight BP, Sturdivant JL, Sanghera R, Ellenbogen KA, et al. Head-to-head comparison of arrhythmia discrimination performance of subcutaneous and transvenous ICD arrhythmia detection algorithms: the START study. J Cardiovasc Electrophysiol. 2012;23(4):359–66.
43. de Vreede-Swagemakers JJ, Gorgels AP, Dubois-Arbouw WI, Van Ree JW, Daemen MJ, Houben LG, et al. Out-of-hospital cardiac arrest in the 1990s: a population-based study in the Maastricht area on incidence, characteristics and survival. J Am Coll Cardiol. 1997;30(6):1500–5.
44. Stecker EC, Vickers C, Waltz J, Socoteanu C, John BT, Mariani R, et al. Population-based analysis of sudden cardiac death with and without left ventricular systolic dysfunction: two-year findings from the Oregon Sudden Unexpected Death Study. J Am Coll Cardiol. 2006;47(6):1161–6.

Chapter 17
Cardiac Resynchronization Therapy in Heart Failure

Michael A. Samara and David S. Feldman

Introduction

Heart failure pharmacotherapy including beta-blockers (BB), angiotensin converting enzyme inhibitors/Angiotensin II Receptor Blockers (ACEi/ARB), and aldosterone antagonists have resulted in dramatic improvements in the morbidity and mortality of patients with heart failure (HF) with a reduced ejection fraction. However, in many patients, medical management alone is insufficient to achieve adequate symptom control and HF associated morbidity and mortality remains high. In a subgroup of these patients with prolonged QRS duration, particularly with left bundle branch block (LBBB) morphology, cardiac resynchronization therapy (CRT) has demonstrated additional benefit. Currently CRT is indicated for patients with NYHA functional class II-IV heart failure, severe systolic dysfunction (left ventricular ejection fraction (LVEF) $\leq$35 %) and interventricular conduction delay. Over the last two decades it has become a key component of the staged treatment of HF [1].

Competing Interests The authors declare no competing interests.

M.A. Samara, MD (✉)
Minneapolis Heart Institute, 920 East 28th Street, Suite 300,
Minneapolis, MN 55407, USA

Department of Advanced Heart Failure/Transplant Cardiology/Mechanical Circulatory Support, Minneapolis Heart Institute of Abbott Northwestern Hospital,
920 East 28th Street, Suite 300, Minneapolis, MN 55407, USA
e-mail: michael.samara@allina.com

D.S. Feldman, MD, PhD
Heart, Lung and Vascular Institute, University of Cincinnati Medical Center, Medical Science Building, 231 Albert Sabin Way, Cincinnati, OH 45267, USA

H. Eisen (ed.), *Heart Failure*, DOI 10.1007/978-1-4471-4219-5_17

Background and Rationale for Use

The deleterious effects of dyssynchronous activation of the ventricular myocardium were first noted almost 90 years ago when Wiggers demonstrated a reduction in the rate of LV pressure rise (dP/dt) and peak power production with right ventricular (RV) pacing [2]. More recently Askenazi et al. demonstrated the incremental reduction in dp/dT and LV peak pressure incurred when moving from right atrial pacing with normal ventricular conduction, to RV (AV sequential) pacing, to direct RV pacing with loss of AV synchrony. They further demonstrated that RV pacing not only had acute hemodynamic effects, but also led to a significant reductions in the LVEF over time [3]. Burkhoff and colleagues demonstrated that an inverse linear relationship existed between the QRS duration and LV pressure production [4]. In addition to detrimental effects on systolic function, Zile et al. demonstrated that diastolic properties and LV filling were also degraded with RV pacing with reductions in the isovolumic pressure decline and myocardial emptying rate [5]. In addition to the acute effects on hemodynamics and medium term effects on LV remodeling, increasing degrees of QRS prolongation are at least a marker for worse prognosis in advanced systolic HF. This was demonstrated in post-hoc analysis of the VEST (Vesnarinone) trial demonstrating a fivefold reduction in cumulative survival for patients with a QRS duration >220 ms versus those with normal QRS duration [6].

The prevalence of interventricular conduction delays in patients with advanced systolic HF (perhaps up to 1/3 of all HF patients) and the aforementioned observations lead several groups to question whether resynchronization of myocardial activation could result in improved hemodynamics and long-term outcomes. Mower and colleagues were the first to formally theorize that simultaneous pacing of both ventricles would reduce both electrical and mechanical dyssynchrony [7]. Cazeau et al., were the first to experiment with this approach in humans at Paris' Hôpital Lariboisière. A standard dual chamber AV pacemaker was modified to pace both atria and both ventricles simultaneously—the LV lead having been implanted via thoracotomy. The group demonstrated that in eight subjects with QRS prolongation and end-stage HF despite maximal medical therapy, biventricular (BiV) pacing increased the mean cardiac index by 25 % and decreased the pulmonary capillary wedge pressure by 17 % [8]. Following their initial success, a number of small observational studies were performed demonstrating a variety of clinical benefits ultimately confirmed in large randomized studies.

Nelson and colleagues went on to demonstrate that in patients with LBBB (mean QRS duration 179 ± 3 ms) and severe systolic dysfunction, LV or BiV pacing resulted in a nearly instantaneous improvement in dP/dt and pulse pressure with a reduction in the arterial-coronary sinus oxygen difference and thus the myocardial oxygen consumption [9]. This critical observation underscores the key difference between CRT and inotropic agents which achieve their augmentation of contractility via an increase in myocardial oxygen consumption likely accounting for the adverse long-term effects that have been observed in clinical trials of these agents [10].

Not surprisingly, electrical and mechanical dyssynchrony are associated with cellular pathophysiology with important regional changes in myocardial gene expression for stress remodeling proteins such as mitogen-activated protein kinases, altered cell survival signaling, reduced L-type calcium currents, and decreased adrenergic responsiveness with varying degrees of reversibility following resynchronization therapy [11].

Types of Dyssynchrony and Physiologic Consequences

The normal electrical activation of the ventricular myocardium results in simultaneous activation of the right and left bundles of the Purkinje system culminating in the generation of symmetric counterforces during cardiac ejection. The normal Purkinje system is electrically isolated from the myocardium except at the apically located terminal Purkinje-myocardial junctions facilitating the normal apical to basal mechanical activation and contraction. When this is interrupted due to conduction block, dyssynchronous activation of the myocardium results. Also common in the setting of advanced systolic heart failure is first degree AV block with associated alterations in atrioventricular synchrony. Cumulatively these conduction disturbances (particularly in the context of LBBB) result in three types of dyssynchrony with important implications for cardiac performance.

Intraventricular Dyssynchrony

Dyssynchronous activation of the LV myocardium with LBBB results in early, unloaded contraction of the interventricular septum. Rather than contributing to a rise in LV pressure, this contraction is primarily converted to prestretch of the lateral wall. This results in reductions in stroke volume, dP/dt, and pulse pressure and ultimately worsening LV systolic function and mitral regurgitation due to uncoordinated contraction of the papillary muscles. These derangements in turn contribute to progressive adverse remodeling and the "vicious cycle" of HF pathophysiology.

Interventricular Dyssynchrony

With LBBB and RV pacing there is early RV activation resulting in a disadvantageous pressure gradient between the RV and LV. This gradient precipitates a reduction in the RV stroke volume and concordant reduction in LV preload. While CRT is conventionally thought of as a therapy for LV failure there is emerging evidence that correcting interventricular dyssynchrony may have benefits for RV performance.

Haddad et al. recently presented data suggesting that patients undergoing CRT-D implantation had significant improvements in their RV ejection fraction, end-systolic volume, and RV peak filling rate [12].

AV Dyssynchrony

While not the primary target of CRT, correction of AV dyssynchrony has increasingly been regarded as a critical function of CRT. Advanced first degree AV block is common in systolic heart failure and results in increased left atrial pressures, decreased LV diastolic filling times and diastolic mitral regurgitation due to the superimposition of atrial contraction (which occurs too early) and early diastolic LV filling. The echocardiographic hallmark of this phenomenon is fusion of the A and E waves. In contrast, short AV delays also reduce LV preload by causing interruption of active atrial transport via premature closure of the mitral valve.

Clinical Trial Data

Investigators have taken a stepwise approach to the evaluation of CRT beginning with small studies investigating the acute hemodynamic effects of CRT in patients with severe HF and culminating in large studies assessing mortality and long-term clinical outcomes in thousands of patients with milder degrees of HF. The seminal studies from this clinical trial program are summarized below:

NYHA FC III-IV Early clinical trials on CRT focused on patients with NYHA class III or IV HF despite optimal medical therapy (OMT), and severe LV systolic dysfunction (LVEF <35 %) with evidence of electrical dyssynchrony defined as QRS prolongation of at least 120–150 (ms).

PATH-CHF Encouraged by the short-term results of hemodynamic studies involving CRT, Auricchio et al. set out to define the longer term effects of biventricular or univentricular (LV) stimulation on functional capacity in 41 patients [13]. They demonstrated a net increase in peak oxygen consumption (peak VO_2) from 12.5 to 15.2 ml/kg/m/in ($p = 0.002$) and an improvement in 6-min walk from 342 to 416 m. PATH-CHF was the first study to establish the durability of CRTs effects with these clinical benefits persisting after 12 months of therapy [13].

MUSTIC Cazeau et al. performed a single-blind, randomized, controlled crossover study assessing the clinical effects of CRT in patients with NYHA class III–IV symptoms and QRS durations >150 ms. Their unique crossover design overcame some of the methodological barriers of PATH-CHF which as a non-blinded study relying on effort dependent clinical endpoints like peak VO_2 and 6-min walk was

susceptible to obvious biases. The study consisted of two phases including a 3-month period of active therapy (AV sequential pacing with CRT) and a 3-month period of inactive (ventricular inhibited pacing) allowing each patient to function as his/her own control. The group found that patients receiving CRT had improved 6-min walk distances, an 8 % increase in peak VO_2, improved quality-of-life scores as assessed by the Minnesota Living With Heart Failure Questionnaire (MLWHFQ), and a 2/3 reduction in HF hospitalizations [14].

MIRACLE Abraham et al., performed the first large-scale, double-blind, randomized clinical trial assessing the efficacy of CRT in patients with QRS durations >130 ms. All enrolled patients (n = 453) were implanted with CRT capable devices and then randomized to atrial-biventricular pacing vs. no pacing [15]. At 6 months of follow-up the CRT group experienced improvements in 6-min walk (+39 vs. +10 m, p = 0.005), functional class, quality of life, and EF (+4.6 % vs. −0.2 %, p<0.001). Also observed was a reduction in HF hospitalizations (8 vs. 15 %). While generally safe, this large scale study highlighted some of the potential complications of CRT implantation including failure to place a coronary sinus lead in 8 % of patients, coronary sinus perforation, and death [15]. The MIRACLE trial led to approval of CRT by the Food and Drug Administration (FDA).

MIRACLE-ICD CRTs rise was contemporaneous with a period of rapidly evolving guidelines for implantable cardioverter defibrillator (ICD) therapy. Young et al. went on to perform an analogous study in and identical patient population receiving devices with combined CRT and ICD functionality [16]. Three hundred sixty-nine patients were randomized to a control (ICD on/CRT off) or CRT group (ICD on/CRT on). At 6 months the CRT group had greater improvements in quality of life, functional class, and peak VO_2, but no difference in 6-min walk, EF, HF hospitalizations, or survival. Of critical importance, MIRACLE ICD highlighted the fact that the benefits of CRT could be achieved without evidence of proarrhythmia or compromise in ICD function.

Meta-analysis of Studies with NYHA Class III-IV HF A 2007 Meta-analysis published in the *Journal of the American Medical Association* summarized the results of the 14 randomized trials performed up to that point including 4420 patients [17]. This demonstrated improvements in NYHA functional class, 6-min walk, and quality of life metrics. There was an overall reduction in the rate of HF associated hospitalizations (RR 0.63, 95 % CI 0.43–0.93) as well as a reduction in all-cause mortality (RR 0.78, 95 % CI 0.67–0.91) driven by a reduction in deaths from "pump-failure" (RR 0.64; 95 % CI 0.49–0.84) [17]. These benefits were achieved with a high rate of procedural success (93 %) and low risk of complications.

COMPANION While early studies hinted towards a potential improvement in hard clinical outcomes such as HF hospitalizations and HF and all-cause mortality, this question was first directly addressed in an appropriately powered study by Bristow et al. who randomized 1520 patients with QRS duration >120 ms in a 1:2:2

ratio to OMT, CRT-pacemaker (CRT-P), or CRT-defibrillator (CRT-D) [18]. In addition to conventional criteria for CRT enrolled patients had to have at least one HF hospitalization in the year prior to randomization. Compared to OMT, CRT-P and CRT-D both demonstrated reductions in the primary composite endpoint of time to death from or hospitalization for any cause (Hazard ratio 0.81 and 0.80 respectively). The combined end point of death from or hospitalization for HF was reduced by 34 % in the CRT-P group and 40 % in the CRT-D group. CRT-P patients had a non-significant reduction in all cause mortality whereas patients with CRT-D had a significant 36 % reduction in the risk of all cause mortality ($p = 0.003$) [18]. The COMPANION trial led to FDA approval of combined CRT-D devices.

CARE-HF Cleland et al. further examined the effects of CRT-P versus OMT on morbidity and mortality in 813 patients followed for 29 months and established for the first time that CRT-P alone provided a mortality benefit in patients with QRS duration >120 ms. Patients with CRT-P had a 37 % reduction in the primary endpoint a composite of death from any cause or unplanned hospitalization for a major cardiovascular event. Similarly there was a 36 % reduction in the secondary endpoint of all cause mortality [19]. The study also demonstrated a reduction in end-systolic volume index, mitral regurgitant jet volume, and improvement in LVEF and QoL. Subsequent longer-term follow-up from the CARE-HF investigators demonstrated that these reductions in mortality are durable and that they were due to a reduction in both sudden cardiac death and pump failure [20]. It is interesting to note that unlike prior studies (including COMPANION) the inclusion criteria for patients with intermediate QRS durations (i.e., between 120 and 149 ms) required two of three additional echocardiographic features of dyssynchrony including: aortic preejection delay of more than 140 ms, an interventricular mechanical delay of more than 40 ms, or delayed activation of the posterolateral LV wall [19].

NYHA FC I-II The clinical trial program outlined above provided conclusive evidence that CRT reduced HF associated morbidity and mortality in patients with severe systolic heart failure. However, as the majority of HF patients are NYHA FC I and II, investigators began to ask whether earlier application of CRT could result in an inflexion point in the natural history of the disease.

MIRACLE-ICD II Abraham et al. first assessed the efficacy of CRT-D in patients with NYHA class II symptoms and a QRS duration >130 ms [21]. CRT-D treated patients had no significant improvement in peak VO_2 but did see improvement in ventricular remodeling (LV systolic and diastolic volumes and LVEF). CRT-D patients demonstrated significant improvements in NYHA class and ventilator efficiency (VE/VCO_2) a well validated and effort-independent predictor of survival in patients with advanced HF [21].

REVERSE Linde and Packer et al., examined the effects of CRT-D in patients with NYHA I and II HF with QRS durations >120 ms and with LVEF ≤40 % [22]. The large, randomized, double-blind trial enrolled 610 patients randomized 2:1 to

CRT-D versus ICD alone. The primary endpoint was the novel clinical composite score which classified patients as "improved," "unchanged," or "worsened" based on a combination of mortality, HF hospitalizations, withdrawal from the study, or worsening NYHA class. The study included an American arm that proceeded for 12 months and a European arm that extended follow-up to 24 months. While there was no difference In the clinical composite score, CRT-D patients demonstrated significant reductions in the LV end-systolic volume index, improvements in LVEF, and a delay in the time-to-first HF hospitalization (hazard ratio: 0.47, p = 0.03).

RAFT Tang et al., assessed the efficacy of CRT added to ICD therapy to reduce HF morbidity and hospitalizations in patients with NYHA FC II and III HF, QRS duration >120 ms, and LVEF <30 % [23]. In pre-specified subgroup analysis both patients with NYHA FC II and III symptoms had significant reductions in the composite endpoint of death or hospitalization for HF. Somewhat surprisingly, only the patients with NYHA II symptoms had a statistically significant reduction in all cause mortality (Hazard ratio 0.71; 95 % CI 0.56–0.91).

MADIT-CRT Moss et al. performed the largest and longest follow-up study to date of CRT in patients with mild HF (NYHA class I–II) in 1820 patients with LVEF of 30 % or less and QRS duration >120 ms [24]. Importantly only NYHA class I patients with ischemic cardiomyopathy were included in the study. They demonstrated that during an average follow-up of 2.4 years CRT lead to a 34 % reduction in the primary endpoint of death from any cause or nonfatal HF event. This was driven largely by a 41 % reduction in HF events in the CRT group. Pre-specified subgroup analysis demonstrated that the majority of the clinical benefit was seen in patients with LBBB and QRS duration of ≥150 ms. In contrast to RAFT there was no demonstrable reduction in the risk of mortality in the CRT group.

Meta-analysis of Studies with NYHA Class I-II HF A meta-analysis and systematic review of CRT in patients with mild HF (NYHA FC I–II) was performed by Santangeli et al. [25]. These authors reviewed results from CONTAK-CD, MIRACLE-ICD-II, REVERSE, MADIT-CRT, and RAFT with 4213 patients (91 % of whom were NYHA II functional class). They demonstrated a reduction in mortality (OR 0.78, 95 % CI 0.63–0.97) and HF events (OR 0.63; 95 % CI 0.52–0.76) [25]. In addition, they demonstrated beneficial reverse remodeling with an improvement in LVEF of 4.8 % (95 % CI 0.9–8.7 %) and reduction in LV end-systolic volume index of −19.4 ml/m^2 (95 % CI −18.2 to −20.7 ml/m^2).

While it is tempting to lump NYHA I and II patients together in this analysis, it is essential to note that only 372 patients (<20 % of patients enrolled in REVERSE and MADIT-CRT and no patients in RAFT or MIRACLE-ICD II) were NYHA FC I. In fact in REVERSE, patients were required to have previously had NYHA II symptoms before enrollment. In the European REVERSE study, results trended toward favoring CRT-OFF in the NYHA I cohort. Subgroup analysis from MADIT-CRT demonstrated inconclusive results in NYHA I patients with ischemic cardio-

myopathy. With uncertainty about benefit and increased early risk of adverse events (13 % in CRT-D patients vs. 6.7 % in ICD only patients in RAFT) guideline societies have generally tempered or removed recommendations for implantation in patients with NYHA I symptoms [23, 26].

Current Guidelines

In 2011 the Heart Failure Society of America (HFSA) updated their guideline recommendations to reflect the growing appreciation of a concentration of CRT's benefits in patients with LBBB and QRS duration ≥150 ms and the general paucity of data to support CRT in NYHA class I patients [26, 27]. In 2012 the American College of Cardiology, American Heart Association, and Heart Rhythm Society (ACC/AHA/HRS) combined guidelines have been modified to similarly reflect these changes [28] (Table 17.1). Importantly all CRT guidelines are predicated on the expectation of ongoing guideline supported OMT.

Implantation and Follow-Up

While initial studies in CRT necessitated epicardial LV lead placement via thoracotomy, currently the vast majority of patients can be successfully provided LV pacing via transvenous coronary sinus lead placement. The procedure is performed in an electorphysiology laboratory. Following creation of a subcutaneous pocket, RA and RV leads are placed with a standard approach via the axillary or cephalic vein (Fig. 17.1). A coronary sinus occlusion venogram is performed to identify a target vein and then using various guidewires and catheters the coronary sinus lead is positioned. This lead should ideally be positioned in the mid posterolateral aspect of the LV, thereby maximizing spatial separation from the RV lead. This degree of separation when assessed by a standard lateral chest roentogram has been shown to be predictive of acute hemodynamic response to CRT [29]. Pacing thresholds are assessed and because of the proximity of the posterolateral LV to both the left phrenic nerve and the diaphragm itself, diaphragmatic capture is assessed for.

Maximizing the likelihood of CRT response requires maintenance of continuous or near-continuous BiV pacing. While the precise threshold for optimal effect is unknown, prior retrospective analysis of large CRT trials demonstrated that the maximum benefit in reduction of HF hospitalizations and mortality was seen in patients receiving ≥92 % BiV pacing [30] (See Fig. 17.2). Maximizing BiV pacing requires programming algorithms allowing for AV intervals short enough to minimize native conduction but long enough to facilitate optimal ventricular loading. Individual optimization of the AV delay was incorporated into most of the landmark CRT trials listed above.

Table 17.1 ACC/AHA 2013 revised guidelines for CRT

Recommendations	Class of recommendation	Level of evidence
CRT is indicated for patients who have LVEF ≤35 %, sinus rhythm, LBBB with a QRS ≥150 ms, and NYHA class II, III, or ambulatory IV symptoms on OMT	I	A: NYHA III/IV B: NYHA II
CRT can be useful for patients who have LVEF ≤35 %, sinus rhythm, a non-LBBB pattern with QRS ≥150 ms, and NYHA class III/ambulatory class IV symptoms on OMT	IIa	A
CRT can be useful for patients who have LVEF ≤35 %, sinus rhythm, LBBB with a QRS 120–149 ms, and NYHA class II, III, or ambulatory IV symptoms on OMT	IIa	B
CRT can be useful in patients with AF and LVEF ≤35 % on GDMT if (a) the patient requires ventricular pacing or otherwise meets CRT criteria and (b) AV nodal ablation or rate control allows near 100 % ventricular pacing with CRT	IIa	B
CRT can be useful for patients on OMT who have LVEF ≤35 % and are undergoing new or replacement device with anticipated ventricular pacing (>40 %)	IIa	C
CRT may be considered for patients who have LVEF ≤35 %, sinus rhythm, a non-LBBB pattern with a QRS duration of 120–149 ms, and NYHA class III/ambulatory class IV on OMT	IIb	B
CRT may be considered for patients who have LVEF ≤35 %, sinus rhythm, a non-LBBB pattern with QRS ≥150 ms, and NYHA class II symptoms on OMT	IIb	B
CRT may be considered for patients who have LVEF ≤30 %, ischemic etiology of HF, sinus rhythm, LBBB with QRS ≥150 ms, and NYHA class I symptoms on OMT	IIb	C
CRT is not recommended for patients with NYHA class I or II symptoms and non-LBBB pattern with QRS <150 ms	III: No Benefit	B
CRT is not indicated for patients whose comorbidities and/or frailty limit survival to <1 y	III: No Benefit	C

Reprinted from *Journal of the American College of Cardiology*, Yancy et al. [28], © 2013, with permission from Elsevier
OMT optimal medical therapy

Many methods for echo guided AV optimization exist. These rely on achieving optimal separation of the A and E waves on Pulsed-wave Doppler of the mitral inflow, optimizing the Doppler-derived rate of pressure rise (derived from analysis of the mitral regurgitant jet), optimizing the myocardial performance index (Tei Index), or maximizing the LV outflow tract or aortic flow velocity profile (VTI) [31]. Prospective studies assessing the effect of automated or echo-guided AV optimization have demonstrated no benefit in functional status, quality-of-life, or ventricular remodeling versus a fixed AV delay of 120 milliseconds [32]. Similarly, while current devices allow for multiple configurations of biventricular or LV pacing, recent studies have failed to demonstrate a clear benefit of biventricular pacing

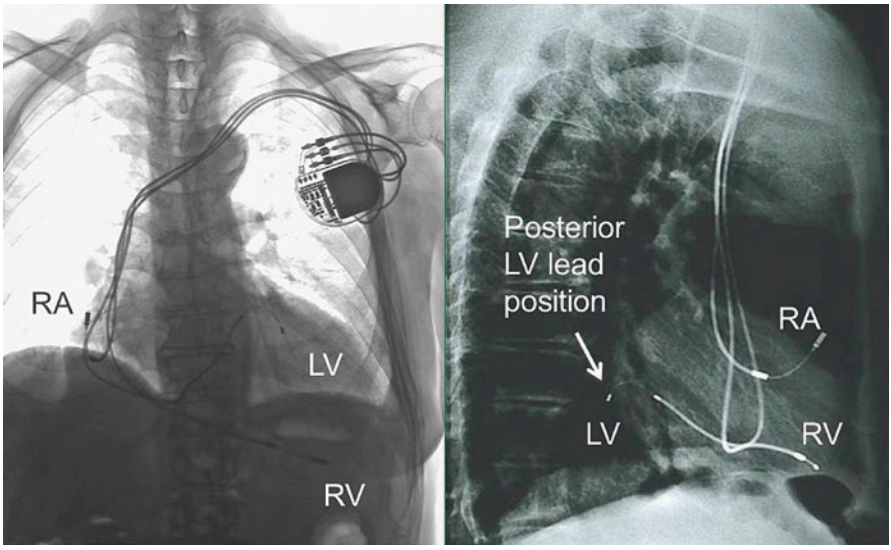


Fig. 17.1 Ideal lead position by AP and lateral CXR. Note the position of the LV lead in the mid to basal aspect of the posterolateral wall. Also note the degree of spatial separation between the RV and LV lead tips in the lateral projection

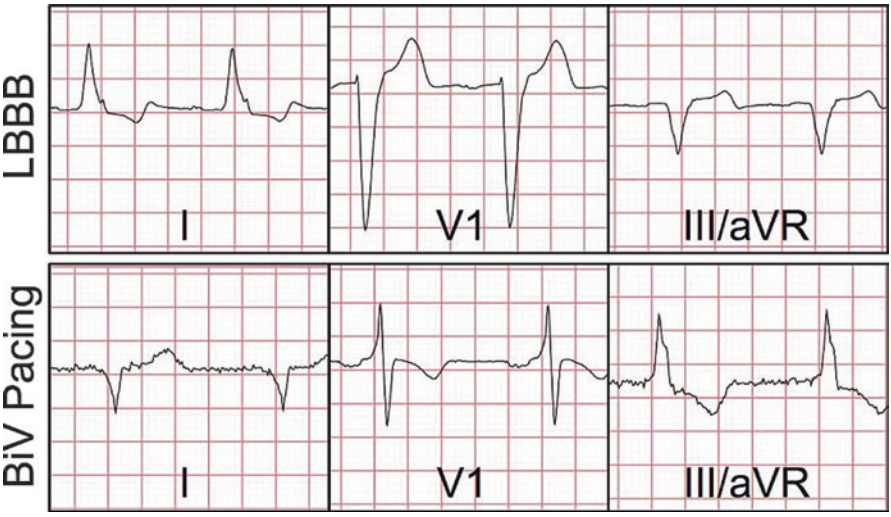


Fig. 17.2 ECG changes associated with biventricular stimulation. Top row demonstrates typical ECG findings of complete left bundle branch block (*LBBB*). The bottom row demonstrates desired changes in the ECG accompanying biventricular (*BiV*) pacing. Stimulation from the posterolateral aspect of the LV generates anterior forces represented as a positive deflection in the anteroseptal precordial leads (V1–V3). The left-to-right and basal-to-apical progression of electrical activation from an optimally positioned lead should also result in the reversal of polarity in leads I, III, and aVR demonstrated above

over LV only pacing [33]. While failing to consistently demonstrate efficacy in clinical trials, in individual patients AV optimization can be critical to maximizing the frequency of ventricular pacing.

Safety and Complications

Between 2 and 6 % of LV leads cannot be placed via the transvenous approach and require epicardial lead placement via thoracotomy [34]. Between 4 and 10 % of patients experience a clinically significant lead dislodgement necessitating repositioning [17]. The incidence of other complications has been assessed and reported in a recent review in the *Journal of the American Medical Association* [17]. In 54 reviewed studies including over 6000 patients the implant success rate was 93 % with peri-procedural complications occurring in 4 % of cases and peri-procedural death occurring in 0.3 % of patients [17]. Coronary sinus dissection or perforation can occur, but is rarely a fatal complication owing to the relatively low pressure of the cardiac venous system with pericardial effusion/tamponade complicating only 0.6–1.2 % of cases. Just over 1 % of patients developed device site infections consistent with the reported risk of infectious complications of 1–2 % for all implanted electrophysiologic devices.

Clinical Response and Nonresponders

One of the challenges in assessing CRT efficacy in clinical trials has been disagreement regarding what outcomes should be used to assess response. Fornwalt et al. recently assessed the agreement among the 15 most common response-criteria used in 26 published CRT studies. They found that 99 % of patients in these studies were CRT "responders" on the basis of at least 1 criteria, but that 75 % of comparisons between response-criteria demonstrated poor agreement [35]. The selection of response-criteria also has important implications on trial design as endpoints such as quality of life, 6-min walk, and peak VO_2 are either subjective or effort dependent measures that are susceptible to bias. Substudy analysis from MADIT-CRT began to identify characteristics associated with patients who are "super-responders" to CRT [36]. Table 17.2 presents other clinical features demonstrating efficacy in predicting response to CRT along with supporting references [36–44]. Importantly, to date, no features have demonstrated more reliability in predicting response to CRT than QRS duration and the presence of LBBB [45].

While the majority of appropriately selected patients derive clinical benefit from CRT, approximately 30 % of patients with appropriate QRS criteria are nonresponders without improvement in symptoms, ventricular remodeling, or HF hospitalizations. Mullens et al. demonstrated that a multi-disciplinary CRT nonresponder clinic could successfully identify and intervene on omissions or insufficiencies in

Table 17.2 Conventional predictors of CRT response [36–44]

	Response more likely	Response less likely
Qrs duration [36]	≥150 ms	<150 ms
BBB pattern [36]	LBBB	RBBB or IVCD
Cardiomyopathy [36]	Nonischemic	Ischemic
Gender [36]	Female	Male
Dyssynchrony [37, 41]	Present	Absent
BMI <30 kg/m^2 [36]	Present	Absent
Left atrial size [36]	Smaller	Larger
Scar burden [42, 43]	Low burden	High Burden
	Non-transmural	Transmural
	Posterolateral viable	Posterolateral scar
Mitral regurgitation [38, 39]	Mild-moderate	Severe
RV dysfunction [40]	None-mild	Severe
Lead position [44]	Posterior or lateral	Anterior or apical

the care of CRT nonresponders in a positive way. Interventions addressed suboptimal AV delay, loss of BiV pacing due to arrhythmia, suboptimal LV lead position, and suboptimal HF pharmacotherapy [46].

In the case of patients who do respond to CRT it is critical that the augmentation of blood pressure and cardiac performance provided by CRT be used as an opportunity to titrate neurohormonal antagonists. Small restrospective studies have demonstrated that CRT facilitates titration of BB and ACEI with simultaneous weaning of diuretics [47].

Atrial Fibrillation

Atrial fibrillation (AF) is exceedingly common in patients with HF and becomes more prevalent with increasing degrees of HF severity. The OPTIME CHF and CONSENSUS studies assessing the utility of milrinone and enalapril respectively in patients with NYHA IV symptoms demonstrated a prevalence of 35–50 % [48]. It is therefore not surprising that AF is amongst the most common reasons for loss of BiV pacing by facilitating rapid AV conduction that outpaces programmed AV delays or exceeding the upper tracking limit. For this reason CRT trials have uniformly excluded patients with AF.

Particularly in patients with AF it is critical to confirm biventricular pacing by ECG as device diagnostics may spuriously report BiV pacing. Kamath et al. demonstrated that 12-lead Holter monitoring in patients with permanent atrial fibrillation frequently revealed inadequate BiV pacing percentages in patients with device diagnostics reporting very high rates of BiV pacing [49]. Approaches to AF in CRT include algorithms to achieve higher BiV pacing rates including ventricular sensed response, conducted AF response, and atrial tracking recovery; intensification of

rate control; anti-arrhythmic drug therapy; and ultimately AV nodal ablation. Ganesan et al. performed a meta-analysis examining the utility of AVN ablation in AF patients with CRT. They demonstrated that AVN ablation was associated with significant reductions in all-cause and cardiovascular mortality, as well as improvement in mean NYHA functional class when compared to rate control strategies [50]. The updated ACC/AHA/HRS guidelines provide a IIa indication for CRT in these patients only if appropriate measures are taken to achieve high rates of BiV pacing (Table 17.1).

Controversies in CRT

Mechanical Dyssynchrony and Narrow Complex QRS

Currently, only a minority of HF patients meet the QRS criteria for CRT and not all CRT candidates are clinical responders. As such, there are ongoing efforts to identify measures of mechanical dyssynchrony that can assist in better predicting response. Beshai et al. assessed the utility of CRT in 172 patients with narrow QRS complexes but with echocardiographic evidence of mechanical dyssynchrony (defined as opposing-wall delay of ≥65 ms on tissue Doppler imaging or a mechanical dyssynchrony in the septal-to-posterior wall of ≥130 ms) in the ReithinQ trial. They found that while CRT treated patients had a significant improvement in NYHA class there was no significant improvement in quality of life, 6-min walk, LV reverse remodeling, or the primary endpoint of peak VO_2 [51]. The Predictors of Response to CRT (PROSPECT) trial assessed the efficacy of 12 echocardiographic parameters of mechanical dyssynchrony in predicting CRT response in 498 patients as evinced by an improvement in clinical composite score and a ≥15 % reduction in the LV end systolic volume at 6 months. In general these parameters demonstrated poor sensitivity and specificity with receiver operating characteristic area under the curves (ROC AUC) for most parameters falling between 0.5 and 0.6 [52].

In contrast to these disappointing results, the Speckle Tracking and Resynchronization (STAR) study assessed the ability of radial, circumferential, transverse, and longitudinal strain evidence of mechanical dyssynchrony (≥130 ms opposing wall delay) to predict improvements in LVEF and adverse long-term events including death, transplant, or left ventricular assist device therapy. Radial and transverse dyssynchrony predicted improved LVEF response. Interestingly, patients undergoing CRT without transverse or radial dyssynchrony had a significantly higher rate of adverse HF endpoints [37]. In the NARROW-CRT study, Muto et al., demonstrated that in patients with ischemic cardiomyopathy, narrow QRS complexes and echocardiographic evidence of mechanical dyssynchrony (≥60 ms difference in septal and lateral time-to-peak systolic velocity), CRT-D resulted in improvements in clinical composite scores and a reduction in the composite endpoint of HF hospitalization, HF death, and spontaneous ventricular fibrillation [41].

While intriguing STAR and NARROW-CRT were small studies and require corroboration in larger scale trials. While data has not yet been published, the largest study to date investigating CRT in patients with narrow QRS complexes, EchoCRT was terminated early due to futility after recruiting over 1000 patients [53].

Patients with NYHA Class IV HF

The majority of patients in CRT trials of advanced HF patients had NYHA class III symptoms with ambulatory class IV patients representing a small minority. These were truly ambulatory patients with resting HF symptoms and did not include patients requiring inotropic or parenteral vasodilator therapy. Sub-study analysis of 217 ambulatory class IV patients from the COMPANION trial demonstrated that CRTP and CRTD provided substantial reductions in HF hospitalization and all-cause mortality [54]. Subsequent studies have demonstrated improvements in ventricular remodeling and clinical composite scores. Despite these benefits, studies continue to show that 1- and 2-year mortality remain high in these patients at 25 % and 38 % respectively [55]. CRT should generally not be regarded as a salvage therapy for end-stage ACC/AHA stage D HF patients.

Patients with LVEF >35 %

There are several studies examining the utility of CRT in patients with moderately reduced LV systolic function (LVEF 35–45 %). Substudy analysis from the PROSPECT trial including 86 patients with LVEF >35 % demonstrated benefits comparable to patients with more severely depressed EFs in LV end systolic volume and clinical composite score [56]. In the BLOCK-HF trial, Curtis et al. examined the role of CRT vs. RV pacing in 691 patients with advanced atrioventricular block necessitating pacing and an LVEF ≤50 % with NYHA class I–III symptoms. They demonstrated a 26 % reduction in the primary composite endpoint of time to death from any cause, urgent care visit for HF, or a 15 % or more increase in LV end-systolic volume index in patients with a mean QRS duration of 122 ms. The role of CRT in this population is to be further addressed prospectively in the currently enrolling MIRACLE EF trial which will assess the utility of CRT-P in patients with QRS duration >30 ms and LVEF 35–50 % [57].

Summary

CRT has emerged as a critically important therapy for patients with persistent symptoms of systolic HF despite optimal medical therapy. An extensive program of clinical trials has demonstrated substantial benefits in HF morbidity and mortality in

appropriately selected patients. Current efforts focus on refining candidate selection to identify patients most likely to respond and perhaps expand candidacy to patients who do not meet conventional criteria.

References

1. Jessup M, Brozena S. Heart failure. N Engl J Med. 2003;348(20):2007–18.
2. WIggers CJ. The muscle reactions of the mammalian ventricles to artificial surface stimuli. Am J Phys. 1925;73:346–78.
3. Askenazi J, Alexander JH, Koenigsberg DI, Belic N, Lesch M. Alteration of left ventricular performance by left bundle branch block simulated with atrioventricular sequential pacing. Am J Cardiol. 1984;53(1):99–104.
4. Burkhoff D, Oikawa RY, Sagawa K. Influence of pacing site on canine left ventricular contraction. Am J Phys. 1986;251(2 Pt 2):H428–35.
5. Zile MR, Blaustein AS, Shimizu G, Gaasch WH. Right ventricular pacing reduces the rate of left ventricular relaxation and filling. J Am Coll Cardiol. 1987;10(3):702–9.
6. Gottipaty V, Krelis S, Lu F. Vesnarinone study analysis (Abstract 847–4). J Am Coll Cardiol. 1999;33(2):145.
7. Lattuca JJ, Cohen TJ, Mower MM. Biventricular pacing to improve cardiac hemodynamics. Clin Rev. 1990;38:882.
8. Cazeau S, Ritter P, Bakdach S, Lazarus A, Limousin M, Henao L, et al. Four chamber pacing in dilated cardiomyopathy. Pacing Clin Electrophysiol. 1994;17(11 Pt 2):1974–9.
9. Nelson GS, Berger RD, Fetics BJ, Talbot M, Spinelli JC, Hare JM, et al. Left ventricular or biventricular pacing improves cardiac function at diminished energy cost in patients with dilated cardiomyopathy and left bundle-branch block. Circulation. 2000;102(25):3053–9.
10. Thackray S, Easthaugh J, Freemantle N, Cleland JGF. The effectiveness and relative effectiveness of intravenous inotropic drugs acting through the adrenergic pathway in patients with heart failure—a meta-regression analysis. Eur J Heart Fail. 2002;4(4):515–29.
11. Kass DA. Pathobiology of cardiac dyssynchrony and resynchronization. Heart Rhythm. 2009;6(11):1660–5.
12. Haddad H, Dwivedi G, Haddad T, Abo-Shasha R, McArdle B, Wells RG, et al. The effect of CRT therapy on RV function in patients with severe LV dysfunction: a Matched Control Study. J Am Coll Cardiol. 2013;61(10_S):e649.
13. Auricchio A, Stellbrink C, Sack S, Block M, Jü V, Bakker P, et al. Long-term clinical effect of hemodynamically optimized cardiac resynchronization therapy in patients with heart failure and ventricular conduction delay. J Am Coll Cardiol. 2002;39(12):2026–33.
14. Cazeau S, Leclercq C, Lavergne T, Walker S, Varma C, Linde C, et al. Effects of multisite biventricular pacing in patients with heart failure and intraventricular conduction delay. N Engl J Med. 2001;344(12):873–80.
15. Abraham WT, Fisher WG, Smith AL, Delurgio DB, Leon AR, Loh E, et al. Cardiac resynchronization in chronic heart failure. New Engl J Med. 2002;346(24):1845–53.
16. Young JB, Abraham WT, Smith AL, Leon AR, Lieberman R, Wilkoff B, Canby RC, Schroeder JS, Liem LB, Hall S, Wheelan K; Multicenter InSync ICD Randomized Clinical Evaluation (MIRACLE ICD) Trial Investigators. Combined cardiac resynchronization and implantable cardioversion defibrillation in advanced chronic heart failure: the miracle icd trial. JAMA 2003;289(20):2685–94.
17. McAlister Fa EJHN et al. Cardiac resynchronization therapy for patients with left ventricular systolic dysfunction: a systematic review. JAMA. 2007;297(22):2502–14.
18. Bristow MR, Saxon LA, Boehmer J, Krueger S, Kass DA, De Marco T, et al. Cardiac-resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure. New Engl J Med. 2004;350(21):2140–50.

19. Cleland JGF, Daubert J-C, Erdmann E, Freemantle N, Gras D, Kappenberger L, et al. The effect of cardiac resynchronization on morbidity and mortality in heart failure. New Engl J Med. 2005;352(15):1539–49.
20. Cleland JGF, Daubert J-C, Erdmann E, Freemantle N, Gras D, Kappenberger L, et al. Longer-term effects of cardiac resynchronization therapy on mortality in heart failure [the CArdiac REsynchronization-Heart Failure (CARE-HF) trial extension phase]. Eur Heart J. 2006;27(16):1928–32.
21. Abraham WT, Young JB, León AR, Adler S, Bank AJ, Hall SA, et al. Effects of cardiac resynchronization on disease progression in patients with left ventricular systolic dysfunction, an indication for an implantable cardioverter-defibrillator, and mildly symptomatic chronic heart failure. Circulation. 2004;110(18):2864–8.
22. Linde C, Abraham WT, Gold MR, St. John Sutton M, Ghio S, Daubert C. Randomized trial of cardiac resynchronization in mildly symptomatic heart failure patients and in asymptomatic patients with left ventricular dysfunction and previous heart failure symptoms. J Am Coll Cardiol. 2008;52(23):1834–43.
23. Tang ASL, Wells GA, Talajic M, Arnold MO, Sheldon R, Connolly S, et al. Cardiac-resynchronization therapy for mild-to-moderate heart failure. New Engl J Med. 2010;363(25):2385–95.
24. Moss AJ, Hall WJ, Cannom DS, Klein H, Brown MW, Daubert JP, et al. Cardiac-resynchronization therapy for the prevention of heart-failure events. New Engl J Med. 2009;361(14):1329–38.
25. Santangeli P, Di Biase L, Pelargonio G, Dello Russo A, Casella M, Bartoletti S, et al. Cardiac resynchronization therapy in patients with mild heart failure: a systematic review and meta-analysis. J Interv Card Electrophysiol. 2011;32(2):125–35.
26. Stevenson WG, Hernandez AF, Carson PE, Fang JC, Katz SD, Spertus JA, et al. Indications for cardiac resynchronization therapy: 2011 update from the Heart Failure Society of America Guideline Committee. J Card Fail. 2012;18(2):94–106.
27. Sipahi I, Carrigan TP, Rowland DY, Stambler BS, Fang JC. Impact of qrs duration on clinical event reduction with cardiac resynchronization therapy: meta-analysis of randomized controlled trials. Arch Intern Med. 2011;171(16):1454–62.
28. Yancy CW, Jessup M, Bozkurt B, Masoudi FA, Butler J, McBride PE, et al. 2013 ACCF/AHA guideline for the Management of Heart FailureA Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2013;62(13):147–239.
29. Heist EK, Fan D, Mela T, Arzola-Castaner D, Reddy VY, Mansour M, et al. Radiographic left ventricular–right ventricular interlead distance predicts the acute hemodynamic response to cardiac resynchronization therapy. Am J Cardiol. 2005;96(5):685–90.
30. Koplan BA, Kaplan AJ, Weiner S, Jones PW, Seth M, Christman SA. Heart failure decompensation and all-cause mortality in relation to percent biventricular pacing in patients with heart failure. J Am Coll Cardiol. 2009;53(4):355–60.
31. Dimaano VLJ, Abraham TP. The role of echocardiography and tissue doppler imaging in optimal cardiac resynchronization therapy. In: Abraham WT, Baliga RR, editors. Cardiac resynchronization therapy in heart failure. Philadelphia: Lippincott Williams & Wilkins; 2010. p. 59–75.
32. Ellenbogen KA, Gold MR, Meyer TE, Fernndez Lozano I, Mittal S, Waggoner AD, et al. Primary results from the smartdelay determined av optimization: a comparison to other av delay methods used in cardiac resynchronization therapy (SMART-AV) Trial: a randomized trial comparing empirical, echocardiography-guided, and algorithmic atrioventricular delay programming in cardiac resynchronization therapy. Circulation. 2010;122(25):2660–8.
33. Boriani G, Gardini B, Diemberger I, Bacchi Reggiani ML, Biffi M, Martignani C, et al. Meta-analysis of randomized controlled trials evaluating left ventricular vs. biventricular pacing in heart failure: effect on all-cause mortality and hospitalizations. Eur J Heart Fail. 2012;14(6):652–60.

34. León AR, Abraham WT, Curtis AB, Daubert JP, Fisher WG, Gurley J, et al. Safety of transvenous cardiac resynchronization system implantation in patients with chronic heart failure: combined results of over 2,000 patients from a multicenter study program. J Am Coll Cardiol. 2005;46(12):2348–56.
35. Fornwalt BK, Sprague WW, BeDell P, Suever JD, Gerritse B, Merlino JD, et al. Agreement is poor among current criteria used to define response to cardiac resynchronization therapy. Circulation. 2010;121(18):1985–91.
36. Hsu JC, Solomon SD, Bourgoun M, McNitt S, Goldenberg I, Klein H, et al. Predictors of super-response to cardiac resynchronization therapy and associated improvement in clinical outcome: the MADIT-CRT (Multicenter Automatic Defibrillator Implantation Trial With Cardiac Resynchronization Therapy) Study. J Am Coll Cardiol. 2012;59(25):2366–73.
37. Tanaka H, Nesser H-J, Buck T, Oyenuga O, RA J, et al. Dyssynchrony by speckle-tracking echocardiography and response to cardiac resynchronization therapy: results of the Speckle Tracking and Resynchronization (STAR) study. Eur Heart J. 2010;31(14):1690–700.
38. Stefan L, Sedláček K, Černá D, Krýže L, Vančura V, Marek T, et al. Small left atrium and mild mitral regurgitation predict super-response to cardiac resynchronization therapy. Europace. 2012;14(11):1608–14.
39. Stefan L, Sedláček K, Černá D, Krýže L, Vančura V, Marek T, Kautzner J. Small left atrium and mild mitral regurgitation predict super-response to cardiac resynchronization therapy. Europace. 2012;14(11):1608–14.
40. Sade LE, Özin B, Atar I, et al. Right ventricular function is a determinant of long-term survival after cardiac resynchronization therapy. J Am Soc Echocardiogr. 2013;26(7):706–13.
41. Muto C, Solimene F, Gallo P, Nastasi M, La Rosa C, Calvanese R, et al. A randomized study of CRT-D versus dual-chamber ICD in ischemic cardiomyopathy with narrow QRS: the NARROW-CRT Study. Arrhythmia and Electrophysiology: Circulation; 2013.
42. Jansen AHM, Bracke F, JM v D, KH P, JC P, van den Bosch HCM, et al. The influence of myocardial scar and dyssynchrony on reverse remodeling in cardiac resynchronization therapy. Eur J Echocardiogr. 2008;9(4):483–8.
43. Hummel JP, Lindner JR, Belcik JT, Ferguson JD, Mangrum JM, Bergin JD, et al. Extent of myocardial viability predicts response to biventricular pacing in ischemic cardiomyopathy. Heart Rhythm. 2005;2(11):1211–7.
44. Dong Y-X, Powell BD, Asirvatham SJ, Friedman PA, Rea RF, Webster TL, et al. Left ventricular lead position for cardiac resynchronization: a comprehensive cinegraphic, echocardiographic, clinical, and survival analysis. Europace. 2012;14(8):1139–47.
45. Dupont M, Rickard J, Baranowski B, Varma N, Dresing T, Gabi A, et al. Differential response to cardiac resynchronization therapy and clinical outcomes according to QRS morphology and QRS duration. J Am Coll Cardiol. 2012;60(7):592–8.
46. Mullens W, Grimm RA, Verga T, Dresing T, Starling RC, Wilkoff BL, et al. Insights from a cardiac resynchronization optimization clinic as part of a heart failure disease management program. J Am Coll Cardiol. 2009;53(9):765–73.
47. Aranda JM, Woo GW, Schofield RS, Handberg EM, Hill JA, Curtis AB, et al. Management of heart failure after cardiac resynchronization therapy. J Am Coll Cardiol. 2005;46(12):2193–8.
48. Savelieva I, John Camm A. Atrial fibrillation and heart failure: natural history and pharmacological treatment. Europace. 2004;5:5–19.
49. Kamath GS, Cotiga D, Koneru JN, Arshad A, Pierce W, Aziz EF, et al. The utility of 12-lead holter monitoring in patients with permanent atrial fibrillation for the identification of nonresponders after cardiac resynchronization therapy. J Am Coll Cardiol. 2009;53(12):1050–5.
50. Ganesan AN, Brooks AG, Roberts-Thomson KC, Lau DH, Kalman JM, Sanders P. Role of av nodal ablation in cardiac resynchronization in patients with coexistent atrial fibrillation and heart failure. J Am Coll Cardiol. 2012;59(8):719–26.
51. Beshai JF, Grimm RA, Nagueh SF, Baker JH, Beau SL, Greenberg SM, et al. Cardiac-resynchronization therapy in heart failure with narrow qrs complexes. N Engl J Med. 2007;357(24):2461–71.

52. Chung ES, Leon AR, Tavazzi L, Sun J-P, Nihoyannopoulos P, Merlino J, et al. Results of the Predictors of Response to CRT (PROSPECT) Trial. Circulation. 2008;117(20):2608–16.
53. NCT00683696: Echocardiography Guided Resynchronization Therapy (EchoCRT) 2013; Available from: http://clinicaltrials.gov/ct2/show/study/NCT00683696?show_locs=Y.
54. Lindenfeld J, Feldman AM, Saxon L, Boehmer J, Carson P, Ghali JK, et al. Effects of cardiac resynchronization therapy with or without a defibrillator on survival and hospitalizations in patients with New York Heart Association class IV heart failure. Circulation. 2007;115(2):204–12.
55. van Bommel RJ, van Rijnsoever E, Borleffs CJW, Delgado V, Marsan NA, Bertini M, et al. Effect of cardiac resynchronization therapy in patients with New York Heart Association functional class IV heart failure. Am J Cardiol. 2010;106(8):1146–51.
56. Chung ES, Katra RP, Ghio S, Bax J, Gerritse B, Hilpisch K, et al. Cardiac resynchronization therapy may benefit patients with left ventricular ejection fraction >35 %: a PROSPECT trial substudy. Eur J Heart Fail. 2010;12(6):581–7.
57. NCT01735916: MIRACLE EF Clinical Study. 2013. [Cited 2013]. Available from: http://clinicaltrials.gov/ct2/show/NCT01735916.

Chapter 18
Revascularization and Heart Failure

John W. C. Entwistle III and Andrew S. Wechsler

Abbreviations

AWESOME	Angina with extremely serious operative mortality evaluation
CABG	Coronary artery bypass grafting
CASS	Coronary Artery surgery study
CCS	Canadian cardiovascular society
CHF	Congestive heart failure
DES	Drug-eluting stent
DSE	Dobutamine stress echocardiography
HEART	Heart failure revascularization trial
IABP	Intra-aortic balloon pump
IMA	Internal mammary artery
LAD	Left anterior descending
LVAD	Left ventricular assist device
LVEDVI	Left ventricular end diastolic volume index
LVESVI	Left ventricular end systolic volume index
LVEF	Left ventricular ejection fraction
MRI	Magnetic resonance imaging
NYHA	New York Heart Association
OMM	Optimal medical management
PARR-2	PET and Recovery following revascularization

J.W.C. Entwistle III, MD, PhD (✉)
Jefferson University Hospital, Department of Surgery, Division of Cardiothoracic Surgery, 1025 Walnut Street Suite 607, College Bldg., Philadelphia, PA 19107, USA
e-mail: john.entwistle@jefferson.edu

A.S. Wechsler, MD
Drexel University College of Medicine, Department of Cardiothoracic Surgery, 245 North 15th Street MS 111, Philadelphia, PA 19102, USA
e-mail: andrew.wechsler@drexelmed.edu

H. Eisen (ed.), *Heart Failure*, DOI 10.1007/978-1-4471-4219-5_18

PAsP	Pulmonary artery systolic pressure
PCI	Percutaneous coronary intervention
PET	Positron emission tomography
REHEAT	Revascularization in ischemic heart failure trial
SPECT	Single-photon emission computed tomography
STICH	Surgical treatment for ischemic heart failure
SVR	Surgical ventricular reconstruction

Introduction

Management of patients with important myocardial dysfunction and concomitant coronary artery disease can be challenging. There is a dearth of data from randomized studies to help guide the decision-making process, and the available data can be confusing due to small sample sizes, inconsistent definitions, lack of rigorous criteria for study enrollment and the retrospective nature of many studies. The increase in public reporting of surgical and interventional cardiologic results may potentially lead to pressure to deny high-risk patients appropriate therapy if there is unclear evidence for benefit, especially if there is a sense that the risk-stratification system will not adequately account for the risk factors. A clear understanding of the available data can help ensure that patients receive appropriate revascularization when there is a reasonable chance for improved survival or symptom abatement.

For the typical patient with ischemic cardiomyopathy, the decision to proceed with revascularization is relatively easy based on the patient's symptoms and coronary anatomy as there are large studies or guidelines to support that decision. Occasionally, an assessment of myocardial viability may be useful in guiding the decision. However, some patients need additional evaluation as there are findings that lead to a very high operative mortality or suggest less opportunity for favorable long-term outcome with revascularization, and patients with those factors should only receive revascularization with caution. An understanding of the available data can help simplify the decision-making process.

The Coronary Artery Surgery Study (CASS) was an early attempt to compare bypass surgery with medical therapy [1]. While it included patients with a depressed left ventricular ejection fraction (LVEF), those with an LVEF of <35 % were excluded from the trial and is precisely the group of patients that leads to many of the clinical dilemmas today. More recently, a few randomized trials have studied the management of patients with ischemic cardiomyopathy and significantly decreased LVEF and had the potential to put some of these questions to rest. The results of the Surgical Treatment for Ischemic Heart Failure (STICH) trial [2] were controversial at best. The Heart Failure Revascularization Trial (HEART) [3] was closed prematurely due to withdrawal of funding related to slow patient recruitment, and the PET and Recovery Following Revascularization (PARR-2) [4] trial looked specifically at PET-guided management of patients rather than the relative merits of surgery versus medical management. Despite these publications, the management of this patient group is not much clearer than it was a decade ago.

The key factor in directing patient care should always be improvement of the patient's condition, whether that be fewer symptoms or better survival. Revascularization in ischemic cardiomyopathy can be achieved in many patients with low surgical risk. While it is clear that some patients represent high surgical risk, most patients with ischemic cardiomyopathy are at high risk for medical management as well. In order to make the choice between high-risk surgery and high-risk medical management, it is important to understand the outcomes of both therapies and to try to select that which is best for the individual patient.

Major Trials

CASS Registry

The first large-scale study to assess the relative roles of medical management and revascularization in patients with ischemic cardiomyopathy was the CASS Registry [5]. This study used a large cohort of non-randomized patients who did not meet the entry criteria for the CASS study and were followed for outcomes. In the subgroup with an EF $\leq$ 35 %, there were 420 patients treated medically and 231 treated with coronary artery bypass grafting (CABG). There were several different baseline characteristics, and 30 % of the CABG patients underwent myocardial plication or resection for aneurysm as well. After controlling for preoperative variables, patients who underwent surgery had better outcomes than their medically treated counterparts, with the greatest benefit seen in patients with an ejection fraction <25 %. In that group, 5-year survival after CABG was 63 % versus 43 % in medically-managed patients. Patients who presented with angina had greater symptomatic improvement with surgery (30.2 % versus 9.8 %) while only 6.4 % of surgical patients and 5.8 % of medical patients presenting with heart failure symptoms were free of limitation. While survival for patients with angina was much better with surgery, those whose primary symptom was dyspnea or fatigue had a 3-year mortality of 45.2 % in both groups. Although this study was non-randomized, it represented a large patient population that was closely followed and provided the basis for the treatment of patients with ischemic cardiomyopathy for many years. It helped define the mantra that patients with ischemic cardiomyopathy and angina should undergo revascularization or, alternatively, demonstrated that clinicians were able to successfully use undefined patient characteristics to select therapies for their patients.

STICH

The STICH Trial was an NIH-funded study designed to answer two basic questions. The main focus of the study was to determine if patients who were candidates for CABG and had a large area of anterior akinesia or dyskinesia were better treated with CABG alone or CABG plus surgical ventricular reconstruction (SVR)

(Hypothesis 2). This portion of the study was highly criticized for deviations from its protocol involving patient enrollment and management. The other question was whether patients with a reduced ejection fraction and coronary artery disease were better treated with optimal medical management (OMM) or OMM plus CABG (Hypothesis 1). There were 1212 patients with an EF $\leq$ 35 % randomized in the Hypothesis 1 arm of the trial [2]. Patients with $\geq$50 % stenosis of the left main (LM), or with Canadian Cardiovascular Society (CCS) Class III or IV angina were excluded from the trial as these patients were felt to be best served with surgical therapy. While the overall death rate was similar (41 % medical versus 36 % CABG), the rate of cardiovascular death was less in the CABG group (33 % medical versus 28 % CABG, p = 0.05), and the CABG group had a lower combined outcome of death from any cause or readmission for cardiovascular cause. One concern with the study was the high crossover rate such that 17 % of the patients assigned to OMM alone received CABG and 9 % of the patients randomized to CABG were treated medically. The study was designed to assess therapy on an intent-to-treat basis, so the large number of cross-over patients may have contributed to the apparently equivalent results. When analyzed in an as-treated manner, there was a survival advantage for surgery that was also present when cross-over patients were excluded and only per-protocol patients that received their assigned therapy were included. While well-intentioned, the conclusion of the study that there is no difference between survival in medically managed and revascularized patients is flawed due to the high crossover rate and the intention-to-treat analysis, and may be used to deny patients appropriate therapy.

Another issue with the STICH trial is that only about 50 % of the cohort underwent any sort of viability testing before randomization, limiting the ability to do effective subgroup analysis. An attempt to analyze the effects of viability on outcome [6] showed that unadjusted mortality with revascularization was lower in patients with viable myocardium, but this difference was not present after adjustment for baseline variables. In addition, there did not appear to be a survival benefit for surgical patients over their medical counterparts regardless of viability on an intent-to-treat basis. However, this study also had several problems, most notably the potentially non-random manner in which viability tests were ordered such that patients with a preoperative viability study may have been significantly different from those without such a test. The preoperative variables published in the two STICH reports contain sufficiently different data sets making comparison of the groups difficult, but it appears that the patients who underwent preoperative viability testing had more heart failure symptoms than those who did not, suggesting that a selection bias did occur. In addition, amongst the patients studied, the viable and non-viable patient groups had several key differences in baseline characteristics, such as EF, left ventricular end diastolic volume index (LVEDVI) and left ventricular end systolic volume index (LVESVI). In the presence of these confounding variables, viability may not be an independent risk factor for poor outcome, but may still be a marker of risk. In the cohort of patients undergoing SVR in addition to revascularization (Hypothesis 2), the degree of volume reduction was judged by many critics to be inadequate, possibly explaining the conclusion of the study that

there was not additional benefit in SVR over revascularization alone. Since SVR is felt by many to be useful in the treatment of patients with heart failure symptoms due to a large anterior akinetic area following myocardial infarction, the criteria for patient enrollment in this study were questioned as there were many patients whose ischemic symptoms were greater than their heart failure symptoms and patients were included who did not have evidence of prior myocardial infarction but were subject to anterior volume reduction operations.

HEART

The HEART Trial [3] was designed to help determine the optimal management of patients with a low ejection fraction and coronary artery disease in the absence of angina. It was established as a trial of patients with an EF $\leq$ 35 % with demonstrated viability who were randomized to either conservative management or angiography followed by either percutaneous coronary intervention (PCI) or CABG as judged appropriate. While there was no difference in outcome between the conservative and invasive management strategies, the study was underpowered as there were only 138 patients enrolled due to slow recruitment of patients and subsequent withdrawal of funding. Although this study was unsuccessful in answering its intended question, it raises the issue that patients with ischemic cardiomyopathy and heart failure symptoms may be equally served with revascularization or conservative management. However, a study powered appropriately to answer this question is still needed.

Duke Databank

The Duke Cardiovascular Disease Databank is a large clinical dataset of patients treated at Duke University Hospital that started enrolling patients in 1969. It includes data on over 200,000 patients and has been a source of information on a variety of cardiovascular problems. In a report of 1391 patients with ischemic cardiomyopathy and heart failure symptoms with an EF < 40 % and New York Heart Association (NYHA) Class II–IV congestive heart failure (CHF), O'Conner et al. [7] looked at outcomes in patients treated medically and compared them to patients treated surgically between 1969 and 1994. There were many differences in the baseline characteristics between the medical and surgical groups. After adjustment for these differences, short-term and long-term outcomes were analyzed. For short-term survival, medical management was superior for single vessel disease. There was no difference for two-vessel disease, and a trend to favor surgery for triple vessel disease. However, all groups were best served with surgery for survival greater than 30 days as this allowed the impact of up-front surgical risk to diminish. Surgery was favored regardless of age, EF, NYHA Class or angina status. More recently,

Velazquez et al. [8] applied the STICH enrollment criteria to the Duke Databank to compare medical and surgical management in ischemic cardiomyopathy. Patients with LM > 50 %, CCS Class III–IV, acute myocardial infarction or those treated with PCI were excluded. A total of 763 patients were included, 624 who had received medical treatment and 139 who underwent CABG. After applying propensity analysis methods, there was a survival benefit that favored surgical management through 10 years. While these two studies are from a single institution and are retrospective in nature, they are some of the largest studies that are available to help guide management in these patients.

The CASS Registry [5] and Duke Database [7, 8] studies support revascularization in patients with ischemic cardiomyopathy. The same applies for the STICH Trial [2] on an "as treated" basis. The guidelines for revascularization reflect these concepts and provide the basis for patient selection in many cases. Many patients with ischemic cardiomyopathy can undergo revascularization with an acceptable operative mortality, and long-term outcome with surgical management is superior to medical management in many of these patients.

Patient Selection

LM and Angina

The decision to revascularize a patient with ischemic cardiomyopathy needs to be based on patient symptoms, myocardial assessment and clinical judgment. Often, the decision to offer revascularization is relatively easy such as in patients with stenosis of the left main artery or significant angina and is supported by published guidelines. Significant left main stenosis is considered an indication for CABG [9] with or without symptoms. As such, these patients have been excluded from randomized trials of medical versus surgical therapy in ischemic cardiomyopathy. In the absence of other factors that would significantly elevate the risk of intervention, patients with LM stenosis ≥50 % should undergo revascularization regardless of the ejection fraction. Similarly, significant angina is considered an indication for revascularization in the presence of double- or triple-vessel disease, or significant stenosis of the proximal left anterior descending (LAD) [9], even in the presence of a diminished ejection fraction. In the presence of compelling coronary anatomy and significant angina (CCS Class III or IV), especially in the absence of significant heart failure symptoms, additional assessment is usually not necessary before proceeding with revascularization as the operative mortality is relatively low, symptomatic improvement is good and the results with revascularization are considerably better than with medical management.

Patients who are asymptomatic or have milder degrees of angina may also be appropriate for revascularization. In the 2004 American College of Cardiology and American Heart Association [9] CABG guidelines, CABG is recommended as a Class I indication in patients with asymptomatic ischemia, mild angina or stable

angina with triple vessel disease, with a larger survival benefit compared to medical therapy when the ejection fraction is less than 50 %. Similar recommendations are given for stable angina with 2-vessel disease. CABG in patients with stable angina with proximal LAD disease and an ejection fraction <50 % is a Class IIa indication. One caveat for these recommendations is that patients with mild systolic dysfunction have a significantly lower operative mortality than those with more severe dysfunction. While few cardiac surgeons would hesitate to follow these guidelines on a patient with an ejection fraction of 40–45 %, the data that supports CABG in EF less than 35 % in the absence of significant angina is less robust and these patients may require additional evaluation such as viability testing, assessment of ventricular size or evaluation for dyssynchrony.

Viability

There is consensus that revascularization is appropriate when there is myocardial viability in the area of intended revascularization such that the procedure can either restore flow to jeopardized myocardium or prevent future ischemic events. Angina may be used as a marker of viability [10, 11], although there is not perfect correlation between symptoms and viability as assessed noninvasively. Current guidelines [12] recommend assessment of myocardial ischemia and viability in patients with ischemic cardiomyopathy who may be candidates for revascularization in the absence of angina as a Class IIa indication.

Viability can be assessed by several means. Dobutamine stress echocardiography (DSE), single-photon emission computed tomography (SPECT), positron emission tomography (PET) and magnetic resonance imaging (MRI) are the most commonly utilized methods. They work by assessing cellular integrity, metabolic function, microcirculation or contractile reserve. Each has strengths and weaknesses, but there is no apparent difference in clinical outcome based on the test chosen [13, 14]. Ideally, viability testing would accurately determine how much of the dysfunctional myocardium may recover function with restoration of blood flow and how much is scar and is incapable of functional recovery. Myocardial stunning is defined as myocardium that has normal blood flow but is dysfunctional due to an acute event. Stunned myocardium has the potential to recover full function in the absence of additional injury. In the setting of ischemic cardiomyopathy, myocardium may be adequately perfused at rest but be underperfused during stress, creating stunning due to repeated episodes of ischemia. As this process continues, the stunned segments may progress to become hibernating myocardium. Hibernating myocardium is dysfunctional myocardium that has down-regulated its pattern of genetic expression in response to chronic inadequate blood flow, and has the potential for full recovery with the resumption of normal perfusion. Transmural scar is a full thickness myocardial injury that is permanent, while non-transmural scar represents an area of non-viable tissue (often subendocardium) with viable myocardium making up the rest of the thickness of the ventricular wall. While an area of non-transmural

myocardium may appear viable on some studies due to perfusion of the adjacent viable tissue, the scar may limit the ability of this muscle to produce a contractile segment. The critical distinction between stunned and hibernating myocardium is that stunned myocardium usually recovers function within 3 months whereas hibernating myocardium may take longer to recover [15].

In a given patient, the presence or absence of viability is generally based on the presence of dysfunctional but viable myocardium in sufficient amount to be clinically significant with the understanding that enough myocardium needs to be salvageable with revascularization for the patient to gain a survival or symptom advantage over medically treated patients. Quantification of viability is often made first by assessing the number of dysfunctional myocardial segments that are viable by one of the accepted methods. The percentage of dysfunctional segments in patients with ischemic cardiomyopathy varies significantly. Three studies labeled 25 % [16], 69 % [15] and 46 % [17] of the studied segments dysfunctional, and 37 % [16], 45 % [15] and 81 % [17] of those segments were viable in the same studies, respectively, with the remaining dysfunctional segments representing scar. Once the viable segments have been identified, the myocardium of patients as a whole is then labeled as viable or non-viable depending upon the percentage of dysfunctional segments in a given patient that are viable. Typically, a patient with approximately 25 % of dysfunctional segments identified as viable is considered to have myocardial viability. Percentages of patients with viability vary greatly from 27 to 81 % [6, 10, 13, 16, 18, 19], with much of the variability likely due to patient selection rather than the method used to ascertain viability.

An early report of the use of PET scanning to determine the influence of viability on outcomes in ischemic cardiomyopathy included 93 patients referred for PET scans at a central facility [20] who were treated at their local hospitals. There were 50 patients who were treated medically and 43 who underwent CABG in this multicenter retrospective study. Predictors of survival included CHF class, history of prior MI and mismatch on the PET scan. Interestingly, the authors defined mismatch as >5 % of the ventricle showing mismatch between perfusion and glucose metabolism, in contrast to most other studies where viability is usually defined as ≥25 % of the myocardium with perfused but dysfunctional segments. In this study of unmatched patients, those with PET mismatch had better survival (75 % vs. 30 % at 4 years) and more improvement in CHF and angina symptoms than their medical counterparts. In patients without mismatch, there was a non-significant improvement in survival if the patient had severe angina but no difference if there were no mismatch and minimal angina. Patients with a low EF and severe angina had better survival than their medical counterparts regardless of the presence of viability, confirming that this group of patients does not need to be studied for viability prior to operation. In terms of symptomatic improvement, there was mild improvement in CHF symptoms in medically treated patients. Surgical patients had improved angina class, and an improvement in heart failure class that was more apparent in patients with PET mismatch. Those without mismatch but with severe angina had a trend towards better outcomes with revascularization. Amongst medically-treated patients, those with mismatch had poorer survival than those without (30 % vs.

52 %). The study demonstrated that patients with viable myocardium should be considered for revascularization regardless of symptoms and it confirmed that patients with angina should undergo revascularization without regard to viability.

Bax et al. [21] evaluated 68 patients with preoperative DSE followed by revascularization by CABG (n = 60) or angioplasty (n = 8). Sixty two patients had radionuclide ventriculography before and 3 months after revascularization. Viability was associated with better post-operative outcomes. Viable patients had improvement in EF, NYHA Class and CCS Class, while non-viable patients as a whole showed improvement only in CCS. While there was improvement in NYHA Class in 21 % of the individuals without viability, this was not seen in the group as a whole. There was also a higher event rate in patients with non-viable myocardium when defined as a combined outcome of cardiac death, MI and readmission for CHF. The viability of the myocardium also influenced the recovery of myocardium. On follow-up examination, there was improvement in 27 % of the dysfunctional segments of myocardium. Improvement occurred in 90 % of the viable segments compared to 25 % of the non-viable segments. The improvement in contraction of non-viable segments demonstrates either lack of reproducibility of test methods or difficulty in determining viability by non-invasive means, and it suggests that the presence or absence of viability alone cannot be use to predict outcome.

A similar lack of perfect correlation between viability and recovery was reported by Mandegar et al. [22]. In 85 patients with ischemic cardiomyopathy who were deemed viable by DSE, 17.6 % of the patients did not show an improvement in EF after CABG despite an improvement seen on DSE at the time of initial evaluation. The average improvement in EF was 9.9 %, and patients with a higher LVESV had a lower likelihood of EF recovery, in contrast to other data that showed no correlation between ventricular size and EF improvement [21]. The number of viable segments on DSE correlated with outcome. Patients with 6 or more viable segments out of a possible 16 segments had a favorable outcome regardless of the LVESV, but LVESV played an important role in determining outcome in patients with <6 viable segments. In other words, the extent of remodeling becomes an independent predictor of outcome in patients with limited myocardial viability.

In the multicenter PARR-2 trial, 430 patients with ischemic cardiomyopathy were randomized to standard therapy or to have a preoperative PET scan to help guide therapy [4]. The hypothesis was that the information gained from a PET scan in addition to standard of care studies would influence patient management and improve survival. This study demonstrated a trend towards reduction of cardiac events with PET-guided therapy but no difference in the primary outcome of death, MI or cardiac rehospitalization at 1 year. Abraham et al. [23] reported a post hoc analysis of the PARR-2 patients who received care at the University of Ottawa Heart Institute, termed the Ottawa-FIVE study. This was done because the authors from Ottawa had enrolled the majority of the PARR-2 patients and they felt that their results may have differed from those of the other centers, many of which did not have PET scanning on site and may have felt less confident in using PET results to make important patient management decisions. The Ottawa-FIVE PET-assisted subgroup had fewer patients (19 %) reach the composite endpoint compared to stan-

dard care (41 %) despite 78 % of the latter group undergoing non-PET viability testing based on standard clinical criteria. The difference in outcome could not be explained solely on the incidence of revascularization since the percentage of patients who underwent revascularization was the same in the PET-assisted and standard care groups. Further, while the Ottawa-FIVE PET-assisted group had better outcomes than the non-Ottawa PARR-2 patients, the Ottawa standard care group fared worse than their PARR-2 counterparts. It appears that the Ottawa-FIVE group, taken as a whole, did about as well as the non-Ottawa PARR-2 patients. Therefore, while there is a suggestion that preoperative PET scanning may be useful in determining the treatment plan for patients with ischemic cardiomyopathy even if they have undergone viability assessment by other means, the data is not clear on this issue. This was also seen in another study where PET was used to guide revascularization decisions [24]. The standard care group had a higher operative mortality and lower long-term survival than those who underwent PET-guided revascularization, but the survival in the patients excluded from CABG due to the PET scan results was so poor that the survival in the overall group was roughly similar between PET-guided therapy and non-PET-guided therapy. Thus, the benefit to PET scanning may be in withholding surgery from those who will do poorly with either treatment rather than increasing overall patient survival.

Viability testing in ischemic cardiomyopathy has limited value. It is not necessary to determine viability through additional studies in patients with significant angina, as they will do better with revascularization than medical management. It may have use in predicting operative risk and symptomatic improvement in patients with heart failure as a dominant symptom. Patients with severe ischemic cardiomyopathy and significant heart failure are less likely to have improvement in symptoms or ejection fraction after revascularization. When performed, viability testing should be used only as one criteria in the decision to perform revascularization, not as an absolute requirement, as some patients without viability will benefit from revascularization.

Mode of Revascularization

Many studies have been conducted to examine the relative benefits and effectiveness of CABG versus PCI in the treatment of patients with coronary artery disease. While the specifics of the studies have varied, they tend to show similar findings: short- and medium-term mortality rates are similar for the two therapies; long-term survival is better with CABG; reintervention rates are higher with PCI; and CABG offers more complete revascularization. Similar results have been seen in patients with ischemic cardiomyopathy. Gioia et al. [25] published a non-randomized multicenter study looking at 220 patients with an EF $\leq$ 35 % who underwent PCI with a drug-eluting stent (DES) or CABG. DES patients had fewer treated vessels (1.3 vs. 3), lower 6-month mortality and a higher reintervention rate. However, CABG patients had better relief from heart failure symptoms. There was no difference in

survival or cardiovascular outcomes at 2 years despite only 83 % of CABG patients receiving an IMA graft and thienopyridine use for only 3–6 months after DES implantation.

Sedlis et al. [26] reported the results of the Angina With Extremely Serious Operative Mortality Evaluation (AWESOME) trial and registry subgroups with an EF < 35 %. The trial patients (n = 94) were randomized to PCI or CABG to treat medically refractory ischemia, while the registry patients (n = 352) underwent PCI or CABG by either physician or patient choice. While there were some baseline differences in the registry patients, there was no difference in 36-month survival between the treatment groups. These data suggest that revascularization can be performed with either PCI or CABG with equivalent medium-term outcomes with the caveat that all of the patients had significant angina and patients who were asymptomatic or only had symptoms of heart failure were excluded from the trial.

The Revascularization in Ischemic Heart Failure Trial (REHEAT) [27] was a non-randomized prospective case-controlled comparison of PCI and CABG in 109 patients with an EF < 40 %. There were 55 patients treated with PCI (1.8 vessels treated) and 54 patients who underwent CABG (2.8 bypass grafts). All patients had significant angina, viability by DSE and/or ischemia by a treadmill stress test. Short-term survival was better in patients undergoing PCI. There was no difference in survival at 36 months and better long-term event-free survival rates in CABG patients. Long-term functional status was better in PCI patients by treadmill testing but the NYHA and CCS Classes were the similar in both groups.

A meta-analysis of 4766 patients in 19 studies [28] determined that PCI had a low in-hospital mortality rate and an acceptable long-term mortality rate. In addition, it found no difference between CABG and PCI long-term outcomes, although this study is limited by the inherent issues associated with the meta-analysis methodology. While PCI and CABG may be options for revascularization in patients with ischemic cardiomyopathy, some studies have been limited to patients with ischemia or viability [26, 27] and have not included patients with heart failure as the predominant symptom. In addition none of the studies have looked at long-term results (5 – 10 years).

The quality of the target vessels is an important factor in determining outcomes following surgical revascularization. In a study of 908 patients with ischemic cardiomyopathy undergoing surgical revascularization, target coronary arteries were graded as good, fair or poor based on vessel size and presence of diffuse disease [29]. Predictors of survival (mean 65 months) included good or fair coronary status, viability in the areas grafted and complete revascularization. These were also factors in event-free survival. This study clearly demonstrated that patients with a poor ventricle need complete revascularization, and that the quality of the target vessels is important in making that feasible.

Choosing to treat a patient with ischemic cardiomyopathy with revascularization requires a careful analysis of their symptoms and substrate. While PCI and CABG are both reasonable options in ischemic cardiomyopathy, one may have advantages in a given patient and be the preferred method. It is important to provide complete revascularization when possible. When the patient has a poor ventricle and poor targets, medical management may be the preferred option.

Other Risk Factors

Dyssynchrony

Cardiac resynchronization therapy has emerged as a way to improve cardiac function in patients with left bundle branch block and heart failure symptoms. Mechanical dyssynchrony has been evaluated as a prognostic marker for success after revascularization and must be distinguished from electrical dyssynchrony in that many of these patients have a narrow QRS on the EKG. Mechanical dyssynchrony can be assessed by tissue Doppler, gated PET and SPECT. Penicka et al. [30] reported 215 patients with ischemic cardiomyopathy and an EF < 40 % with NYHA Class I–III CHF symptoms who underwent CABG. All were assessed for viability by SPECT and dyssynchrony by tissue Doppler. The in-hospital mortality was 11.6 %. In patients with pre-CABG dyssynchrony ≥119 ms, the operative mortality was 27 % compared to 3 % in patients without dyssynchrony. The presence of dyssynchrony led to a poor outcome regardless of viability seen on SPECT scan. In addition to use as a preoperative predictor of poor outcome, the presence or absence of dyssynchrony after operation was a marker for long-term outcome. Post-operative dyssynchrony ≥72 ms with 5 or fewer viable segments was associated with a higher rate of late death and rehospitalization compared to patients without dyssynchrony and larger areas of viability. In another study from the same group, 79 patients with a EuroSCORE >10 % underwent MRI to assess viability and tissue Doppler to measure dyssynchrony [31]. EuroSCORE underestimated mortality in patients without viability but gave a reasonable assessment of risk in patients with viability. In patients with dyssynchrony ≥105 ms, 30-day mortality was 61 % compared to 11 % in the absence of dyssynchrony. This study demonstrates the important impact of dyssynchrony in patients who have an elevated operative risk and the inaccuracy of using standard risk models to assess patient risk when dyssynchrony is present. In an observational study that used gated PET to assess dyssynchrony [32], mechanical dyssynchrony was an independent predictor of mortality in patients regardless of whether they were treated with revascularization or medically managed, and patients who underwent CABG had better survival than those treated medically at all levels of dyssynchrony. However, the risk of death with CABG approached that of medical management at the extremes of dyssynchrony. This study suggests that patients with dyssynchrony are better treated with surgery and should be offered operation, albeit at higher risk, unless they have severe dyssynchrony.

These studies demonstrate that a focus on dyssynchrony may allow for better patient selection than by looking at ejection fraction alone. While assessment of mechanical dyssynchrony is more difficult than EF, there may be no survival advantage with revascularization in patients with severe dyssynchrony, justifying the additional diagnostic study in patients without other clear indications for revascularization.

Ejection Fraction

There is conflicting evidence assessing whether ejection fraction is a predictor of outcome following revascularization. Low EF has been linked with higher operative mortality [31, 33, 34], but this has not been seen in every study [35]. Long-term survival has been shown to be influenced by preoperative EF [24], while others have shown no correlation [33, 35]. Determining the link between EF and mortality is complicated by other factors that coexist with low EF such as large ventricular volumes or non-viability. These other factors are associated with a poor outcome, making the identification of EF as an independent risk factor difficult. While EF should be taken into consideration when deciding for or against operation, other factors such as viability, symptoms, LV size and the state of compensation may be more important.

Ventricular Size or Volume

One of the greatest predictors of long-term survival in heart failure patients is left ventricular volume. The risk for early death with a severely enlarged heart is significantly higher than with mild LV enlargement. Ventricular volume has also been evaluated as a risk factor for poor outcome following CABG in ischemic cardiomyopathy. Kim et al. [36] reported outcomes in 42 patients with an EF $\leq$ 30 % who underwent volume determinations by radionuclide angiography. The decision to operate was based on clinical grounds more than the results of viability testing. The patients were divided into groups based on the LVESVI. Group A had an LVESVI < 100 ml/m^2 and Group B > 100 ml/m^2. The operative mortality was 5 % in both groups, and there was a non-significant improvement in 2-year survival in Group A compared to Group B. More patients in Group A had Class III–IV CHF before operation than in Group B, yet all Group A patients improved to NYHA Class I–II. In contrast, fewer patients in Group B were in Class III–IV CHF before operation because many of these patients would have been referred for heart transplantation rather than CABG. Yet, the Group B patients that did undergo CABG were unlikely to improve to Class I–II CHF. Of the 6 Group B patients with preoperative Class III–IV CHF, only 2 improved to Class I–II and one died after operation. In contrast to the differential effect with heart failure symptoms, both groups experienced decreased angina with CABG. Similar results were seen in 75 patients followed for 8 years after CABG [37] who had preoperative DSE to assess viability. This group was highly selected in that all patients had evidence of viability and those treated with IABP support were excluded. There was 89.3 % survival at 8 years. In patients with a LVESVI < 100 ml/m^2, there was a 72.1 % freedom from CHF symptoms while only 46.9 % of patients with an LVESVI > 100 ml/m^2 were free from symptoms. There was an improvement in NYHA Class at 4 years, but there was no difference in heart failure symptoms between the preoperative and 8-year time points, suggesting that the symptomatic improvement in CHF is not durable even in patients with preoperative viability.

Bax et al. [38] reported on 79 patients with ischemic cardiomyopathy who underwent preoperative assessment by both PET and SPECT. Viability was present in 49 of the patients. Of the viable patients, 5 died before reassessment at 1 year, 24 had an improvement in EF and 20 showed no improvement in EF. In contrast, the nonviable patients had no improvement in EF as a group, although 11 of 27 individual patients did show some improvement. The greatest predictor of improvement in EF was the LVESV, in that patients with a large ventricle were less likely to show an improvement, these results being similar to that seen by Mandegar et al. [22]. In the article by Bax et al. [38], patients were followed for 3 years. Events were characterized as death, MI and hospital readmission for CHF. The event rate strongly correlated with ventricular size. The event rate in patients with an LVESV $\geq$ 130 mL was 37 %, in LVESV $\geq$ 160 mL was 53 % and in LVESV $\geq$ 180 mL was 63 %. The event rate was 67 % in patients with a large LV without viability compared to 5 % if the ventricles were small with viability.

Preoperative left ventricular size has been associated with outcome independent of viability or ejection fraction. In the severely enlarged heart, remodeling may be so severe that the myocardium is essentially end-stage and is not capable of improving despite revascularization. Patients with severely enlarged ventricles may be better treated by means other than revascularization.

Very Poor Prognostic Signs

The overall mortality rate for patients with ischemic cardiomyopathy undergoing operation is in the range of 3–10 %, although there have been reports with higher and lower mortality rates. Much of this variability depends upon patient selection. Many studies have noted subgroups of patients that have fared much worse than the other patients. Patients with very poor prognostic signs should probably not undergo revascularization without careful consideration since an operative mortality of 20–30 % could easily eliminate any survival advantage that revascularization could otherwise bestow. Table 18.1 [11, 30, 31, 33, 34, 39, 40] lists many of the factors that have been found to put patients at very high operative risk.

Decompensated Patients

While many of the observational studies excluded patients with recent myocardial infarction or worsening heart failure, some have included patients who had more acute presentations. Elefteriades et al. [33] reported on 83 patients with ischemic cardiomyopathy (EF $\leq$ 30 %) who underwent CABG. While the overall mortality rate was 8.4 %, it was 22.7 % in patients who were admitted to the ICU immediately before operation due to cardiogenic shock compared to 3.3 % in those who were stable prior to operation. Emergency operation was also cited as a risk factor for

Table 18.1 Factors that indicate very high operative risk [11, 30, 31, 33, 34, 39, 40]

Risk factor	Mortality associated	Mortality without	Reference
Dyssynchrony by tissue Doppler			
≥119 ms	27 %	3 %	Penicka et al. [30]
>105 ms with EuroSCORE >10	61 %	11 %	Maruskova et al. [31]
Cardiogenic shock	22.7 %	3.3 %	Elefteriades et al. [33]
Elevated filling pressures			
LVEDP ≥ 23 mmHg	20 %	2.7 %	Bouchart et al. [39]
LVEDP ≥ 20 mmHg	3× increase		Pocar et al. [40]
Emergent operation	25 %	n/a	Bouchart et al. [39]
	38.9 %	n/a	Fedoruk et al. [11]
Pulmonary artery pressure (systolic) >70	25 %	n/a	Hovnanian et al. [34]

perioperative death by others [11, 29, 35, 39]. In the study by Bouchart et al. [39], 49 of 141 patients with an EF ≤ 25 % had a transmural infarction within 30 days of operation and 37 patients underwent operation within 24 h of catheterization due to clinical need. The operative mortality was 25 % in those patients requiring operation within 12 h of catheterization. Pocar et al. [40] studied 45 patients with significant heart failure (NYHA Class III–IV) who had undergone preoperative PET scanning prior to elective CABG. While these patients were clinically stable, the preoperative hemodynamics demonstrated a degree of decompensation in many of them. An LVEDP ≥ 25 mmHg was associated with a threefold increase in the risk of death and an LVEDP ≥ 20 mmHg was associated with an increased need for IABP support. None of the patients with an LVEDP ≥ 25 mmHg improved to NYHA Class I. A high operative mortality was also seen by Bouchart et al. [39] where patients with an LVEDP ≥ 23 mmHg had a mortality of 20 % compared to 2.7 % without this risk factor. One theory is that an elevated LVEDP inhibits diastolic flow of the subendocardium and this is responsible for the poor results seen with an elevated LVEDP. Thus, patients who are unstable should be stabilized and optimized if possible before undergoing revascularization. Alternatively, high LVEDP may be a marker for more advanced cardiac injury, decompensation or remodeling, and should prompt consideration for other therapies.

Other High Risk Patients

Elevated pulmonary artery pressure has also been indicted as a significant risk factor in patients undergoing revascularization. Hovnanian et al. [34] reported on 244 patients with an EF ≤ 35 % who had viability by thallium scanning. In-hospital mortality was 3.7 %, but was 25 % in those patients with a pulmonary artery systolic pressure (PAsP) >70 mmHg. However, 17 % of the patients had a mitral valve intervention as well as CABG, making it more difficult to apply these data to patients with coronary disease alone. Selim Isbir et al. [41] also reported a negative survival

effect with an elevated pulmonary artery pressure by multivariate analysis, but no value was given above which the risk rises and pulmonary artery catheters were not placed preoperatively on a routine basis.

NYHA

Many of the patients with ischemic cardiomyopathy have symptoms of CHF. Those with important angina in addition to heart failure symptoms have good survival and symptom relief with revascularization. However, patients with predominantly Class IV CHF symptoms are at higher operative risk [29, 34, 39], have lower long-term survival [34, 35, 39] and have less resolution of their symptoms [37]. It may be difficult to opt for revascularization in a patient with no angina and Class IV heart failure symptoms, especially when the operative mortality can reach 29 % [39], but these same patients are also at high risk for death with medical management alone. Choosing the patient with stable Class IV heart failure symptoms for revascularization and directing the decompensated patients towards medical management, heart transplantation or ventricular assist device therapy may minimize the operative risk and maximize outcomes.

Patient Optimization

The best results are clearly seen in patients who can undergo elective operation and those with compensated symptoms. Appropriate patient selection is the single greatest factor in achieving low operative mortality. In terms of conduct of the operation, myocardial protection is critical to limit additional ischemic damage. Complete revascularization is important in all patients, especially those with ischemic cardiomyopathy [29]. Perioperative management with an intra-aortic balloon pump (IABP) has been shown to be beneficial [41]. The operation also needs to be conducted in a time-efficient manner as longer cross-clamp and bypass times have been associated with lower survival [41]. Choice of conduit may not be as important in ischemic cardiomyopathy as it is with a normal ventricle. Selim Isbir et al. [41] used the left internal mammary artery (IMA) in only 50.4 % of patients and found no correlation between IMA use and outcome out to 4 years. Even though there is evidence that some patients without ischemic cardiomyopathy may benefit from the use of bilateral IMA grafts, it was not better than the use of single IMAs in patients with an ejection fraction <30 %, although there was slightly better outcome with bilateral IMAs seen in patients with an EF $\geq$ 30 % [42]. While these results may be influenced by patient selection in that patients with lower risk may have received bilateral IMAs, these results probably reflect the relative dominance of the cardiomyopathy in determining long-term outcomes rather than the details of the revascularization.

Results

Angina/CHF

One of the main reasons to perform revascularization is to improve symptoms. Angina is present in a significant number of patients with ischemic cardiomyopathy. Revascularization leads to significant improvement in angina score [16, 33], even in the absence of viability [21]. As angina usually signifies the presence of viability, its improvement without demonstrated viability probably represents a limitation in the assessment techniques. The improvement in CHF seems less robust, but improvement can occur [16, 33], although not in the absence of viability [21]. Unfortunately, the improvement in CHF symptoms may not be durable [37]. The improvement in angina and CHF is independent from any change in EF [43]. Patients with ischemic cardiomyopathy who are referred for revascularization can expect improvement in angina symptoms, but should only expect improvement in CHF symptoms if there is myocardial viability present.

EF/Volumes

Ejection fraction is a marker for mortality in patients with heart failure. Many studies have shown an improvement in EF following revascularization [27, 39], although some have only shown improvement in patients with viability [21, 22, 37, 38]. In general, there is no consistent improvement in EF in patients with nonviable myocardium [21, 38]. Some have shown that recovery of EF is dependent upon LVESV [16, 22], with larger ventricles showing less likelihood for recovery of EF. Finally, the status of the coronary arteries to be revascularized plays a role in the recovery of ventricular function. EF improved in patients with good or fair coronary arteries but did not change in patients with poor target vessels [29].

While revascularization may improve ejection fraction, it is not clear that this improvement correlates with better outcome. In a study of 104 patients with ischemic cardiomyopathy and EF $\leq$ 30 % [43] with preoperative and postoperative assessment of EF, only 68 of the patients demonstrated an improvement in EF of $\geq$5 % above baseline. In this group, the EF increased from 24 to 39 %. In contrast, the remaining patients showed no significant improvement (<5 %). Despite this difference in response to revascularization, survival was the same in both groups. In addition, both groups had equivalent improvements in angina and heart failure symptoms. Thus, the improvement in EF may make clinicians feel better about performing revascularization, but is probably not a clinically important marker of outcome.

Similar to EF, ventricular dimensions may improve with revascularization. Bouchart et al. [39] reported a decrease in LVEDVI in patients with ischemic cardiomyopathy who underwent revascularization but these changes were not seen by others [27]. Even if the ventricular dimensions improve with revascularization, there is no evidence that this will lead to a clinically relevant improvement in outcome.

Survival

Based on the few randomized and several non-randomized comparison studies, it is clear that select patients do much better with revascularization than with medical management alone. Many studies have shown good results in patients undergoing revascularization but lack a comparison group, making it difficult to make a definitive statement of benefit. In one large meta-analysis of 4119 patients from 26 studies, 5-year survival was an impressive 73.4 % in patients undergoing on-pump revascularization [44]. This compares favorably to medical management which has been associated with an annual mortality rate of 16 % in patients with viability and 6.2 % in those who were non-viable [13]. Several authors have identified groups of patients who are at high risk for death following surgical revascularization. These patients may be the most difficult to manage, as they likely also have poor outcome with medical management alone. While they may have a high operative mortality, it may be superior to their results with medical management, but may not be high enough to be cost-effective or worth it for the patient and their family. Until better data is available to determine the relative effectiveness of revascularization and medical management in these high-risk patients, other options should be considered.

Other Options

Yoon et al. reported their results in 1468 patients with an EF < 30 %. Patients were either treated with CABG, CABG with mitral valve repair or replacement, CABG with SVR or listing for transplantation. Viability testing was performed in only about 20 % of the patients. The treatment plan was based on the clinical situation. In their retrospective analysis, they determined that most patients would have benefited most with either CABG or listing for transplantation, despite the 18 % mortality seen on the waiting list in this cohort. The authors believe that mitral repair in ischemic cardiomyopathy provides few benefits to most patients. The addition of mitral repair to CABG in patients with 3+ or 4+ mitral regurgitation has been shown to produce no survival benefit and no long-term relief from significant heart failure over CABG alone [45]. Left ventricular reconstruction is, at best, useful in a limited number of patients with ischemic cardiomyopathy as it works best in the setting of an anterior-septal infarct. Although the STICH Trial has cast some doubt about its use in a larger patient population, other data document marked symptomatic improvement and survival benefit when compared with historic controls [46, 47]. If patients are deemed extraordinarily high risk for CABG with little probability of symptomatic or survival benefit, then transplantation is a reasonable option with excellent results. However, despite the potential favorable outcome with transplantation, donor shortages have resulted in long wait lists with the potential for

significant mortality while awaiting transplantation, eliminating this as an option for many patients who are in need of timely intervention. In addition, the use of organs for patients who have other treatment options may deny patients who require transplant a chance at life.

With the advent of smaller, more durable left ventricular assist devices (LVADs), this may be a better option than revascularization for many of these high-risk patients. In the elective setting and good patient selection, LVAD therapy can achieve 95.8 % 3-year survival [48]. Even in a broader group of patients, therapy with modern LVADs achieves better survival than medical therapy in end-stage cardiomyopathy [49, 50]. In addition, heart failure symptoms are greatly improved and the results seem to be durable with more consistent relief of heart failure symptoms than seen in patients undergoing revascularization. This therapy is particularly suited for many of the patients who are considered high risk for revascularization alone - those with very large ventricles, NYHA Class IV symptoms, low cardiac index, high LVEDP and significant mitral regurgitation. In addition, since LVAD therapy does not rely on the adequacy of LV function, the presence of viability is not a concern. As devices continue to improve and costs are lowered, this will likely become the treatment of choice for patients with ischemic cardiomyopathy with important risk factors for revascularization alone.

Conclusion

Patients with significant stenosis of the left main coronary artery or significant angina should undergo revascularization unless there are compelling reasons to treat them medically. Those with significant angina do not need routine viability testing before operation. When indicated, viability testing can be performed by SPECT, DSE, PET or MRI and the choice of testing method should be made based primarily on local expertise. Patients with viability should not be treated with medical management alone as the magnitude of improvement in survival with surgery is probably greatest in patients with myocardial viability. Angina will often improve after revascularization, regardless of the results of viability testing. Symptoms of heart failure are more likely to improve if there is viability, but this improvement may not be durable as the underlying cardiomyopathy is still present. Low ejection fraction should not preclude operation by itself, but may be a marker for higher surgical risk. EF is more likely to improve in patients who exhibit viability, but this may not be clinically relevant.

Patients at very high-risk for early mortality should receive revascularization only after careful consideration of other options, and modification of their risk factors if possible. These include patients who have had a recent myocardial infarction, very large ventricles, dyssynchrony as assessed by tissue Doppler, or hemodynamic parameters consistent with cardiogenic shock. These patients should be strongly considered for alternative therapies such as transplantation or LVAD support.

References

1. Coronary artery surgery study (CASS): a randomized trial of coronary artery bypass surgery. Survival data. Circulation. 1983;68(5):939–950.
2. Velazquez EJ, Lee KL, Deja MA, Jain A, Sopko G, Marchenko A, STICH Investigators, et al. Coronary-artery bypass surgery in patients with left ventricular dysfunction. N Engl J Med. 2011;364(17):1607–16.
3. Cleland JG, Calvert M, Freemantle N, Arrow Y, Ball SG, Bonser RS, et al. The Heart Failure Revascularisation Trial (HEART). Eur J Heart Fail. 2011;13(2):227–33.
4. Beanlands RS, Nichol G, Huszti E, Humen D, Racine N, Freeman M, PARR-2 Investigators, et al. F-18-fluorodeoxyglucose positron emission tomography imaging-assisted management of patients with severe left ventricular dysfunction and suspected coronary disease: a randomized, controlled trial (PARR-2). J Am Coll Cardiol. 2007;50(20):2002–12.
5. Alderman EL, Fisher LD, Litwin P, Kaiser GC, Myers WO, Maynard C, et al. Results of coronary artery surgery in patients with poor left ventricular function (CASS). Circulation. 1983;68(4):785–95.
6. Bonow RO, Maurer G, Lee KL, Holly TA, Binkley PF, Desvigne-Nickens P, STICH Trial Investigators, et al. Myocardial viability and survival in ischemic left ventricular dysfunction. N Engl J Med. 2011;364(17):1617–25.
7. O'Connor CM, Velazquez EJ, Gardner LH, Smith PK, Newman MF, Landolfo KP, et al. Comparison of coronary artery bypass grafting versus medical therapy on long-term outcome in patients with ischemic cardiomyopathy (a 25-year experience from the Duke Cardiovascular Disease Databank). Am J Cardiol. 2002;90(2):101–7.
8. Velazquez EJ, Williams JB, Yow E, Shaw LK, Lee KL, Phillips HR, et al. Long-term survival of patients with ischemic cardiomyopathy treated by coronary artery bypass grafting versus medical therapy. Ann Thorac Surg. 2012;93(2):523–30.
9. Eagle KA, Guyton RA, Davidoff R, Edwards FH, Ewy GA, Gardner TJ, American College of Cardiology, American Heart Association Task Force on Practice Guidelines, American Society for Thoracic Surgery and the Society of Thoracic Surgeons, et al. ACC/AHA 2004 guideline update for coronary artery bypass graft surgery: summary article: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Update the 1999 Guidelines for Coronary Artery Bypass Graft Surgery). Circulation. 2004;110(9):1168–76 . Erratum in: Circulation. 2005;111(15):2014.
10. Auerbach MA, Schöder H, Hoh C, Gambhir SS, Yaghoubi S, Sayre JW, et al. Prevalence of myocardial viability as detected by positron emission tomography in patients with ischemic cardiomyopathy. Circulation. 1999;99(22):2921–6.
11. Fedoruk LM, Tribble CG, Kern JA, Peeler BB, Kron IL. Predicting operative mortality after surgery for ischemic cardiomyopathy. Ann Thorac Surg. 2007;83(6):2029–35.
12. Hunt SA, Abraham WT, Chin MH, Feldman AM, Francis GS, Ganiats TG, et al. American College of Cardiology Foundation; American Heart Association. 2009 Focused update incorporated into the ACC/AHA 2005 Guidelines for the Diagnosis and Management of Heart Failure in Adults A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines Developed in Collaboration With the International Society for Heart and Lung Transplantation. J Am Coll Cardiol. 2009;53(15):e1–e90 . Erratum in: J Am Coll Cardiol. 2009;54(25):2464.
13. Allman KC, Shaw LJ, Hachamovitch R, Udelson JE. Myocardial viability testing and impact of revascularization on prognosis in patients with coronary artery disease and left ventricular dysfunction: a meta-analysis. J Am Coll Cardiol. 2002;39(7):1151–8.
14. Lin LC, Ho YL, Wu CC, Chen MF, Liau CS, Su CT, et al. Comparison of simultaneous dobutamine echocardiography and thallium-201 stress-reinjection single-photon emission computed tomography in predicting improvement of chronic myocardial dysfunction after revascularization. Am J Cardiol. 2000;86(3):293–8.

15. Bax JJ, Visser FC, Poldermans D, Elhendy A, Cornel JH, Boersma E, et al. Time course of functional recovery of stunned and hibernating segments after surgical revascularization. Circulation. 2001;104(12 Suppl 1):I314–8.
16. Schinkel AF, Poldermans D, Rizzello V, Vanoverschelde JL, Elhendy A, Boersma E, et al. Why do patients with ischemic cardiomyopathy and a substantial amount of viable myocardium not always recover in function after revascularization? J Thorac Cardiovasc Surg. 2004;127(2):385–90.
17. Hernandez-Pampaloni M, Bax JJ, Morita K, Dutka DP, Camici PG. Incidence of stunned, hibernating and scarred myocardium in ischaemic cardiomyopathy. Eur J Nucl Med Mol Imaging. 2005;32(3):314–21.
18. Schinkel AF, Bax JJ, Boersma E, Elhendy A, Roelandt JR, Poldermans D. How many patients with ischemic cardiomyopathy exhibit viable myocardium? Am J Cardiol. 2001;88(5):561–4.
19. Rizzello V, Poldermans D, Schinkel AF, Biagini E, Boersma E, Elhendy A, et al. Long term prognostic value of myocardial viability and ischaemia during dobutamine stress echocardiography in patients with ischaemic cardiomyopathy undergoing coronary revascularisation. Heart. 2006;92(2):239–44.
20. Di Carli MF, Maddahi J, Rokhsar S, Schelbert HR, Bianco-Batlles D, Brunken RC, et al. Long-term survival of patients with coronary artery disease and left ventricular dysfunction: implications for the role of myocardial viability assessment in management decisions. J Thorac Cardiovasc Surg. 1998;116(6):997–1004.
21. Bax JJ, Poldermans D, Elhendy A, Cornel JH, Boersma E, Rambaldi R, et al. Improvement of left ventricular ejection fraction, heart failure symptoms and prognosis after revascularization in patients with chronic coronary artery disease and viable myocardium detected by dobutamine stress echocardiography. J Am Coll Cardiol. 1999;34(1):163–9.
22. Mandegar MH, Yousefnia MA, Roshanali F, Rayatzadeh H, Alaeddini F. Interaction between two predictors of functional outcome after revascularization in ischemic cardiomyopathy: left ventricular volume and amount of viable myocardium. J Thorac Cardiovasc Surg. 2008;136(4):930–6.
23. Abraham A, Nichol G, Williams KA, Guo A, deKemp RA, Garrard L, PARR 2 Investigators, et al. 18F-FDG PET imaging of myocardial viability in an experienced center with access to 18F-FDG and integration with clinical management teams: the Ottawa-FIVE substudy of the PARR 2 trial. J Nucl Med. 2010;51(4):567–74.
24. Boehm J, Haas F, Bauernschmitt R, Wagenpfeil S, Voss B, Schwaiger M, et al. Impact of preoperative positron emission tomography in patients with severely impaired LV-function undergoing surgical revascularization. Int J Card Imaging. 2010;26(4):423–32 . PubMed PMID: 20091350.
25. Gioia G, Matthai W, Gillin K, Dralle J, Benassi A, Gioia MF, et al. Revascularization in severe left ventricular dysfunction: outcome comparison of drug-eluting stent implantation versus coronary artery by-pass grafting. Catheter Cardiovasc Interv. 2007;70(1):26–33.
26. Sedlis SP, Ramanathan KB, Morrison DA, Sethi G, Sacks J, Henderson W, Department of Veterans Affairs Cooperative Study #385, Angina With Extremely Serious Operative Mortality Evaluation (AWESOME) Investigators. Outcome of percutaneous coronary intervention versus coronary bypass grafting for patients with low left ventricular ejection fractions, unstable angina pectoris, and risk factors for adverse outcomes with bypass (the AWESOME Randomized Trial and Registry). Am J Cardiol. 2004;94(1):118–20.
27. Buszman P, Szkróbka I, Gruszka A, Parma R, Tendera Z, Leśko B, et al. Comparison of effectiveness of coronary artery bypass grafting versus percutaneous coronary intervention in patients with ischemic cardiomyopathy. Am J Cardiol. 2007;99(1):36–41.
28. Kunadian V, Pugh A, Zaman AG, Qiu W. Percutaneous coronary intervention among patients with left ventricular systolic dysfunction: a review and meta-analysis of 19 clinical studies. Coron Artery Dis. 2012;23(7):469–79.
29. Kleikamp G, Maleszka A, Reiss N, Stüttgen B, Körfer R. Determinants of mid- and long-term results in patients after surgical revascularization for ischemic cardiomyopathy. Ann Thorac Surg. 2003;75(5):1406–12.

30. Penicka M, Bartunek J, Lang O, Medilek K, Tousek P, Vanderheyden M, et al. Severe left ventricular dyssynchrony is associated with poor prognosis in patients with moderate systolic heart failure undergoing coronary artery bypass grafting. J Am Coll Cardiol. 2007;50(14):1315–23.
31. Maruskova M, Gregor P, Bartunek J, Tintera J, Penicka M. Myocardial viability and cardiac dyssynchrony as strong predictors of perioperative mortality in high-risk patients with ischemic cardiomyopathy having coronary artery bypass surgery. J Thorac Cardiovasc Surg. 2009;138(1):62–8.
32. AlJaroudi W, Alraies MC, Hachamovitch R, Jaber WA, Brunken R, Cerqueira MD, et al. Association of left ventricular mechanical dyssynchrony with survival benefit from revascularization: a study of gated positron emission tomography in patients with ischemic LV dysfunction and narrow QRS. Eur J Nucl Med Mol Imaging. 2012;39(10):1581–91.
33. Elefteriades JA, Tolis Jr G, Levi E, Mills LK, Zaret BL. Coronary artery bypass grafting in severe left ventricular dysfunction: excellent survival with improved ejection fraction and functional state. J Am Coll Cardiol. 1993;22(5):1411–7.
34. Hovnanian AL, Matos Soeiro A, Serrano CV, Oliveira SA, Jatene FB, Stolf NA, et al. Surgical myocardial revascularization of patients with ischemic cardiomyopathy and severe left ventricular disfunction. Clinics (Sao Paulo). 2010;65(1):3–8.
35. Trachiotis GD, Weintraub WS, Johnston TS, Jones EL, Guyton RA, Craver JM. Coronary artery bypass grafting in patients with advanced left ventricular dysfunction. Ann Thorac Surg. 1998;66(5):1632–9.
36. Kim RW, Ugurlu BS, Tereb DA, Wackers FJ, Tellides G, Elefteriades JA. Effect of left ventricular volume on results of coronary artery bypass grafting. Am J Cardiol. 2000;86(11): 1261–4, A6.
37. Soliman Hamad MA, Tan ME, van Straten AH, van Zundert AA, Schönberger JP. Long-term results of coronary artery bypass grafting in patients with left ventricular dysfunction. Ann Thorac Surg. 2008;85(2):488–93.
38. Bax JJ, Schinkel AF, Boersma E, Elhendy A, Rizzello V, Maat A, et al. Extensive left ventricular remodeling does not allow viable myocardium to improve in left ventricular ejection fraction after revascularization and is associated with worse long-term prognosis. Circulation. 2004;110(11 Suppl 1):II18–22.
39. Bouchart F, Tabley A, Litzler PY, Haas-Hubscher C, Bessou JP, Soyer R. Myocardial revascularization in patients with severe ischemic left ventricular dysfunction. Long term follow-up in 141 patients. Eur J Cardiothorac Surg. 2001;20(6):1157–62.
40. Pocar M, Moneta A, Grossi A, Donatelli F. Coronary artery bypass for heart failure in ischemic cardiomyopathy: 17-year follow-up. Ann Thorac Surg. 2007;83(2):468–74.
41. Selim Isbir C, Yildirim T, Akgun S, Civelek A, Aksoy N, Oz M, et al. Coronary artery bypass surgery in patients with severe left ventricular dysfunction. Int J Cardiol. 2003;90(2–3):309–16.
42. Galbut DL, Kurlansky PA, Traad EA, Dorman MJ, Zucker M, Ebra G. Bilateral internal thoracic artery grafting improves long-term survival in patients with reduced ejection fraction: a propensity-matched study with 30-year follow-up. J Thorac Cardiovasc Surg. 2012;143(4):844–53.
43. Samady H, Elefteriades JA, Abbott BG, Mattera JA, McPherson CA, Wackers FJ. Failure to improve left ventricular function after coronary revascularization for ischemic cardiomyopathy is not associated with worse outcome. Circulation. 1999;100(12):1298–304.
44. Kunadian V, Zaman A, Qiu W. Revascularization among patients with severe left ventricular dysfunction: a meta-analysis of observational studies. Eur J Heart Fail. 2011;13(7):773–84.
45. Mihaljevic T, Lam BK, Rajeswaran J, Takagaki M, Lauer MS, Gillinov AM, et al. Impact of mitral valve annuloplasty combined with revascularization in patients with functional ischemic mitral regurgitation. J Am Coll Cardiol. 2007;49(22):2191–201.
46. Athanasuleas CL, Buckberg GD, Stanley AW, Siler W, Dor V, DiDonato M, RESTORE Group, et al. Surgical ventricular restoration: the RESTORE Group experience. Heart Fail Rev. 2004;9(4):287–97.

47. Dor V, Civaia F, Alexandrescu C, Sabatier M, Montiglio F. Favorable effects of left ventricular reconstruction in patients excluded from the Surgical Treatments for Ischemic Heart Failure (STICH) trial. J Thorac Cardiovasc Surg. 2011;141(4):905–16 , 916.e1–4.
48. Boyle AJ, Ascheim DD, Russo MJ, Kormos RL, John R, Naka Y, et al. Clinical outcomes for continuous-flow left ventricular assist device patients stratified by pre-operative INTERMACS classification. J Heart Lung Transplant. 2011;30(4):402–7.
49. Slaughter MS, Rogers JG, Milano CA, Russell SD, Conte JV, Feldman D, HeartMate II Investigators, et al. Advanced heart failure treated with continuous-flow left ventricular assist device. N Engl J Med. 2009;361(23):2241–51.
50. Rose EA, Gelijns AC, Moskowitz AJ, Heitjan DF, Stevenson LW, Dembitsky W, Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure (REMATCH) Study Group, et al. Long-term use of a left ventricular assist device for end-stage heart failure. N Engl J Med. 2001;345(20):1435–43.

Chapter 19
Valve Repair and Replacement in Congestive Heart Failure

Salil V. Deo[†] and Soon J. Park

Mitral Regurgitation

Introduction

The mitral valve consists of two leaflets, two papillary muscles, and multiple chordae, which transmit the command of the papillary muscle to the leaflets. Yet this simple description does not do justice the extremely complex interplay of these structures, which helps to promote a well-functioning competent mitral valve. While degenerative mitral valve disease affects primarily the mitral valve leaflets, mitral regurgitation in congestive heart failure primarily involves the annular and sub-valvar apparatus. Carpentier was the first to introduce a systematic classification of mitral valve disease [1], which is based on the mechanism of mitral regurgitation. Thereafter many labels like "ischemic", "cardiomyopathy induced", "functional" or "non-organic" have been interchangeably used to define this condition. Yet in reality the degree and mechanism of regurgitation changes according to the extent of left ventricular dysfunction [2–5]. As Repogle et al. [5] have described, ischemic mitral regurgitation (IMR) can be divided into the following categories: (a) Acute MR: This can be due to myocardial infarction and associated papillary muscle ischemia or ventricular dysfunction. (b) MR due to end-stage Ischemic cardiomyopathy & (c) Chronic MR: Ischemic heart disease with changes in the regional wall motion leading to chronic mitral regurgitation. Another group of patients who

[†]Dedicated to the memory of Vasudeo A Deo and Guruji Vasant Deo; I do not have words to express my love for these two souls.

S.V. Deo, MS, MCh • S.J. Park, MD (✉)
Division of Cardiac Surgery, University Hospitals, Case Western Reserve University, Cleveland, OH 44106, USA
e-mail: svd14@case.edu; soon.park@uhhospitals.org

H. Eisen (ed.), *Heart Failure*, DOI 10.1007/978-1-4471-4219-5_19

further confuse the overall picture are those with coronary artery disease and associated mitral valve prolapse or myxomatous mitral valve disease [6]. In an attempt to provide some clarity to the situation, it is prudent to separate these patients into two main entities; Ischemic mitral regurgitation (IMR) and Functional mitral regurgitation (FMR) [7].

Ischemic Mitral Regurgitation

The basis for IMR is a localized change in the ventricular geometry. McGee et al. have demonstrated increase incidence of IMR with inferior as compared to anterior wall ischemia [8]. A similar finding was detected by echocardiographic analysis of segmental leaflet anatomy [9]. There are subtle differences in mitral pathology depending upon the location of the infarction. Three-dimensional echocardiography has demonstrated that anterior infarction is associated with more depressed left ventricular function, annular dilatation in the antero-posterior axis and annular flattening [10–12]. Inferior infarction has a higher tendency to cause early IMR, likely due to greater dis co-ordination of the papillary muscles [13, 14]. Greater leaflet tension with resultantly more MR occurs when the papillary muscles are displaced in a postero-lateral and apical direction [15]. This phenomenon is more likely with inferior rather than anterior infarction. Dis-synchrony among left ventricular myocardium especially at the area of papillary muscle insertion is an important contributory factor for IMR [16].

Annular dilatation is associated with IMR too, but unlike FMR it is not the primary cause of regurgitation. In fact patients with acute IMR may have significant regurgitation due to a disturbed ventriculo-annular relationship without much annular dilatation.

Functional Mitral Regurgitation

FMR should be reserved for patients with depressed left ventricular function and dilated cardiomyopathy, whether it is ischemic or idiopathic. Studies have demonstrated that leaflet tethering due to alteration in left ventricular global geometry is the primary etiology of FMR [17–20]. Animal models have demonstrated that FMR depends on the left ventricle developing a globular shape [19]. Annular dilatation, which takes place predominantly in a septo-posterior direction, has been found to be an important factor for the production of FMR, with limited regurgitation in patients with minimal increase in annular size [21]. A geometrical change in the left ventricle, promotes increase in the inter-papillary distance, resulting in restricted leaflet motion and a reduction in the coaptation area [22].

Thus IMR and FMR are the two end-points of the entire spectrum of mitral regurgitation associated with congestive heart failure. In the real world, patients may present with a variable combination of both conditions (Fig. 19.1) [7].

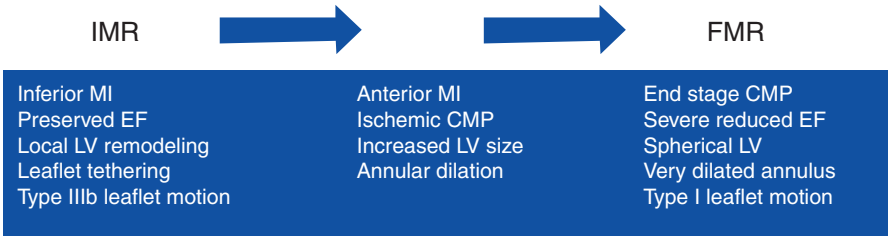


Fig. 19.1 This figure demonstrates the subtle differences in ischemic mitral regurgitation (IMR) and functional mitral regurgitation (FMR) (Reprinted from Timek and Miller [7], © 2011, with permission from Elsevier)

Dynamic Nature of Mitral Regurgitation

IMR/FMR is also very dynamic in nature with variation in severity over time and level of activity. Inotropes will increase the *dp/dt* promoting more closing of the valve and reducing MR [23, 24]. Conditions (anesthesia, diuretic therapy) leading to a reduction in preload and left ventricular diastolic size will reduce MR [25]. Lancellotti et al. have demonstrated the importance of exercise echocardiography as a tool in unmasking MR in patients with congestive heart failure [26, 27]. A change in the effective regurgitant orifice area (EROA) is due to a systolic expansion of the mitral annulus; leading to increase in cooptation distance, increase in the tenting area (area between the mitral annulus and the leaflet cooptation line) and the sphericity index (both end-systolic and end-diastolic) [28]. A sudden increase in MR during daily activities can provoke flash pulmonary edema, acute systolic pulmonary hypertension and electromechanical dys-synchrony promoting further MR [27, 29, 30]. Any discrepancy between symptoms and resting echocardiographic findings should be investigated with exercise testing to unmask latent MR. Exercise induced MR is of great prognostic importance in these patients; a change in EROA >13 mm^2 being a significant predictor of late mortality as demonstrated by Lancelotti and colleagues [31, 32] (Fig. 19.2).

Quantification of Ischemic Mitral Regurgitation/ Functional Mitral Regurgitation

The following factors need to be considered for the quantification of IMR/FMR:

(a) Severity of MR; number and direction of the regurgitant jets &
(b) Degree of LV dilatation, dysfunction and remodeling.

Echocardiography needs to focus on both the mitral valve anatomy as well as the LV geometry: The important factors which need to be considered for evaluating a patient with mitral regurgitation are: LV indices: left ventricular volumes,

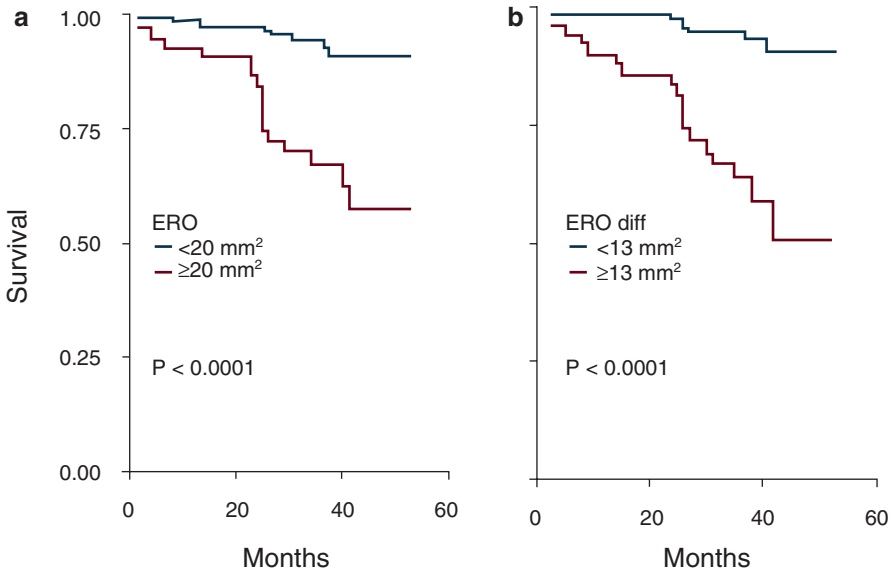


Fig. 19.2 Lancellotti and colleagues demonstrated that survival was significantly different in patients stratified by effective regurgitant orifice (*ERO*); important cut-off values being ERO ≥20 mm^2 at rest (**a**) and an increase in ERO ≥ 13 mm^2 on exercise (**b**) (Reprinted with permission from Lancellotti et al. [31] by permission of Oxford University Press)

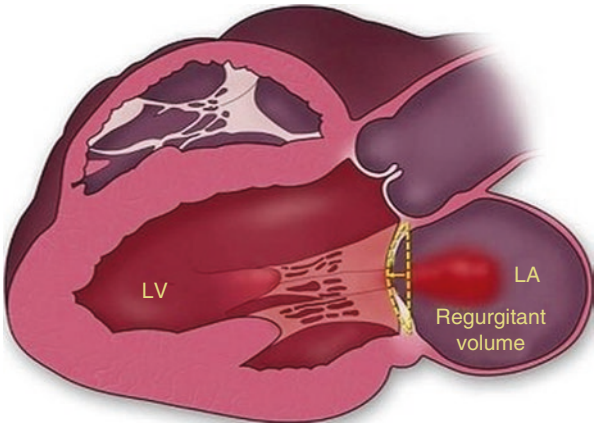


Fig. 19.3 A diagrammatic representation of the co-aptation depth (H), the tenting area (T) and Regurgitant volume; all are important in the quantification of mitral regurgitation (Reprinted with permission from Agricola et al. [16], by permission of Oxford University Press)

ejection fraction, sphericity index, the diastolic function and wall motion abnormalities & MV indices: mitral annular dimensions, effective regurgitant orifice area (EROA), co-aptation depth, tenting area and tenting volume on 3-D Echo (Fig. 19.3) [16]. Table 19.1 denotes the measurements obtained with echocardiographic examination of 21 control subjects and 128 patients with left ventricular dysfunction (<50 %).

Table 19.1 denotes the measurements obtained with echocardiographic examination of 21 control subjects and 128 patients with left ventricular dysfunction (<50 %)

	Comparison with controls			Comparison within LVD					Correlation with ERO	
Variable	Control (n = 21)	LVD (n = 128)	*p*	No MR (n = 21)	ERO <10 mm^2	ERO 10 – <20 mm^2	ERO >20 mm^2	*p* for trend	*r*	*p*
Baseline characteristics										
Age, y	62 ± 10	65 ± 13	0.20	57 ± 16	68 ± 13	65 ± 14	68 ± 11	0.03	0.20	0.02
Sex, % males	57	65	0.50	76	42	70	68	0.56	−0.14	0.12
BSA, m^2	1.9 ± 0.3	1.9 ± 0.2	0.52	2.0 ± 0.2	1.8 ± 0.3	1.9 ± 0.2	1.9 ± 0.2	0.61	−0.04	0.70
SBP, mmHg	134 ± 19	125 ± 21	0.05	126 ± 18	133 ± 21	127 ± 21	116 ± 19	**0.003**	−0.37	**0.0001**
CI, $L/min^2/m^2$	2.9 ± 0.4	2.4 ± 0.5	**0.0003**	2.7 ± 0.5	2.6 ± 0.5	2.4 ± 0.5	2.3 ± 0.6	**0.0005**	−0.34	**0.0001**
Global LV remodeling										
EDVI, ml/m^2	65 ± 10	149 ± 46	**<0.0001**	115 ± 28	150 ± 34	145 ± 52	169 ± 46	**0.0001**	0.49	**0.0001**
ESVI, ml/m^2	24 ± 6	106 ± 43	**<0.0001**	78 ± 29	108 ± 33	104 ± 51	119 ± 42	**0.002**	−0.31	**0.0005**
Systolic L/D	2.5 ± 0.5	1.5 ± 0.2	**<0.0001**	1.6 ± 0.2	1.4 ± 0.2	1.5 ± 0.2	1.4 ± 0.2	**0.012**	−0.31	**0.0005**
Diastolic L/D	1.9 ± 0.2	1.4 ± 0.2	**0.0001**	1.5 ± 0.2	1.3 ± 0.2	1.4 ± 0.1	1.3 ± 0.2	**0.007**	−0.29	**0.001**
EF, %	64 ± 4	31 ± 9	**<0.0001**	34 ± 10	28 ± 7	30 ± 10	31 ± 9	0.83	−0.09	0.32
ESWS, g/cm^2	158 ± 26	271 ± 67	**<0.0001**	244 ± 56	284 ± 81	281 ± 65	267 ± 65	0.68	0.13	0.17

Reprinted with permission from Yiu et al. [33] © 2000, with permission from Wolters Kluwer Health, Inc

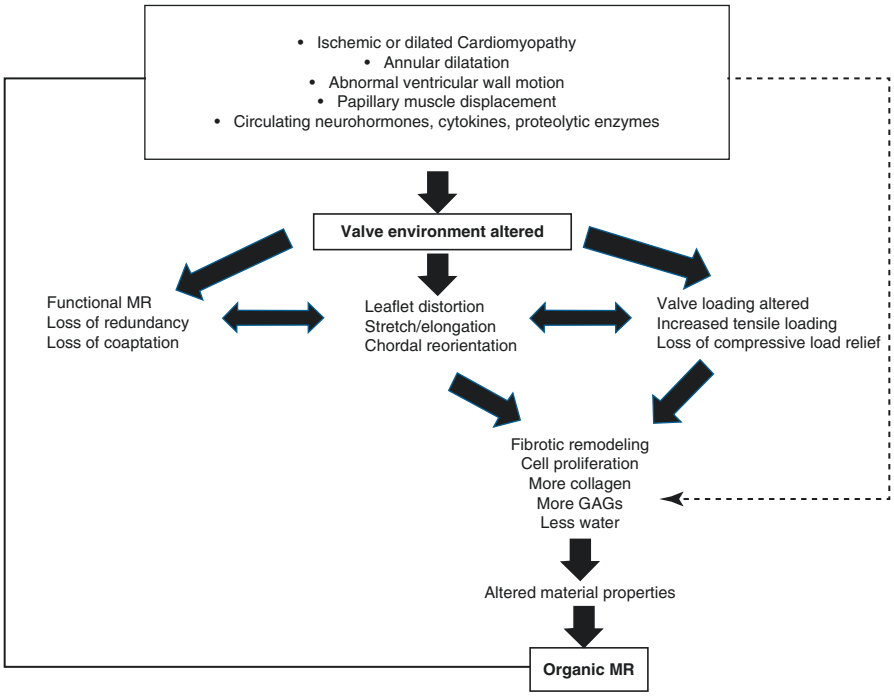


Fig. 19.4 The flowchart by Gravnde-Allen et al. demonstrates changes in leaflet structure and composition in ischemic/functional mitral regurgitation (Reprinted from Grande-Allen et al. [34], © 2005, with permission from Elsevier)

Secondary Changes in Leaflet Structure

Although this is primarily a condition of the left ventricle, the leaflets themselves are far from innocent by-standers in the disease process (Fig. 19.4). While the leaflets may appear grossly normal at surgery, significant biochemical changes have been identified in the leaflets in patients with long-standing cardiomyopathy. Grande-Allen and colleagues studied leaflet tissue obtained from recipient hearts explanted at the time of transplantation and tested them with tissue obtained from normal hearts at autopsy. Biochemically these leaflets had a higher cellular count (78 % more), higher collagen density (15 % more) and lower water content (7 % less). These changes made the leaflets thicker and less pliable compared to their normal counterparts. The chordae tendinae also had a smaller cross-sectional area compared to the normal cohort. The leaflets were 28–41 % longer than normal [34]. The leaflet length correlated with left atrial diameter, annular diameter while thickness correlated with annular size as well as left ventricular and left atrial dimensions [34].

Importance of Mitral Regurgitation on Survival with Heart Failure

The presence of IMR has a profound influence on survival. In 1988, Hickey et al. demonstrated a 34 % increase in mortality for patients with severe IMR compared to those with coronary artery disease and no MR. Even patients with mild IMR had a 4 % increase in mortality above baseline [35]. The Survival and Ventricular enlargement study (SAVE) demonstrated that even the presence of mild MR was an independent risk factor for cardiovascular mortality (Relative Risk = 2(1.28–3.04)) during a 3.5 years follow-up period [36]. Grigioni and colleagues compared 194 (IMR+) and 104 (IMR –ve) after matching them for age, gender and ejection fraction over a patient-year period of 817 years [37]. The IMR cohort experienced a much higher long-term mortality (62 +/− 5 % vs 39 +/− 6 %; $p < 0.001$) at the end of 5 years, with the presence of IMR independently affecting survival on a multivariate analysis. The mean ejection fraction in this study was in the approximate range of 26–36 % for both cohorts (Fig. 19.5).

Trichon et al. evaluated 2057 pts with symptomatic systolic heart failure undergoing evaluation in the cardiac catheterization laboratory over a 14-year period. While 56 % had IMR of any grade, importantly almost half of these patients had moderate/

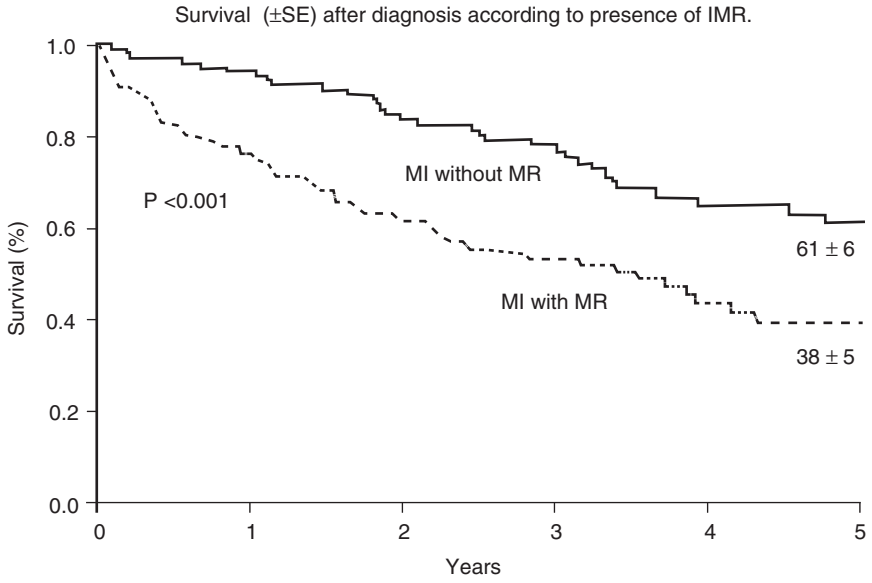


Fig. 19.5 Patients with ischemic MR clearly have a poorer survival as demonstrated by this Kaplan-Meier curve (Reprinted from Grigioni et al. [37], © 2001, with permission from Wolters Kluwer Health Inc./American Heart Publications)

severe IMR. They have demonstrated a 40 % survival at 5 years and have demonstrated that the presence of even moderate IMR is a risk factor for early mortality [38]. A study from the University of Michigan in 1421 patients with congestive heart failure (LV ejection fraction <35 %) demonstrated 50 % survival of 628 +/− 47 days for patients with severe IMR [39]. Importantly almost 50 % of the patients in this study had at least moderate MR, which demonstrates the important relationship between left ventricular systolic dysfunction and the presence of MR. Ellis et al. demonstrated an inferior outcomes in patients with IMR undergoing percutaneous intervention, especially in the subset of patients with LVEF <40 % [40].

Thus many retrospective studies have demonstrated poorer survival in patients with IMR with approximately 40 %–50 % survival at the end of 3–5 years.

What Degree of Ischemic Mitral Regurgitation Should Be Addressed?

All agree that moderate-severe IMR should be addressed at the time of coronary artery bypass grafting (CABG) [41, 42]. Correcting regurgitation at the time of CABG improves exercise capacity, symptoms and promotes reverse ventricular remodeling [43, 44]. The American College of Cardiology recommends concomitant mitral valve surgery in patients with LVEF <40 % with severe symptomatic mitral regurgitation. The committee prefers valve repair; but if that is not possible then replacement should be carried out with chordal preservation [45].

Results of Repair and Replacement with Ischemic/ Functional Mitral Regurgitation

David and colleagues were among the first to demonstrate good results with mitral valve replacement while preserving the subvalvar apparatus [46]. Bolling and Bach were the first to demonstrate successful mitral annuloplasty (MVA) in patients with cardiomyopathy. They were successful in operating on 16 patients (mean ejection fraction 16 +/− 5 %) without peri-operative mortality and demonstrated significant improvements in stroke volume, ejection fraction and cardiac output with concomitant reduction in regurgitant volume and fraction [2]. This landmark achievement disputed the theory of the "pop-off" effect of the mitral valve for a failing left ventricle. The Bolling hypothesis is that there is an " annular solution for a ventricular problem… such that reconstruction of the mitral valve annulus` geometric abnormality by an undersized ring restores valvular competency, alleviates excessive ventricular workload, improves ventricular geometry and improves ventricular function". This concept was validated by the Stanford group using animal models [47]. Mihaljevic and colleagues studied patients undergoing CABG + MVA (290) and CABG alone (100) and presented their results in a propensity-matched cohort [48]. A restrictive

annuloplasty with the use of both rigid rings (22 %) (Carpentier-Edwards Classic Annuloplasty ring, Edward Lifesciences, Irvine, CA), partially flexible posterior annuloplasty bands (63 %) (Cosgrove-Edwards Annuloplasty system, Edward Lifesciences, Irvine, CA) and even posterior suture plication with autologous pericardium or Peri-Guard graft (6.9 %) (Baxter Healthcare Corp., Deerfield, IL) was performed. Their estimated survival for MVA + CABG (92 %, 74 % and 39 %) and CABG (88 %, 75 % and 47 %) at the end of 1, 5 and 10 years was comparable ($p = 0.3$). In the early period of follow-up, renal insufficiency, severe wall motion abnormalities, and surgery in an earlier time period were the predictors of mortality. For the late constant hazard phase insulin dependent diabetes, renal insufficiency, older age, were significant predictors. The benefit of MVA was in abolishing early post-operative MR. Unfortunately this study failed to demonstrate any incremental clinical benefit of concomitant MVA. In fact they caution that the longer ischemic time needed for MVA could be detrimental in the sick, old patient. They have projected a recurrence of 3 +/ 4 + MR in 9 % and 20 % in the CABG + MVA cohort at the end of 1 and 5 years respectively. Grossi et al. [42] studied a cohort of 223 patients over two decades, with 152 undergoing MVA (77 % ring and 23 % suture annuloplasty). As they have found the era of surgery to be an important predictor of outcome, we will concentrate on their results in patients operated after 1988. Analyzing their entire cohort, they report that type of surgery (repair vs replacement), papillary muscle rupture, congestive heart failure and acute MR impair long-term survival. In their contemporary series of patients (surgery after 1988) however, outcome are poorer for mitral valve replacement (hazard Ratio; 0.45(0.22–0.93)) and emergency surgery (hazard ratio 0.19(0.06–0.64)). Using complicated statistical models, they conclude that NYHA functional class and patient selection determine outcome rather than surgical procedure. Impressively almost 82 % from the MVA cohort were free of significant MR. They recommend restrictive MVA as the first strategy for patients with an annular pathology, while those with significant leaflet tethering or papillary muscle dysfunction would do better with posterior chordal preservation and MVR. Mayo Clinc recently presented their experience of 431 patients who underwent mitral valve repair/replacement for ischemic MR over a 14 year period [6]. Overall survival for the entire cohort was 82.7 %, 55.2 % and 24.3 % at the end of 1, 5 and 10 years respectively. All patients in the repair cohort underwent either an undersized band or rigid ring annuloplasty. Details of sub-annular apparatus preservation are unfortunately not available in individual patients due to the retrospective nature of the study, although institutional policy is to perform at least posterior chordal preservation. Prior CABG, emergency surgery and age were risk factors for early mortality (<1 year) while age, renal insufficiency and diabetes contributed to the late constant hazard phase. These results are similar to those at the Cleveland Clinic [48]. This underlines the importance of patient factors rather than procedure to late outcome.

Fukuda and colleagues [49] reported results of 126 patients with severe left ventricular dysfunction (≤30 %), who underwent mitral valve annuloplasty. They found that annuloplasty is not a predictor of improved survival. However they, as well as many others have demonstrated an improved quality of life and functional capacity after mitral valve surgery.

Two important issues regarding repair of ischemic mitral regurgitation are recurrent regurgitation and a more recently introduced concept of exercise induced mitral stenosis. The incidence of recurrent regurgitation after repair is not small. Gilinov et al. have reported a repair failure rate of 9 % over a 5-year period [41]. Chan and co-workers have demonstrated a recurrence rate of 23 % in their study evaluating 65 patients with mitral valve repair [50].

Exercise induced mitral stenosis is being increasingly reported with patients undergoing restrictive annuloplasty [51]. Magne and co-workers have reported increase in trans-valvular gradients with restrictive annuloplasty leading to pulmonary hypertension and increased clinical symptoms [51]. Some authors have implicated left ventricular dysfunction and pulmonary vascular disease rather than mitral valve gradients as the cause for pulmonary hypertension after ischemic mitral valve repair [52, 53].

Geometric Rings for Ischemic Mitral Regurgitation

The Geoform™ ring (Edwards Lifesciences, Irvine, CA) has a unique three dimensional shape designed to reduce the anteroposterior diameter and elevate P_2 segment of the leaflet. DeBonis et al. demonstrated survival of 81.1 +/− 6.6 % at 3.5 years, while recurrent regurgitation was present in 16 %. Significant exercise induced mitral stenosis was not found in any of the survivors. Restricted motion of the posterior leaflet is an important predictor of recurrent regurgitation.

The Carpentier-McCarty-Adams ETLogixring™ is the first ring specifically designed to treat asymmetrical restriction of the posterior leaflet. Initial results are favorable with a low residual grade of regurgitation and improvement in echocardiographic parameters early after surgery [54]. A recent study demonstrates significant reduction ($p < 0.0006$) in the mitral annular diameter, tenting area as well as tenting height after use of the ETLogixring™. They conclude that the ring is useful for selective patients with ischemic mitral regurgitation. While functional mitral stenosis has not been reported with the Geoform™ ring, Martin and colleagues have recently reported their results on 40 patients with the ETLogixring™ [55].

The choice of ring for the repair of ischemic regurgitation is a very complex issue, and an exhaustive discussion regarding this issue is beyond the purview of this article. However while energy and dollars are being spent on devising and marketing new rings, reports are also available demonstrating comparable changes in the geometry of the mitral valve [56].

Percutaneous Techniques to Deal with Mitral Regurgitation

As discussed in the earlier part of the chapter, mortality and morbidity associated with the surgical treatment of mitral regurgitation may be significant. Patients may be denied surgery on the grounds that it is too high risk [57]. Various techniques are present attempting to correct mitral regurgitation in a minimally invasive manner.

A detailed classification (based on functional anatomy) is provided by Chiam and Ruiz in their comprehensive review [58].

Among the many experimental methods, the MitraClip™ (Abbott Vascular, Santa Clara, CA) based on the Alfieri edge-to-edge repair is the only method having entered and completed clinical trials. The technique is based on the open surgical technique of Alfieri where the anterior and posterior leaflets are approximated together to create a double mitral orifice. A steeable catheter is utilized to deploy the clip. The approach is antegrade via a trans-septal puncture. In 2009, Feldman and colleagues reported the mid-term results of the EVEREST (Endovascular Valve Edge-to-edge Repair trial) trial, the first randomized controlled single arm study aimed at assessing feasibility of percutaneous mitral valve repair [59]. A total of 107 patients underwent MitraClip™ repair with <1 % in-hospital mortality. Overall, 74 % had procedural success, defined as residual mitral regurgitation ≤2 + at the end of the procedure. At the end of 1 year, 66 % were free of ≥2 + MR, surgery or death. During surgery, repair was still possible in the majority of patients. Although clip embolization was not an issue, partial clip dislodgement occurred in 9 %. The EVEREST II trial (NCT 00209274) was undertaken comparing surgical repair and MitraClip™ in a 2:1 randomized manner. The non-inferiority end-point of the study was met, demonstrating that device therapy was comparable to surgical repair at the end of 1 year of follow-up. In another sub-study of EVEREST II, high-risk patients (STS score >12 %) undergoing MitraClip™ repair were compared to similar patients electing for optimal medical therapy. This study demonstrated a significant improvement in clinical symptoms and left ventricular reverse remodeling after 12 months in the device cohort. A large clinical study from Germany has also demonstrated the benefit of device therapy, however it is important to note that the follow-up duration of these patients is still limited [60]. Given the relatively high incidence of recurrence of regurgitation in the EVEREST study, careful thought is needed before opting for this procedure and an open discussion with the patient regarding this aspect is important.

Devices can be implanted in the coronary sinus to reduce the septo-anterior dimensions of the mitral valve. The Monarc device® (Edwards Lifesciences, Irvine, CA) consists of proximal self-expandable anchors with a spring-like bridge with shortening forces. The EVOLUTION trial reported a reduction in MR garde in 85.7 % patients with severe regurgitation pre-operatively. The main concern is compression of the circumflex coronary artery, which was present angiographically in 30 % at the end of 6 months. Among these patients, 13.3 % had myocardial infarction. The TITAN trial reported results with the Carillon device (Cardiac Dimension Inc., Kirkland, WA), a fixed-length double anchor implant to be positioned in the coronary sinus. Among 53 patients enrolled in the study, 32 % devices were recaptured after implant, the main reason being circumflex coronary artery compression.

Devices based on these two principles: the edge-to-edge repair and reducing the septo-anterior dimensions are the most promising at the moment. Many other methods are in various stages of experimental trials. Surgical therapy will always remain the gold standard of care for these patients, and the use of alternative

therapies needs to be done with an informed discussion with the patient regarding the possibility of recurrent regurgitation. However, open surgical approach is not without significant morbidity and postoperative recovery. A careful balance needs to be achieved between attaining a better clinical end-point and the patient's quality of life.

To summarize, mitral regurgitation is definitely a predictor of mortality in patients with poor ventricular function. Significant mitral regurgitation (moderate or more) warrants surgical intervention, even more so if done concomitantly with coronary artery surgery. Surgery in the form of a restrictive annuloplasty can be performed with an early mortality of 5–10 %. While late survival will not be favorably altered with mitral valve surgery, quality of life and functional capacity is definitely superior. Mitral valve replacement is comparable to repair with regards outcome, especially if performed using the chordal sparing approach. Patient factors like renal dysfunction, age, diabetes, and era of surgery are important predictors of survival. Important concerns with repair like the risk of recurrence and the risk of inducing functional mitral stenosis have to be considered while making the decision to repair or replace the valve. Geometrically altered rings are available for the repair of ischemic mitral regurgitation; however experience with them is limited when compared to the use of conventional rings and bands for degenerative mitral valve repair. Hence further data is necessary to allow us to make an informed decision regarding choosing any one ring over the other.

Percutaneous techniques are still to find a niche in the armamentarium of available procedures. While they may be beneficial for a select population of very high risk patients, much more data needs to be obtained to determine their place amongst various options already at hand.

Tricuspid Regurgitation

Tricuspid valve disease may occur in patients with congestive heart failure. It is primarily due to two mechanisms: (a) Tricuspid regurgitation (TR) develops secondary to pulmonary hypertension and right ventricular dysfunction (b) Primary tricuspid valve disease can occur due to isolated right ventricular dysfunction or more commonly due to pacemaker lead induced damage.

Secondary TR is the most common tricuspid valve pathology associated with congestive heart failure. Right ventricular dysfunction results in a gradual increase in the annular diameter of the tricuspid valve. This enlargement occurs at the anterior aspect of the annulus corresponding to the right ventricular free wall. Its shape changes from a saddle to a more planar dimension [61]. An enlarged annulus leads to improper cooptation of the leaflets and a predominantly central jet of regurgitation. They may suffer from ascites, pedal edema and hepatomegaly, the classical features of right-sided failure. Additionally they also demonstrate reduced functional capacity, fatigue and dyspnea on exertion.

Dreyfus et al. have demonstrated that TR may fail to resolve after correction of the left sided-pathology [62]. The presence of severe TR is also an independent predictor of mortality [39]. Hence severe TR is best corrected surgically at the time of mitral valve surgery (Class I indication) [63]. Data regarding tricuspid valve surgery in isolated TR or TR after prior correction of left sided pathology is less clear (Class IIA indication) [63]. In patients with ischemic/functional mitral regurgitation, TR is a more important issue. Matsunaga et al. demonstrated a 30 % prevalence of 2+TR in patients undergoing mitral valve surgery. In spite of adopting a very liberal policy towards surgical correction of the tricuspid valve, almost 2/3rd of the patients developed moderate TR at the end of 3 years [64].

Tricuspid valve repair consists of various procedures like (1) autologous procedures viz. bicuspidalization [65] or De Vega annuloplasty & (2) annuloplasty procedures using rigid or flexible bands/rings. A large series of 790 patients demonstrates the use of four different techniques: DeVega repair, Peri-Guard® pericardial strip annuloplasty, Edwards-Cosgrove flexible band and Carpentier-Edwards semi-rigid ring.

Tricuspid valve replacement can be performed using either a mechanical or bioprosthesis. As a general rule, tissue valves are preferred unless specifically contraindicated for other reasons. Readers are encouraged to pursue the article by Chikwe et al. for a detailed description of the available surgical procedures [66].

Concomitant tricuspid valve surgery with mitral procedures can be done very safely (1–2 % early mortality). A comparison of the various available procedures demonstrates more durable results with prosthetic annuloplasty compared to autologous procedures [67].

Results after the surgical repair of isolated tricuspid valve repair are less satisfactory. Severe underlying right ventricular failure has been implicated as an important causative factor. Predictors of poor outcome after isolated tricuspid surgery are poor NYHA functional class, pre-operative hemoglobin and right ventricular end-systolic area [68].

A study reviewing the Mayo Clinic experience with isolated tricuspid valve replacement demonstrated that NYHA class IV and a higher Charlson index were independent predictors for late mortality [69]. The only echocardiographic predictor identified was right index of myocardial performance (RIMP) ratio [69]. Among survivors, almost a quarter needed re-admission for congestive heart failure during the follow-up period. Hence intensive surveillance is important even after surgery to ensure good functional status and quality of life.

The poor results are partly due to a reluctance of surgeons to operate on the tricuspid valve. Analysis of the Society of Thoracic Surgeons cardiac database from 2004–2007 demonstrates that tricuspid valve surgery is conducted in very small numbers [70]. Authors at the Mayo clinic demonstrate that surgery can be done with a reasonable outcome if patients are operated before the onset of severe right ventricular failure [69].

In conclusion, we recommend that patients with 2+TR should undergo concomitant repair at the time of left-sided procedures. Patients with isolated TR have a higher mortality; it is important in these patients to proceed with surgery

before the onset of severe right ventricular failure. Attention to diuretic therapy and fluid balance are important even after surgery to ensure a good functional status and quality of life.

Aortic Regurgitation

Aortic regurgitation produces predominantly a volume overload on the left ventricle. The lesion is well tolerated initially and symptoms are minimal. However a left ventricular end-systolic diameter >50 mmHg is associated with increased mortality, and is an indication for aortic valve replacement. Guidelines recommend surgery even for asymptomatic patients with left ventricular dysfunction (LVEF <50 %), however studies have demonstrated a significant reluctance to conduct surgery in these high-risk patients [63]. The Euro Heart Survey has demonstrated that only 22 % with LVEF in the range of 30–50 % underwent surgery while only 3 % with severe LV dysfunction (LVEF <30 %) received operative intervention [71]. A retrospective single center study demonstrated that only a third of the patients with severe AR and LV dysfunction actually underwent surgery. The pre-operative factors cited for non-intervention were an older age, female gender, presence of diabetes and renal dysfunction, and the need for concomitant procedures. Operative mortality is in the range of 7–10 % [72]. Kamath and co-workers have demonstrated that in severe AR patients with severe LV dysfunction, AVR is an independent predictor of improved survival [73]. AVR had significant survival benefit with 1-year, 2-year, and 5-year survival rates of 88 %, 82 %, and 70 %, respectively, compared to 65 %, 50 %, and 37 %, respectively, in the population who did not receive AVR surgery ($p < 0.001$). Patients with severe LV dysfunction (LVEF <35 %) and (LVEF <20 %) demonstrated a 5-year survival of 70 % and 60 % respectively. Although survival cannot match the age-matched normal population, we have still demonstrated a benefit for surgical intervention. Propensity matched results have also demonstrated the advantage of surgical therapy [72].

A study from the Mayo Clinic demonstrated that preoperative ejection fraction, left ventricular end-systolic dimension, indexed end-systolic dimension, end-diastolic dimension, and indexed end-diastolic dimension were univariate predictors of late ejection fraction. In a multivariate model, the only predictor of late normal ejection fraction was a higher preoperative ejection fraction (odds ratio, 2.85; $p < 0.001$) [74].

Thankfully, regression in left ventricular dimensions has been demonstrated after aortic valve replacement. Bonow et al. monitored changes in left ventricular dimensions and ejection fraction after aortic valve replacement in 61 patients [75]. They utilized echocardiography and radionuclide scanning to assess them over a 7-year period. Between preoperative and early postoperative studies, left ventricular end-diastolic dimension decreased (from 75 ± 6 to 56 ± 9 mm, $p < 0.001$), peak systolic wall stress decreased (from 247 ± 50 to 163 ± 42 dynes), and ejection fraction increased (from 43 ± 9 % to 51 ± 16 %, $p < 0.001$). However patients without early increase in the ejection fraction failed to demonstrate any improvement long-term.

They further demonstrate a significant improvement in ejection fraction even in patients with severe LV dysfunction [72].

Hence, aortic valve replacement is beneficial even in patients with advanced left ventricular dysfunction. Compared to metical therapy, benefit in terms of quality of life and functional capacity is observed after surgery. Associated preoperative factors and a higher operative mortality rate have to be considered when considering surgical intervention in patients with severe aortic regurgitation and left ventricular dysfunction.

Aortic valve replacement is one of the most common adult cardiac procedures performed in the USA. Patients with a poor ejection fraction typically develop a subset of aortic stenosis (AS): a low gradient, low flow (LF-LG) severe AS.

Definition

LF-LG severe AS is defined as a combination of an EOA $\leq$1.0 cm^2 (or EOA index <0.6 cm^2/m^2) with a low mean trans-valvular gradient (less than 40 mmHg). Low-flow mean either a cardiac index <3 l/m^2/min or an ejection fraction (less than 40 or 35 %).

Pseudo-Severe Aortic Stenosis

Patients with primarily left ventricular dysfunction may have a small aortic valve area with low trans-valvular gradient due to their sub-normal stroke volume. The small effective orifice area of the aortic valve in these patients is secondary to incomplete opening during systole.

This stratification has a significant clinical consequence as aortic valve replacement fails to improve the symptomatology in the latter cohort and may actually be detrimental.

Role of Dobutamine Stress Echocardiography

Dobutamine stress echocardiography [76] is implemented as a confirmatory test for assessing LF-LG AS. While true aortic stenosis will present with a significant increase in gradient (mean transvalvular gradient >40 mmHg) with minimally increase flow and aortic valve orifice area (change <0.3 cm^2, valve area <1 cms^2) pseudo-severe aortic stenosis will demonstrate an increased flow without much change in the gradient [63]. The European Committee for guidelines on valvular heart disease recommends this test for all patients with LF-LG AS. Apart from being a diagnostic test, the increase in ejection fraction helps to assess contractile reserve of the left ventricle, an important prognostic indicator [77]. Contractile reserve is defined as an increase in ejection fraction >20 % with dobutamine infusion compared to the baseline [78].

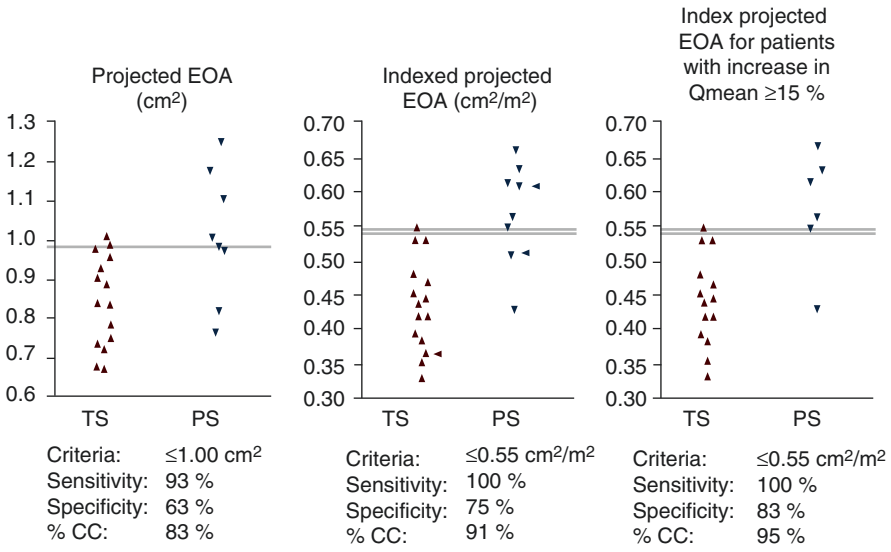


Fig. 19.6 The technique of indexed projected effective orifice area is a reliable test to differentiate true and pseudo-severe aortic stenosis. The panels D-F demonstrate the change of this parameter in patients with true (*red triangles*) and pseudo-severe (*blue triangles*) aortic stenosis (Reprinted with permission Blais et al. [79]. © 2006, with permission from Wolters Kluwer Health Inc)

Momin et al. studied the changes in stroke volume, left ventricular ejection fraction, aortic valve area and mean pressure gradient in patients with and without contractile reserve on DSE. Patients with an intact contractile reserve demonstrated an increase in stroke volume (33 %), LVEF (12 %), aortic valve area (0.1 cm^2) and MPG (47 %). Those devoid of contractile reserve demonstrated minimal increase in values on Dobutamine stress echocardiography.

TOPAS Study

The TOPAS (Truly or Pseudo-Severe Aortic Stenosis) is a prospective study conducted to improve the accuracy of differentiating true from pseudo-aortic stenosis. While authors agree that DSE is a reliable test, stenotic indices obtained from the DSE depend upon the magnitude of flow increase achieved. Blais and co-workers have developed a new stenotic index, the EOA_{proj}which determines the orifice area at a standardized flow rate of 250 ml/s, a constant which they have derived using hydraulic models in the laboratory. Hence they have presented their equation as: $EOA_{proj}=EOA_{rest}+ VC*(250-Q_{rest})$. The authors have further indexed this obtained value to the patient's body surface area to derive the indexed projected EOA. Using a cut-off of ≤ 0.55 cm^2/m^2, the sensitivity of this score increased from 93 to 100 % (Fig. 19.6) [79].

While these investigations are useful to the surgeon for risk stratification, clinical assessment and evaluation of risk factors are essential to implement the correct strategy suited to the individual patient. However, optimal medical therapy has proved inferior to surgical AVR irrespective of contractile flow reserve. Five-year mortality with conservative therapy can be as high as 87 %. Hence many authors recommend valve replacement for patients with LF LG aortic stenosis [77, 79]. Trans-cutaneous aortic valve implantation is emerging as an exciting option for these high-risk patients.

Results of Conventional AVR

Peri-operative Mortality

Overall peri-operative mortality in this cohort remains high; in the range of 9–22 % [77, 80–83]. Cardiogenic shock (79 %), sepsis (9 %), stroke (3 %) and respiratory failure were reported as important causes of death in a multi-centric study from Europe [83]. Univariate analysis of this large cohort of patients demonstrated that a higher EuroSCORE, poorer NYHA functional class, coronary artery disease, and longer surgical duration were important predictors of early mortality. Monin et al. [77] have demonstrated that operative risk is significantly higher for patients with a mean pressure gradient (MPG) <20 mmHg (44 % vs 11 %; p = 0.0006). Multivariate analysis from this cohort defined absence of contractile reserve (Odds ratio 10.9; 95 % confidence interval 2.6–43.3; p = 0.001) and MPG <20 mmHg (Odds ratio 4.7; 95 % confidence interval 1.1–21; p = 0.04) as predictors of peri-operative mortality. Coronary artery disease and prior myocardial infarction are also important in risk stratification [84]. Importantly, Levy et al. [83] have demonstrated that surgical outcomes are better in the present era (2000–2005) (a 10 % reduction in mortality; p = 0.04) in spite of more emergency cases being conducted (a 9 % increase; p = 0.04).

While a risk stratification score selectively devised for this patient population is not yet available, the use of the EuroSCORE or the STS risk score tailored to the individual patient's condition is the best tool to make an informed decision [85, 86]. As described earlier, DSE and contractile reserve are important prognosticators in patient outcome.

Functional Capacity After Aortic Valve Replacement

Multiple authors have demonstrated improved functional status after aortic valve replacement [77, 80, 81] While significantly more improvement was found in patients with a contractile reserve >20 % on DSE, even patients with no reserve did better after aortic valve replacement [77]. The TOPAS study assessed the Duke Activity Score index (DASI) scores and distance covered in the standard 6-min walk

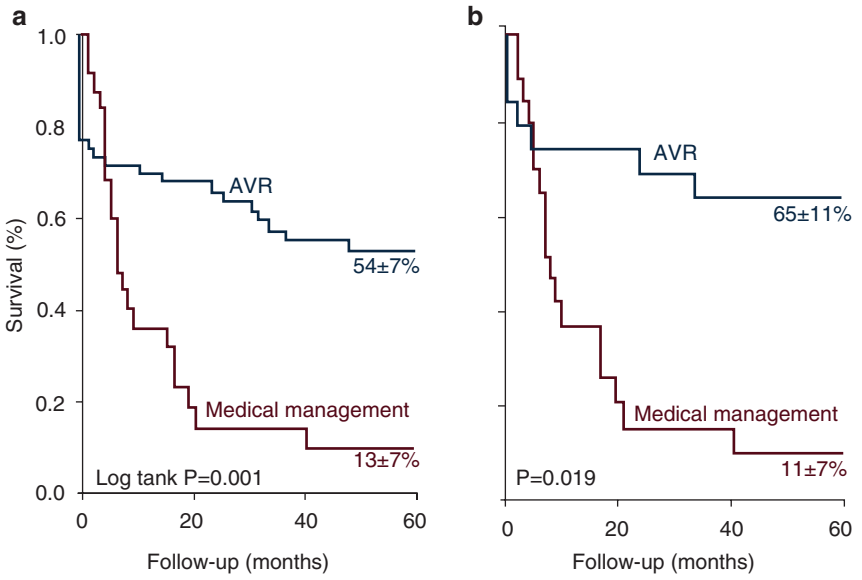


Fig. 19.7 This Kaplan-Meier curve compares survival with aortic valve replacement (AVR) or optimal medical therapy in patients without contractile reserve on Dobutamine Stress Echocardiograph. As depicted, results are significantly superior with AVR; in the entire cohort (**a**) as well a propensity matched sub-group (**b**) (Reprinted with permission from Tribouilloy et al. [80]

test (6 MW) both before and after AVR. They were able to demonstrate a significant increase in both parameters (DASI and 6 MW) in the AVR cohort (ΔDASI: +5.9 ± 3.3 and Δ6 MW: +66 ± 27) while patients maintained with optimal medical therapy actually demonstrated a decline in function at the end of 1 year of follow-up (ΔDASI: −5.5 ± 2.6 and Δ6 MW: −9 ± 22) [87].

Predictors of Long-term Survival

A multi-centric study has demonstrated an overall 5-year survival of 49 ± 4 % after aortic valve replacement [83]. They have demonstrated a significant difference in survival stratified by ejection fraction (less and more than 20 %; p = 0.005), multi-vessel coronary disease (p = 0.002) and EuroScore (less and more than 10; p = 0.0001). Recent European guidelines for valvular heart disease state that the EuroSCORE may overestimate mortality with the Society of Thoracic Surgeons risk calculator being a more accurate predictor in high-risk patients with severe aortic stenosis [63].

Results in patients with no contractile reserve: (Fig. 19.7).

Tribouilloy et al. [80] conducted a prospective multi-centric study of 81 patients with LF-LG aortic stenosis without contractile reserve. While their operative mortality was relatively high (22 %), they demonstrated a significant improvement in 5 year survival in surgically treated patients compared to OMM (54 ± 7 % vs

13 ± 7 %; p = 0.001). Propensity matching demonstrated that an ejection fraction <20 % and coronary artery disease were independent predictors of mortality. Hospital survivors demonstrated a 5-year survival of 69 ± 5 %.

Thus they demonstrated that aortic valve replacement was beneficial even in patients without functional reserve, albeit at the cost of a higher operatively mortality.

Results with Optimal Medical Therapy in Patients with LF-LG Aortic Stenosis

Studies are unanimous in concluding that optimal medical therapy is associated with very poor outcome in these patients. Both survival and functional class are very poor in patients managed non-surgically. Thus in spite of the high early mortality, surgical aortic valve replacement provides the patient with the best odds for a longer and better quality of life.

Role of TAVI in Patients with LF-LG Severe Aortic Stenosis

Fraccaro et al. [88] have presented their data using Edwards SAPIEN / SAPIEN XT™ as well as then Medtronic CoreValve™ in patients with left ventricular dysfunction. They studied 384 patients undergoing transcutaneous aortic valve implantation (TAVI); 50 patients had LVEF <35 % (Group A) while the remaining 334 (Group B) had normal left ventricular function. Patients (n=50) with left ventricular function <35 % had a much higher logistic EuroSCORE™, STS®score, higher degree of renal dysfunction and poorer NYHA functional class. While in-hospital mortality was higher in Group A (14 %) compared to Group B (4 %) (p = 0.004), among hospital survivors cardiovascular mortality was comparable at the end of 1 year (10 % in Group A and 6 % in Group B; p=0.434). In the group A cohort, ejection fraction increased from a baseline of 27.7 ± 6 % to 46.6 ± 13.7 % at the end of 1 year (p < 0.0001). The Authors conclude that further studies are needed to define the role of TAVI in patients with LF-LG severe aortic stenosis, but recommend that left ventricular dysfunction should not be a contraindication for performing TAVI. They further make a recommendation for TAVI without pre-dilatation, as this avoids the need for rapid ventricular pacing which may be very deleterious in these sick patients. (Fig. 19.8) [89].

Conclusion

The treatment of patients with low flow low gradient aortic stenosis requires a coordinated approach between the cardiologist and surgeon. Dobutamine stress echocardiography is an important tool to separate true aortic stenosis from pseudo-aortic stenosis, a stratification having important clinical and therapeutic consequences. In

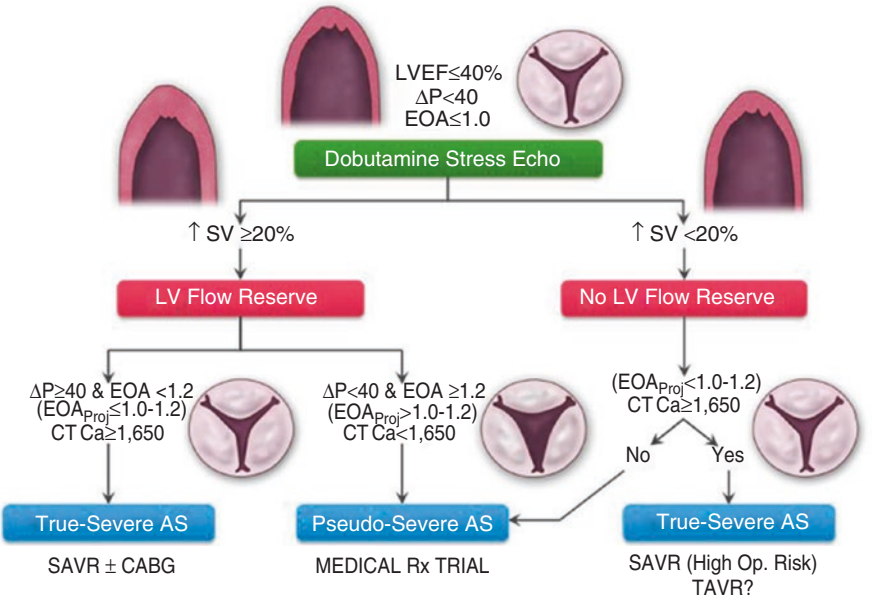


Fig. 19.8 Drs. Pibarot and Dumesnil have outlined this protocol for the management of patients with low-flow low-gradient severe aortic stenosis with a reduced ejection fraction. Abbreviations: *EOA* effective orifice area (in square centimeters), *EOAProj* projected EOA at normal flow rate (in square centimeters); *P* mean transvalvular gradient (in mmHg), *CT Ca* calcium score (in Agatston Unit) on Computerized tomography, *SV* stroke volume, *Op* operative, *SAVR* surgical aortic valve replacement, *TAVR* transcatheter aortic valve replacement (Reprinted and adapted from Pibarot and Dumesnil [89], © 2012, with permission from Elsevier)

spite of the higher operative mortality of surgical aortic valve replacement, this therapy provides better long-term survival and quality of life in the majority of survivors. Trans-cutaneous aortic valve implantation presents an exciting option in these patients; although left ventricular dysfunction should not be a contraindication for this procedure, the exact risk-benefit equation is still unknown.

Transcutaneous Aortic Valve Replacement

Surgical aortic valve replacement (SAVR) is the gold standard for the treatment of critical aortic stenosis. However, significant co-morbidities may make conventional surgery exceedingly high risk. For these patients who are denied SAVR due to risk factors [71], an alternative therapeutic option has emerged due to the pioneering work of Dr. Alain Cribier [90]. From an experimental procedure, TAVI (Transcutaneous aortic valve implantation) is now the go-to procedure for extremely "high-risk" or inoperable patients, with clinical experience reaching the 10 year mark this year [91].

Overview of Current Devices

Presently two devices are widely being used: The Edwards SAPIEN trans-catheter heart valve (Edwards Lifesciences, Irvine, CA) and the Medtronic CoreValve™ (Medtronic Corp, Minneapolis, MN, USA). The SAPIEN valve is designed from bovine pericardium, similar to the Edwards PERIMOUNT® valve. It is treated with the same THERMAFIX™ anti-calcification process implemented for all other valves. The Edwards SAPIEN valve is available in 23 and 26 mm sizes. These valves are recommended for annuli in the range of 18–22 mm and 21–25 mm respectively. The Edwards system has been designed for a trans-femoral or a trans-apical approach and is available in two sheath sizes (25Fr and 28Fr). While the trans-femoral delivery system contains a RETROFLEX 3™ delivery system, the trans-apical valve is placed on the ASCENDRA introducer system™.

The Medtronic CORE-VALVE™ is available in three sizes 26, 29 and 31 mm. The AccuTrak® delivery system is designed to provide a controlled environment of valve delivery without the need for rapid ventricular pacing during deployment. This valve has been designed for delivery via three routes: trans-femoral, direct trans-aortic and via the subclavian artery. Unlike the SAPIEN® valve which is placed intra-annularly, the CORE-VALVE™ is a supra-annular seating valve with a much longer leaflet coaptation zone. This design has been provided to equitably distribute strain along the valve. The frame is provided with 8 mm gaps, which allow adequate coronary ostial perfusion and instrumentation. The CORE-VALVE™ delivery system is much smaller than the SAPIEN® at 18Fr size irrespective of valve size.

Randomized Trials

The first US implant occurred as part of the REVIVAL I study in March 2005. This trial was designed to compare outcomes between TAVI with balloon aortic valvuloplasty. After technical problems due to antegrade implantation, modifications to design were made and the REVIVAL II was introduced, the first patient being enrolled in December 2005. This trial was designed to include only a trans-femoral approach, with 55 patients being enrolled.

The PARTNER (**P**lacement of **A**o**R**tic**T**ra**N**scathet**ER** Valves; Clinicaltrials.gov Identifier: NCT0053084) trial was the first prospective, multi-centric, pivotal, randomized controlled trial conducted to determine the efficacy of TAVI. The PARTNER A study consists of two cohorts: (A) a comparison of TAVI (either trans-femoral or transapical) using the SAPIEN® and SAVR in patients who are deemed high risk. (B) a comparison of trans-femoral TAVI and optimal medical management (OMM) in patients considered inoperable.

The PARTNER IA consisted of 699 high-risk patients with critical calcific aortic stenosis undergoing either transfemoral (TF) or trans-apical (TA) aortic valve

replacement. The study was powered to achieve a statistical significance for all-cause mortality at the 1 year (non-inferiority). After including 492 and 207 patients in the TF and TA cohorts respectively, patients were assigned to TAVI or surgical aortic valve replacement with 1:1 randomization [92, 93].

The PARTNER IB study consisted of 358 patients considered too high risk for conventional surgery, but eligible for transfemoral TAVI. They were randomized equally between TF-TAVI and standard therapy, defined as Balloon aortic valvotomy (78.2 %), medial therapy alone (7.9 %), aortic valve replacement (6.1 %) apical-aortic conduits (3.3 %) or TAVI outside the USA (2.2 %).

The PARTNER committee recently presented 2 year outcomes of the PARTNER IA study [94]. The PARTNER IA study met its non-inferiority end-point demonstrating that TAVI has comparable outcomes to SAVR. The PARTNER IA study met its non-inferiority end-point demonstrating that TAVI has comparable outcomes to SAVR. At the end of 2 years, all-cause mortality was comparable in both SAVR and TAVI cohorts at 35 % and 33.9 % respectively ($p = 0.78$). Bleeding complications were significantly higher in the SAVR cohort (29.5 % vs 19 %; $p = 0.002$) while stroke/TIA were more common in the TAVI cohort (11.2 % vs 6.5 %; $p = 0.05$). Vascular complications were present in 11.6 % of TAVI patients, majority of them were related to the trans-femoral approach. Pacemaker requirement, dialysis, and endocarditis were comparable in both cohorts. Predictors of mortality for the TAVI cohort were a smaller body mass index (Hazard ratio 0.93(0.90, 0.97)), higher mean gradient (Hazard ratio 0.82(0.72, 0.94)), creatinine at baseline (Hazard ratio 1.06(1.00, 1.13)) and prior vascular surgery or stent (Hazard ratio 1.85(1.10, 3.39)). The study demonstrated a satisfactory decline in the mean gradient and increase in the aortic valve area after TAVI during the 2-year follow-up.

The main concerns raised with TAVI were the occurrence of neurological events post-procedure and the presence of residual peri-prosthetic regurgitation. A separate article focusing on neurological events in this PARTNER IA study, demonstrated that there are two distinct hazard phases associated with adverse CNS events. While the initial phase was driven by the procedure (hazard function 2.21 + 0.68) the late phase was predominantly influenced by patient-related factors (like history of prior stroke and NYHA class) [95].

PARTNER investigators have found paravalvular regurgitation to be an important predictor of mortality. The presence of paravalvular leak (mild–severe) increased the odds of mortality twofold (1.43–3.10) over an estimated 3 year period ($p < 0.01$; log-rank test). The valve cover index, defined as 100* [(valve prosthesis diameter-annulus diameter)/valve prosthesis diameter] was lower in patients with para-valvular leak, demonstrating that valve under sizing was an important causative factor [96]. Colli et al. have introduced a calcification score, which allows prediction of post-procedure para- and overall aortic regurgitation [97].

The PARTNER IB cohort results demonstrate significant advantage of TAVI over OMM. TAVI reduced the occurrence of all-cause mortality and re-hospitalizations by 29.1 % at the end of 1 year. The major concern was a higher incidence of stroke

(5 % vs 1.1 %; p = 0.06) and major vascular complications (16.2 % vs 1.1 %; p < 0.001) in the TAVI; important to note that as part of the study design all patients in the TAVI arm underwent a trans-femoral approach. A significant improvement in functional status was present in the TAVI cohort compared to the OMM group.

Data is also available from several registries which look at results of TAVI in the "real world". They all report a procedural success rate ranging from 88 % to more than 95 %. The lowest reported 1-year morality is 6.7 % while 30.7 % is the highest [91].

Valve in Valve

Isolated reports of a valve in valve procedure (TAV in SAV) using the CoreValve® (Medtronic corp., Minneapolis, MN) have been published since 2007 [98]. While this procedure is evolving, coronary ostial occlusion, atheroembolism, and appropriate positioning of the prosthesis are some concerns with the procedure. As experience increases more information regarding feasibility and ease of this "TAV in SAV" procedure in various commercially available stented and stentless valves will be available. Piazza et al. present one of the largest single center series on this subject, having performed this procedure in 20 patients with a reasonable early mortality [99].

Economic Aspects of TAVI

A detailed cost-analysis of the PARTNER study revealed that procedural cost for transapical arm of TAVI ($90,000 ± 40,000) was higher than conventional aortic valve replacement ($80,000 ± 47,000). The cost of a transfemoral and conventional AVR were comparable. However, total expenditure at the end of 1 year in both cohorts was comparable [100]. While TF-TAVI resulted in improved quality of life (QOL) as well as cost benefit, patients undergoing TA-TAVI and conventional AVR had similar procedural cost and QOL scores. Thus they conclude that at present TF-TAVI is economically beneficial to surgical AVR.

On-going Trials

Apart from the PARTNER II study, a search of the website "http://www.clinicaltrials.gov" [101] demonstrates eight other registered trials being conducted worldwide on feasibility of TAVI in a variety of clinical situations. Results of these studies will help us to define a clear set of inclusion and exclusion criteria for the procedure (Table 19.2).

Table 19.2 A brief overview of on-going clinical trials on TAVI abstracted from [99]

Trial	NCT number	Country	Start date	Estimated primary completion date	Estimated enrollment	Outline of trial	Device used
Medtronic Core Valve® US pivotal trial	NCT01240902	USA	November 2010	May 2013	1597	To evaluate the safety and efficacy of the Medtronic CoreValve®in high and very high risk patients with severe aortic stenosis	Medtronic CoreValve®
PARTNER II trial	NCT01314313	USA, Canada	March 2011	January 2015	2500	To evaluate the safety and effectiveness of the Edwards SAPIEN XT transcatheter heart valve and delivery system: NovaFlex(transfemoral) and Ascendra (trans-apical) in patients with symptomatic severe calcific aortic stenosis	Edwards SAPIEN XT®
SURTAVI	NCT01586910	USA, Denmark, Netherlands	March 2012	–	2500	Safety and efficacy study of the Medtronic CoreValve®in intermediate risk patients who need aortic valve replacement	Medtronic CoreValve®

SIMPLIFy TAVI	NCT01539746	Germany	April 2012	April 2013	110	To demonstrate that the avoidance of balloon valvuloplasty for the predilatation of the native aortic valve is associated with a reduction in the composite primary end-point in TAVI patients with severely impaired ejection fraction. (LVEF<35 %)	Medtronic CoreValve®
TAVIvsSAVR	NCT01057173	Denmark	December 2009	December 2013	–	A randomized controlled trial comparing TAVI and SAVR in patients above 70 years with severe aortic stenosis	Medtronic CoreValve®
Clinical evaluation of MDT-2111 in subjects with small aortic annuli and symptomatic severe aortic stenosis	NCT01634269	Japan	July 2012	August 2013	–	To demonstrate the effectiveness of MDT-2111 in the treatment of symptomatic severe aortic stenosis in subjects with small aortic annuli and deemed difficult for surgical operation	23 mm Medtronic CoreValve®using the MDT-2111 system

(continued)

Table 19.2 (continued)

Trial	NCT number	Country	Start date	Estimated primary completion date	Estimated enrollment	Outline of trial	Device used
Clinical evaluation of the MDT-2111 system	NCT01437098	Japan	October 2011	January 2013	–	Clinical evaluation of the MDT-2111 in subjects with symptomatic severe aortic stenosis	Medtronic CoreValve®
SOURCE XT Registry	NCT01238497	Worldwide 104 locations	September 2010	December 2012	2000	To identify patient characteristics and indicators related to complications and clinical benefits for patients with symptomatic severe calcific degenerative aortic stenosis that are undergoing treatment with the commercially available Edwards SAPIEN XT™ Valve, and delivery devices.	Edwards SAPIEN XT®
SOLACE-AU clinical trial	NCT01675596	Australia	April 2012	December 2013	200	The objective of the study is to observe the safety, efficacy and cost effectiveness of the Edwards SAPIEN XT valve for the treatment of severe calcific degenerative aortic stenosis.	Edwards SAPIEN XT®

Table 19.3 An outline of the present recommendations for TAVI in the management of severe calcific aortic stenosis

Recommendations	Class	Level	References
TAVI should only be undertaken with a multidisciplinary 'heart team' including cardiologists and cardiac surgeons and other specialists if necessary	I	C	
TAVI should only be performed in hospitals with cardiac surgery on-site	I	C	
TAVI is indicated in patients with severe symptomatic AS who are not suitable for AVR as assessed by a 'heart team' and who are likely to gain improvement in their quality of life and to have a life expectancy of more than 1 year after considerations of their comorbidities	I	B	[99]
TAVI should be considered in high-risk patients with severe symptomatic AS who may still be suitable for surgery, but in whom TAVI is factored by a 'heart team' based on the individual risk profile and anatomic suitability	IIa	B	[97]

Reprinted with permission from Vahanian et al. [63], © 2012, with permission from Oxford University Press

European Society for Valvular Heart Disease 2012 Guidelines

TAVI is a beneficial therapy in patients with "high-risk" severe calcific aortic stenosis. Patients with a EUROSCORE >20 or an STS score >10 % are well suited to this procedure. Individual patient related factors like age, prior cardiac surgery, especially coronary artery bypass with patent grafts, porcelain aorta, prior mediastinal radiation, and medical risk factors like COPD, oxygen dependency and physical frailty are other factors which needed to be taken into account to reach a well-informed decision regarding patient care. Guidelines recommend that decision to proceed with TAVI or SAVR should be jointly taken by a "heart team" and cardiologists [63, 102] (Tables 19.3 and 19.4)**.**

At present results and outcomes of TAVI at the early phase and studies with a longer follow-up period will be needed to determine the exact indications of TAVI. At present suffice to say that it is an exciting emerging technology, which provides a reasonable alternative in high-risk patients with severe aortic stenosis.

Acknowledgements We would like to thank Dr. Ishan K Shah for his help in the preparation of the manuscript. We also thank Ms. Melody Roller for assisting us to obtain copyright permission for the reproduced figures in this chapter.

Disclosure We do not have any disclosure related to this article.

Table 19.4 A list of absolute and relative contra-indications for TAVI in the management of severe calcific aortic valve stenosis

Absolute contraindications
Absence of a 'heart team' and no cardiac surgery on the site
Appropriateness of TAVI, as an alternative to AVR, not confirmed by a 'heart team'
Clinical
Estimated life expectancy <1 year
Improvement of quality of life by TAVI unlikely because of comorbidities
Severe primary associated disease of other values with major contribution to the patient's symptoms, that can be treated only by surgery
Anatomical
Inadequate annulus size (<18 mm, >29 mm)
Thrombus in the left ventricle
Active endocarditis
Elevated risk of coronary ostium obstruction (asymmetric valve calcification, short distance between annulus and coronary ostium, small aortic sinuses)
Plaques with mobile thrombi in the ascending aorta, or arch
For transfemoral/subclavian approach: inadequate vascular access (vessel size, calcification, tortuosity)
Relative contraindication
Bicuspid or non-calcification
Untreated coronary artery disease requiring revascularization
Hemodynamic instability
LVEF <20 %
For transapical approach: severe pulmonary disease, LV apex not accessible

Reprinted with permission from Vahanian et al. [102], © 2012; with permission from Oxford University Press

References

1. Carpentier A. Cardiac valve surgery – the "French correction". J Thorac Cardiovasc Surg. 1983;86(3):323–37.
2. Bolling SF, Deeb GM, Brunsting LA, Bach DS. Early outcome of mitral valve reconstruction in patients with end-stage cardiomyopathy. J Thorac Cardiovasc Surg 1995; 109(4):676–82; discussion 682–73.
3. Bach DS, Bolling SF. Early improvement in congestive heart failure after correction of secondary mitral regurgitation in end-stage cardiomyopathy. Am Heart J. 1995;129(6): 1165–70.
4. Calafiore AM, Gallina S, Di Mauro M, et al. Mitral valve procedure in dilated cardiomyopathy: repair or replacement? Ann Thorac Surg 2001;71(4):1146–52; discussion 1152–43.
5. Replogle RL, Campbell CD. Surgery for mitral regurgitation associated with ischemic heart disease. Results and strategies. Circulation. 1989;9(6 Pt 2):I122–5.
6. Maltais S, Schaff HV, Daly RC, et al. Mitral regurgitation surgery in patients with ischemic cardiomyopathy and ischemic mitral regurgitation: factors that influence survival. J Thorac Cardiovasc Surg. 2011;142(5):995–1001.
7. Timek TA, Miller DC. Another multidisciplinary look at ischemic mitral regurgitation. Semin Thorac Cardiovasc Surg. 2011;23(3):220–31.

8. McGee EC, Gillinov AM, Blackstone EH, et al. Recurrent mitral regurgitation after annuloplasty for functional ischemic mitral regurgitation. J Thorac Cardiovasc Surg. 2004;128(6):916–24.
9. Bin J, Zhibin C, Weidong R, et al. Assessment of mitral annulus (p3 segment) asymmetric deformity in myocardial infarction with ischemic regurgitation by real time three-dimensional echocardiography. Echocardiography. 2012;29(1):42–50.
10. Watanabe N, Ogasawara Y, Yamaura Y, et al. Geometric differences of the mitral valve tenting between anterior and inferior myocardial infarction with significant ischemic mitral regurgitation: quantitation by novel software system with transthoracic real-time three-dimensional echocardiography. J Am Soc Echocardiogr. 2006;19(1):71–5.
11. Watanabe N, Ogasawara Y, Yamaura Y, et al. Mitral annulus flattens in ischemic mitral regurgitation: geometric differences between inferior and anterior myocardial infarction: a real-time 3-dimensional echocardiographic study. Circulation. 2005;112(9 Suppl):I458–62.
12. Watanabe N, Ogasawara Y, Yamaura Y, et al. Geometric deformity of the mitral annulus in patients with ischemic mitral regurgitation: a real-time three-dimensional echocardiographic study. J Heart Valve Dis. 2005;14(4):447–52.
13. Gorman 3rd JH, Jackson BM, Gorman RC, et al. Papillary muscle discoordination rather than increased annular area facilitates mitral regurgitation after acute posterior myocardial infarction. Circulation. 1997;96(9 Suppl):II-124–7.
14. Gorman 3rd JH, Gorman RC, Jackson BM, et al. Distortions of the mitral valve in acute ischemic mitral regurgitation. Ann Thorac Surg. 1997;64(4):1026–31.
15. He S, Fontaine AA, Schwammenthal E, et al. Integrated mechanism for functional mitral regurgitation: leaflet restriction versus coapting force: in vitro studies. Circulation. 1997;96(6):1826–34.
16. Agricola E, Oppizzi M, Pisani M, et al. Ischemic mitral regurgitation: mechanisms and echocardiographic classification. Eur Heart J Cardiovasc Imaging. 2008;9(2):207–21.
17. TG DS, MA A, GW D, JG B. Mitral valve surgery in advanced heart failure. J Am Coll Cardiol. 2010;55(4):271–82.
18. Kono T, Sabbah HN, Rosman H, et al. Left ventricular shape is the primary determinant of functional mitral regurgitation in heart failure. J Am Coll Cardiol. 1992;20(7):1594–8.
19. Sabbah HN, Kono T, Rosman H, et al. Left ventricular shape: a factor in the etiology of functional mitral regurgitation in heart failure. Am Heart J. 1992;23(4):961–6.
20. Kono T, Sabbah HN, Stein PD, et al. Left ventricular shape as a determinant of functional mitral regurgitation in patients with severe heart failure secondary to either coronary artery disease or idiopathic dilated cardiomyopathy. Am J Cardiol. 1991;68(4):355–9.
21. Boltwood CM, Tei C, Wong M, Shah PM. Quantitative echocardiography of the mitral complex in dilated cardiomyopathy: the mechanism of functional mitral regurgitation. Circulation. 1983;68(3):498–508.
22. Sadeghpour A, Abtahi F, Kiavar M, et al. Echocardiographic evaluation of mitral geometry in functional mitral regurgitation. J Cardiothorac Surg. 2008;3:54.
23. Keren G, Katz S, Strom J, et al. Dynamic mitral regurgitation. An important determinant of the hemodynamic response to load alterations and inotropic therapy in severe heart failure. Circulation. 1989;80(2):306–13.
24. Lancellotti P, Magne J. Stress testing for the evaluation of patients with mitral regurgitation. Curr Opin Cardiol. 2012;27(5):492–8.
25. Bach DS, Deeb GM, Bolling SF. Accuracy of intraoperative transesophageal echocardiography for estimating the severity of functional mitral regurgitation. Am J Cardiol. 1995;76(7):508–12.
26. Lancellotti P, Lebrun F, Pierard LA. Determinants of exercise-induced changes in mitral regurgitation in patients with coronary artery disease and left ventricular dysfunction. J Am Coll Cardiol. 2003;42(11):1921–8.
27. Lebrun F, Lancellotti P, Pierard LA. Quantitation of functional mitral regurgitation during bicycle exercise in patients with heart failure. J Am Coll Cardiol. 2001;38(6):1685–92.

28. Giga V, Ostojic M, Vujisic-Tesic B, et al. Exercise-induced changes in mitral regurgitation in patients with prior myocardial infarction and left ventricular dysfunction: relation to mitral deformation and left ventricular function and shape. Eur Heart J. 2005;26(18):1860–5.
29. Pierard LA, Lancellotti P. The role of ischemic mitral regurgitation in the pathogenesis of acute pulmonary edema. N Engl J Med. 2004;351(16):1627–34.
30. Lancellotti P, Melon P, Sakalihasan N, et al. Effect of cardiac resynchronization therapy on functional mitral regurgitation in heart failure. Am J Cardiol. 2004;94(11):1462–5.
31. Lancellotti P, Gerard PL, Pierard LA. Long-term outcome of patients with heart failure and dynamic functional mitral regurgitation. Eur Heart J. 2005;26(15):1528–32.
32. Lancellotti P, Troisfontaines P, Toussaint AC, Pierard LA. Prognostic importance of exercise-induced changes in mitral regurgitation in patients with chronic ischemic left ventricular dysfunction. Circulation. 2003;108(14):1713–7.
33. Yiu SF, Enriguqez-Sarano M, Tribouilloy C, et al. Determinants of the degree of functional mitral regurgitation in patients with systolic left ventricular dysfunction: a quantitative clinical study. Circulation. 2000;102(12):1400–6.
34. Grande-Allen KJ, Borowski AG, Troughton RW, et al. Apparently normal mitral valves in patients with heart failure demonstrate biochemical and structural derangements: an extracellular matrix and echocardiographic study. J Am Coll Cardiol. 2005;45(1):54–61.
35. Hickey MS, Smith LR, Muhlbaier LH, et al. Current prognosis of ischemic mitral regurgitation. Implications for future management. Circulation. 1988;78(3 Pt 2):I51–9.
36. Lamas GA, Mitchell GF, Flaker GC, et al. Clinical significance of mitral regurgitation after acute myocardial infarction survival and ventricular enlargement investigators. Circulation. 1997;96(3):827–33.
37. Grigioni F, Enriquez-Sarano M, Zehr KJ, et al. Ischemic mitral regurgitation: long-term outcome and prognostic implications with quantitative doppler assessment. Circulation. 2001;103(13):1759–64.
38. Trichon BH, Felker GM, Shaw LK, et al. Relation of frequency and severity of mitral regurgitation to survival among patients with left ventricular systolic dysfunction and heart failure. Am J Cardiol. 2003;91(5):538–43.
39. Koelling TM, Aaronson KD, Cody RJ, et al. Prognostic significance of mitral regurgitation and tricuspid regurgitation in patients with left ventricular systolic dysfunction. Am Heart J. 2002;144(3):524–9.
40. Ellis SG, Whitlow PL, Raymond RE, Schneider JP. Impact of mitral regurgitation on long-term survival after percutaneous coronary intervention. Am J Cardiol. 2002;89(3):315–8.
41. Gillinov AM, Wierup PN, Blackstone EH, et al. Is repair preferable to replacement for ischemic mitral regurgitation? J Thorac Cardiovasc Surg. 2001;122(6):1125–41.
42. Grossi EA, Goldberg JD, LaPietra A, et al. Ischemic mitral valve reconstruction and replacement: comparison of long-term survival and complications. J Thorac Cardiovasc Surg. 2001;122(6):1107–24.
43. Bax JJ, Braun J, Somer ST, et al. Restrictive annuloplasty and coronary revascularization in ischemic mitral regurgitation results in reverse left ventricular remodeling. Circulation. 2004;110(11 Suppl 1):II103–8.
44. Geidel S, Lass M, Schneider C, et al. Downsizing of the mitral valve and coronary revascularization in severe ischemic mitral regurgitation results in reverse left ventricular and left atrial remodeling. Eur J Cardiothorac Surg. 2005;27(6):1011–6.
45. Bonow RO, Carabello BA, Chatterjee K, et al. 2008 focused update incorporated into the ACC/AHA 2006 guidelines for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to revise the 1998 guidelines for the management of patients with valvular heart disease). Endorsed by the Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. J Am Coll Cardiol. 2008;52(13):e1–142.
46. David TE, Uden DE, Strauss HD. The importance of the mitral apparatus in left ventricular function after correction of mitral regurgitation. Circulation. 1983;68(3 Pt 2):II76–82.

47. Tibayan FA, Rodriguez F, Langer F, et al. Undersized mitral annuloplasty alters left ventricular shape during acute ischemic mitral regurgitation. Circulation. 2004;110(11 Suppl 1):II98–102.
48. Mihaljevic T, Lam BK, Rajeswaran J, et al. Impact of mitral valve annuloplasty combined with revascularization in patients with functional ischemic mitral regurgitation. J Am Coll Cardiol. 2007;49(22):2191–201.
49. Fukuda S, Gillinov AM, Song JM, et al. Echocardiographic insights into atrial and ventricular mechanisms of functional tricuspid regurgitation. Am Heart J. 2006;152(6):1208–14.
50. Chan V, Ruel M, Mesana TG. Mitral valve replacement is a viable alternative to mitral valve repair for ischemic mitral regurgitation: a case-matched study. Ann Thorac Surg 2011;92(4):1358–65; discussion 1365–56.
51. Magne J, Senechal M, Mathieu P, et al. Restrictive annuloplasty for ischemic mitral regurgitation may induce functional mitral stenosis. J Am Coll Cardiol. 2008;51(17):1692–701.
52. Kainuma S, Taniguchi K, Toda K, et al. Pulmonary hypertension predicts adverse cardiac events after restrictive mitral annuloplasty for severe functional mitral regurgitation. J Thorac Cardiovasc Surg. 2011;142(4):783–92.
53. Kainuma S, Taniguchi K, Daimon T, et al. Does stringent restrictive annuloplasty for functional mitral regurgitation cause functional mitral stenosis and pulmonary hypertension? Circulation. 2011;124(11 Suppl):S97–106.
54. Daimon M, Fukuda S, Adams DH, et al. Mitral valve repair with Carpentier-McCarthy-Adams IMR ETlogix annuloplasty ring for ischemic mitral regurgitation: early echocardiographic results from a multi-center study. Circulation. 2006;114(1 Suppl):I588–93.
55. Martin CE, Castano M, Gomez-Plana J, et al. Mitral stenosis after IMR ETlogix ring annuloplasty for ischemic regurgitation. Asian Cardiovasc Thorac Ann. 2012;20(5):534–8.
56. Wong VM, Wenk JF, Zhang Z, et al. The effect of mitral annuloplasty shape in ischemic mitral regurgitation: a finite element simulation. Ann Thorac Surg. 2012;93(3):776–82.
57. Mirabel M, Iung B, Baron G, et al. What are the characteristics of patients with severe, symptomatic, mitral regurgitation who are denied surgery? Eur Heart J. 2007;28(11): 1358–65.
58. Chiam PT, Ruiz CE. Percutaneous transcatheter mitral valve repair: a classification of the technology. JACC Cardiovasc Interv. 2011;4(1):1–13.
59. Feldman T, Kar S, Rinaldi M, et al. Percutaneous mitral repair with the MitraClip system: safety and midterm durability in the initial EVEREST (Endovascular Valve Edge-to-Edge REpair Study) cohort. J Am Coll Cardiol. 2009;54(8):686–94.
60. Baldus S, Schillinger W, Franzen O, et al. MitraClip therapy in daily clinical practice: initial results from the German transcatheter mitral valve interventions (TRAMI) registry. Eur J Heart Fail. 2012;14(9):1050–5.
61. Pinney SP. The role of tricuspid valve repair and replacement in right heart failure. Curr Opin Cardiol. 2012;27(3):288–95.
62. Dreyfus GD, Corbi PJ, Chan KM, Bahrami T. Secondary tricuspid regurgitation or dilatation: which should be the criteria for surgical repair? Ann Thorac Surg. 2005;79(1):127–32.
63. Vahanian A, Alfieri O, Andreotti F, et al. Guidelines on the management of valvular heart disease (version 2012): the joint task force on the management of valvular heart disease of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). Eur J Cardiothorac Surg. 2012;42(4):S1–44.
64. Matsunaga A, Duran CM. Progression of tricuspid regurgitation after repaired functional ischemic mitral regurgitation. Circulation. 2005;112(9 Suppl):I453–7.
65. Deloche A, Guerinon J, Fabiani JN, et al. Anatomical study of rheumatic tricuspid valve diseases: application to the study of various valvuloplasties. Ann Chir Thorac Cardiovasc. 1973;12(4):343–9.
66. Chikwe J, Anyanwu AC. Surgical strategies for functional tricuspid regurgitation. Semin Thorac Cardiovasc Surg. 2010;22(1):90–6.
67. McCarthy PM, Bhudia SK, Rajeswaran J, et al. Tricuspid valve repair: durability and risk factors for failure. J Thorac Cardiovasc Surg. 2004;127(3):674–85.

68. Kim YJ, Kwon DA, Kim HK, et al. Determinants of surgical outcome in patients with isolated tricuspid regurgitation. Circulation. 2009;120(17):1672–8.
69. Topilsky Y, Khanna AD, Oh JK, et al. Preoperative factors associated with adverse outcome after tricuspid valve replacement. Circulation. 2011;123(18):1929–39.
70. Rogers JH, Bolling SF. The tricuspid valve: current perspective and evolving management of tricuspid regurgitation. Circulation. 2009;119(20):2718–25.
71. Iung B, Baron G, Butchart EG, et al. A prospective survey of patients with valvular heart disease in Europe: The Euro Heart Survey on valvular heart disease. Eur Heart J. 2003;24(13):1231–43.
72. Chaliki HP, Mohty D, Avierinos JF, et al. Outcomes after aortic valve replacement in patients with severe aortic regurgitation and markedly reduced left ventricular function. Circulation. 2002;106(21):2687–93.
73. Kamath AR, Varadarajan P, Turk R, et al. Survival in patients with severe aortic regurgitation and severe left ventricular dysfunction is improved by aortic valve replacement: results from a cohort of 166 patients with an ejection fraction < or =35%. Circulation. 2009;120(11 Suppl):S134–8.
74. Brown ML, Schaff HV, Suri RM, et al. Indexed left ventricular dimensions best predict survival after aortic valve replacement in patients with aortic valve regurgitation. Ann Thorac Surg. 2009;87(4):1170–5; discussion 1175–76.
75. Bonow RO, Dodd JT, Maron BJ, O'Gara PT, White GG, McIntosh CL, et al. Long-term serial changes in left ventricular function and reversal of ventricular dilatation after valvereplacement for chronic aortic regurgitation. Circulation. 1988;78(5 Pt 1):1108–20.
76. deFilippi CR, Willett DL, Brickner ME, et al. Usefulness of dobutamine echocardiography in distinguishing severe from nonsevere valvular aortic stenosis in patients with depressed left ventricular function and low transvalvular gradients. Am J Cardiol. 1995;75(2):191–4.
77. Monin JL, Quere JP, Monchi M, et al. Low-gradient aortic stenosis: operative risk stratification and predictors for long-term outcome: a multicenter study using dobutamine stress hemodynamics. Circulation. 2003;108(3):319–24.
78. Monin JL, Monchi M, Gest V, et al. Aortic stenosis with severe left ventricular dysfunction and low transvalvular pressure gradients: risk stratification by low-dose dobutamine echocardiography. J Am Coll Cardiol. 2001;37(8):2101–7.
79. Blais C, Burwash IG, Mundigler G, et al. Projected valve area at normal flow rate improves the assessment of stenosis severity in patients with low-flow, low-gradient aortic stenosis: the multicenter TOPAS (Truly or Pseudo-Severe Aortic Stenosis) study. Circulation. 2006;113(5):711–21.
80. Tribouilloy C, Levy F, Rusinaru D, et al. Outcome after aortic valve replacement for low-flow/low-gradient aortic stenosis without contractile reserve on dobutamine stress echocardiography. J Am Coll Cardiol. 2009;53(20):1865–73.
81. Connolly HM, Oh JK, Schaff HV, et al. Severe aortic stenosis with low transvalvular gradient and severe left ventricular dysfunction:result of aortic valve replacement in 52 patients. Circulation. 2000;101(16):1940–6.
82. Pai RG, Varadarajan P, Razzouk A. Survival benefit of aortic valve replacement in patients with severe aortic stenosis with low ejection fraction and low gradient with normal ejection fraction. Ann Thorac Surg. 2008;86(6):1781–9.
83. Levy F, Laurent M, Monin JL, et al. Aortic valve replacement for low-flow/low-gradient aortic stenosis operative risk stratification and long-term outcome: a European multicenter study. J Am Coll Cardiol. 2008;51(15):1466–72.
84. Powell DE, Tunick PA, Rosenzweig BP, et al. Aortic valve replacement in patients with aortic stenosis and severe left ventricular dysfunction. Arch Intern Med. 2000;160(9):1337–41.
85. Malfatto G, Branzi G, Giglio A, et al. Diastolic dysfunction and abnormal exercise ventilation predict adverse outcome in elderly patients with chronic systolic heart failure. Eur J Prev Cardiol. 2012;19(3):396–403.

86. Gardin JM, Leifer ES, Kitzman DW, et al. Usefulness of doppler echocardiographic left ventricular diastolic function and peak exercise oxygen consumption to predict cardiovascular outcomes in patients with systolic heart failure (from HF-ACTION). Am J Cardiol. 2012;110(6):862–9.
87. Clavel MA, Fuchs C, Burwash IG, et al. Predictors of outcomes in low-flow, low-gradient aortic stenosis: results of the multicenter TOPAS study. Circulation. 2008;118:S234–42.
88. Fraccaro C, Al-Lamee R, Tarantini G, et al. Transcatheter aortic valve implantation in patients with severe left ventricular dysfunction: immediate and mid-term results, a multicenter study. Circ Cardiovasc Interv. 2012;5(2):253–60.
89. Pibarot P, Dumesnil JG. Low-flow, low-gradient aortic stenosis with normal and depressed left ventricular ejection fraction. J Am Coll Cardiol. 2012;60(19):1845–53.
90. Cribier A, Eltchaninoff H, Bash A, et al. Percutaneous transcatheter implantation of an aortic valve prosthesis for calcific aortic stenosis: first human case description. Circulation. 2002;106(24):3006–8.
91. Genereux P, Head SJ, Wood DA, et al. Transcatheter aortic valve implantation 10-year anniversary: review of current evidence and clinical implications. Eur Heart J. 2012;33(19):2388–98.
92. Leon MB, Smith CR, Mack M, et al. Transcatheter aortic-valve implantation for aortic stenosis in patients who cannot undergo surgery. N Engl J Med. 2010;363:1597–607.
93. Smith CR, Leon MB, Mack MJ, et al. Transcatheter versus surgical aortic-valve replacement in high-risk patients. N Engl J Med. 2011;364:2187–98.
94. Kodali SK, Williams MR, Smith CR, et al. Two-year outcomes after transcatheter or surgical aortic-valve replacement. N Engl J Med. 2012;366:1686–95.
95. Miller DC, Blackstone EH, Mack MJ, et al. Transcatheter (TAVR) versus surgical (AVR) aortic valve replacement: occurrence, hazard, risk factors, and consequences of neurologic events in the PARTNER trial. J Thorac Cardiovasc Surg. 2012;143(4):832–843.e13.
96. Detaint D, Lepage L, Himbert D, et al. Determinants of significant paravalvular regurgitation after transcatheter aortic valve: implantation impact of device and annulus discongruence. JACC Cardiovasc Interv. 2009;2(9):821–7.
97. Colli A, D'Amico R, Kempfert J, et al. Transesophageal echocardiographic scoring for transcatheter aortic valve implantation: impact of aortic cusp calcification on postoperative aortic regurgitation. J Thorac Cardiovasc Surg. 2011;142(5):1229–35.
98. Wenaweser P, Buellesfeld L, Gerckens U, Grube E. Percutaneous aortic valve replacement for severe aortic regurgitation in degenerated bioprosthesis: the first valve in valve procedure using the Corevalve Revalving system. Catheter Cardiovasc Interv. 2007;70(5):760–4.
99. Piazza N, Bleiziffer S, Brockmann G, et al. Transcatheter aortic valve implantation for failing surgical aortic bioprosthetic valve: from concept to clinical application and evaluation (part 2). JACC Cardiovasc Interv. 2011;4(7):733–42.
100. Reynolds MR, Magnuson EA, Lei Y, et al. Cost-effectiveness of transcatheter aortic valve replacement compared with surgical aortic valve replacement in high-risk patients with severe aortic stenosis: results of the PARTNER (Placement of Aortic Transcatheter Valves) trial (Cohort A). J Am Coll Cardiol. 2012;60(25):2683–92.
101. http://www.clinicaltrials.gov
102. Vahanian A, Alfieri O, Andreotti F, et al. Guidelines on the management of valvular heart disease (version 2012): the joint task force on the management of valvular heart disease of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). Eur J Cardiothorac Surg. 2012;33(19):2451–96.

Chapter 20
Patient Selection for Cardiac Transplantation

Michael L. Craig and Adrian B. Van Bakel

Introduction

Congestive heart failure (HF) remains one of the leading causes of hospitalization in adults in the United States. The direct and indirect costs associated with this illness are estimated at $32 billion for 2013 and projected to reach $70 billion by 2030. The majority of this financial burden arises from the over one million hospitalizations that occur annually for acute decompensated HF [1]. Advances in pharmacologic and device therapy for HF, and their associated reductions in morbidity and mortality, have led to increasing numbers of patients progressing to advanced heart failure. Of the nearly six million adults with congestive heart failure, it is has been estimated that 20 % have ACC Stage D disease—the group of patients who should be considered for advanced heart failure therapies. Unfortunately, this potential pool far exceeds the roughly 2300 cardiac transplantations that are performed yearly in the United States, and the 3700 performed worldwide, in each of the last several years [2].

Cardiac transplantation has offered the greatest morbidity and mortality benefit for patients with end-stage heart failure for many decades. In addition, continued advancements in the field of mechanical circulatory support have expanded the therapeutic strategies available for patients with end-stage heart failure. In this chapter, the process of patient selection for cardiac transplantation will be reviewed with specific emphasis on indications for cardiac transplantation, risk stratification of patients with end-stage heart failure, the process of evaluation, absolute and relative contraindications for cardiac transplantation, and predictors of post-transplant survival.

M.L. Craig, MD (✉) • A.B. Van Bakel, MD, PhD
Division of Cardiology, Medical University of South Carolina,
114 Doughty Street, MSC 592, Charleston, SC 29425, USA
e-mail: craigml@musc.edu; vanbakel@musc.edu

H. Eisen (ed.), *Heart Failure*, DOI 10.1007/978-1-4471-4219-5_20

Indications for Cardiac Transplantation

The International Society for Heart and Lung Transplantation (ISHLT), American College of Cardiology (ACC), American Heart Association (AHA), Heart Failure Society of America (HFSA), European Society of Cardiology (ESC) and the Canadian Cardiovascular Society (CCS) have all published guidelines summarizing the indications for cardiac transplantation. These guidelines are largely centered on the patient with refractory symptoms of HF despite maximal medical and device therapy. The discussion below will focus on the indications for cardiac transplantation and risk stratification for the ambulatory patient with HF followed by brief discussion of those populations deserving special consideration.

Risk Stratification of Patients with Advanced Heart Failure

The goal of any medical therapy is to maximize longevity and quality of life. Though morbidity and mortality for patients with Stage D HF are high, cardiac transplantation also carries inherent short and long-term risks. As such, appropriate risk stratification of patients who may qualify for transplantation is essential to perform transplantation when prognosis is sufficiently poor, while still retaining a high likelihood of success. Realizing the limitations of the New York Heart Association functional classification system, the ACC and the AHA developed the stages of heart failure in 2001 in effort to further define the progression of disease and guide the management of patients with congestive heart failure. According to this classification system, Stage D patients, defined as those who have marked symptoms at rest despite maximal pharmacologic and device therapy, should be considered for advanced heart failure therapies to include cardiac transplantation. The perfect model for identifying the most appropriate patient for cardiac transplantation would include all variables which have been shown to have prognostic value in patients with congestive heart failure. In univariate analysis, ejection fraction, NYHA functional class, hemodynamic abnormalities and markers of poor tissue perfusion have all been shown to predict survival in patients with HF. The challenge lies in the sheer number of variables that ultimately affect the HF phenotype—making the use of one or even a few such variables problematic.

Cardiopulmonary Exercise Testing

Peak oxygen consumption (VO_2), as measured by a cardiopulmonary exercise test (CPX), provides an objective measurement of functional capacity and has proven to be extremely useful in risk stratifying patients with HF. A peak VO_2 of < 14 ml/kg/min has been historically used as an indication for cardiac transplantation; however this threshold was validated in an era prior to the widespread use of current

evidence based pharmacologic and device therapies [3, 4]. More recent studies have shown a peak VO_2 of < 10 ml/kg/min to be a better discriminator of risk for those with end stage HF. In a study of 715 patients referred for cardiac transplantation, those with a peak VO_2 of ≤ 10 ml/kg/min had a 1 year event free survival of 65 %, compared to 77 % for peak VO_2 between 10 and 14 ml/kg/min and 86 % for peak VO_2 > 14 ml/kg/min [5].

The 10 year update of the 2006 International Society for Heart Lung Transplantation (ISHLT) listing criteria for heart transplantation was recently published, further refining CPX listing criteria [6]. A maximal CPX is defined as one in which the respiratory exchange ratio is > 1.05 and anaerobic metabolism is achieved in the setting of optimal medical therapy. In addition, a peak VO_2 of ≤ 12 ml/kg/min was recommended as a guide to listing in patients on beta blocker therapy—in those intolerant of beta blocker therapy, a peak VO_2 of ≤ 14 ml/kg/min should be used. In women and patients under the age of 50, using a peak VO_2 of ≤ 50 % of predicted as a guide to listing received a Class IIa recommendation, while in patients with a submaximal CPX, use of a ventilation equivalent of carbon dioxide (VE/VCO_2) of > 35 as a determinant for listing received a Class IIb recommendation. In obese patients, defined as a body mass index (BMI) > 30 kg/m^2, an adjusted to lean body mass peak VO_2 of < 19 ml/kg/min received a Class IIb recommendation as a guide to selection. Finally, the use of peak VO_2 as the sole criteria for listing received a Class III recommendation. In addition, the presence of a CRT device does not alter the current peak VO_2 cutoff (Class I recommendation).

Although peak VO_2 has been shown to have strong prognostic value in patients referred for cardiac transplant evaluation, the use of any single variable to determine need for transplantation is problematic. With this in mind, several models have been designed, using numerous variables, and have proven to be highly predictive of prognosis in patients with HF.

Heart Failure Risk Models

The Heart Failure Survival Score (HFSS) is a non-invasive risk stratification model that was developed using 80 clinical characteristics from 269 patients and then prospectively validated in 199 patients [7]. Seven characteristics were predictive of survival in multivariate analysis and were used to construct this model: ischemic cardiomyopathy, resting heart rate, left ventricular ejection fraction, interventricular conduction delay (QRS ≥120 ms), mean resting blood pressure, peak VO_2 and serum sodium. Based on the score derived from this model, patients are stratified into low, medium and high risk groups. Events, defined as the need for urgent transplant or death without transplant at 1 year, occurred in 12 %, 40 % and 65 % of the patients in these respective groups. Based on these findings, the authors concluded that patients in the medium and high risk groups should be considered for cardiac transplantation. Although this model was validated in the era prior to widespread use of beta blockers, aldosterone receptor blockers and device therapy, it has been

more recently validated in a modern cohort [5, 8]. The inherent variability of several of the risk factors used, as well as the somewhat arbitrary use of urgent transplantation as a part of the combined endpoint has resulted in some criticism of this model.

The Seattle Heart Failure Score (SHFM) is another multivariate risk model, derived from a cohort of 1125 patients, used to predict one, 2 and 3 year survival in patients with HF. Patients were risk stratified into one of five groups based on a score of −1 to 4. The 2 year survival rate was approximately 93 %, 89 %, 78 %, 58 %, 29 % and 10 % respectively in these five groups. In addition, this model predicts the impact of the addition of pharmacologic and device based therapy on survival—making it a more useful and illustrative tool for patients. This model, which was prospectively validated in 9942 patients with HF with over 17,000 years of follow-up, also benefits from the fact that it was derived in an era with more widespread use of current evidence-based pharmacologic and device therapies [9].

The updated 2016 ISHLT guidelines are more explicit in recommending use of prognosis scoring in addition to CPX testing to determine whether and when to list a candidate for transplantation. The new guidelines suggest a HFSS in the high/medium risk range or a SHFM estimated 1 year survival of < 80 % along with an appropriately low peak VO_2 are adequate criteria for transplant candidacy [6].In addition to the focus on patients with ambulatory Stage D HF, there are several other populations of patients who deserve special consideration. Patients who are hospitalized with refractory cardiogenic shock, dependent on intravenous inotropes for maintenance of end organ perfusion, symptomatic with ventricular arrhythmias refractory to pharmacologic and device therapy, symptomatic with severely limiting ischemia refractory to pharmacologic therapies and not amenable to revascularization, and those with severely symptomatic congenital heart disease not amenable to corrective surgeries may also be considered for cardiac transplantation.

Evaluation for Cardiac Transplantation

Patients with one or more indications for cardiac transplantation should be referred to a heart transplant center for comprehensive evaluation. The number of transplant centers has been on the decline in recent years. Some would argue this trend is a favorable one, as it forces organ implantation and longitudinal care of the transplant recipient into the hands of a skilled few. Of the roughly 3700 transplants that were performed worldwide in 2009, about 50 % were performed in centers that perform more than 20 transplants per year (21 % of all centers), 33 % in centers that perform 10–19 transplants per year (39 % of all centers) and the remaining in centers that perform < 10 transplants per year (40 % of all centers) [2].

The first step in the evaluation process should focus on patient education. As with any other proposed therapy or procedure, the patient should be counseled on the potential short and long-term risk and benefits of cardiac transplantation. While the

expected benefits of improved survival and quality of life with cardiac transplantation are clear, the long-term increased risk of infection, malignancy and renal dysfunction should be discussed—in many respects, patients are trading one disease for another. In the spirit of informed consent, alternative therapies, which may include palliative care and/or left ventricular assist device therapy, should also be discussed. Once education has been completed, the evaluation process may then proceed with a head-to-toe medical, social and financial evaluation. This next stage should be conducted by a multidisciplinary team that should be comprised of not only advanced heart failure cardiologists, cardiothoracic surgeons and consulting physicians but also transplant coordinators, mid-level providers, pharmacists, social workers, psychologists, financial coordinators, physical and occupational therapists and other allied health professionals. Amongst the group of consulting physicians, a transplant infectious disease specialist, immunologist and cardiac pathologist are invaluable resources. In addition to numerous consultations to assess surgical candidacy, comorbidities, mental capacity, and financial and social support, patients should also undergo thorough diagnostic testing to include imaging and laboratory evaluation to assess end-organ function, glycemic control, bone density, nutritional status, and age appropriate cancer screening.

In addition, ABO blood group typing and quantification of antibodies to human leukocytes antigens (HLAs) are necessary for donor-recipient matching. HLA antibodies are identified and quantified by a method known as panel-reactive antibody (PRA) testing. During this testing, which may be done by solid phase, flow cytometric, or cytotoxic methods, the type and strength of antibodies directed against HLA antigens in the potential donor pool are identified. These results are distilled to a cPRA (expressed as a percent) when using solid phase and flow cytometric assays or a PRA when using cytotoxic methods. The cPRA and PRA are estimates of the potential donor pool that would possess unacceptable HLA antigens. Prior to widespread use of solid phase assays that can identify specific HLA antibodies, patients with a PRA > 10 %, generally required a prospective crossmatch prior to transplantation. The specificity of solid phase and flow cytometric assays now allows virtual crossmatching and thus wider sharing of donor organs without prospective crossmatching. A multidisciplinary approach ensuring appropriate patient selection is not only the most important determinant of post-transplant survival, but is also critical in maintaining proper organ stewardship.

Contraindications for Cardiac Transplantation

The ISHLT, ACC, AHA, HFSA ESC and the CCS have all published guidelines in regard to either contraindications or insufficient indications for cardiac transplantation. In general, there is consensus of opinion in regard to the contraindications for cardiac transplantation.

Pulmonary Hypertension

Acute right ventricular failure (RVF) is one of the most feared perioperative complications of cardiac transplantation and, therefore, preoperative risk stratification is crucial. It has been estimated that as many as 20 % of early deaths in transplanted patients have resulted from increased pre-operative pulmonary vascular resistance (PVR) and the resultant decline in right ventricular function that may ensue postoperatively [10]. Because of the significant morbidity and mortality associated with this dreaded consequence, many different static and dynamic measurements of pulmonary hemodynamic variables have been described to guide the selection of potential candidates. In addition to PVR, specific cutoffs for pulmonary artery systolic pressure (PASP) and transpulmonary gradient (TPG) have been utilized to identify those at increased risk for RVF. Although these absolute limits have been used, a dichotomy does not exist and, therefore, the degree of hemodynamic abnormality may be used to predict incremental risk [11]. 2016 ISHLT guidelines suggest a PASP $\geq$ 50 mmHg, a PVR > 3 Woods units or a TPG $\geq$15 mmHg, may be considered as a relative contraindication for cardiac transplantation [6]. In addition, a PASP > 60 mmHg imposes additional risk for RVF and/or death in those who have either an increased TPG or PVR. In patients with one or more abnormal hemodynamic measurements, a provocative pharmacologic challenge may be considered with one of several different pulmonary and/or systemic vasodilators. Commonly used agents include nitroprusside, nitric oxide, and nitroglycerin. If acceptable hemodynamics cannot be achieved with one or more of these therapies, or such therapy results in significant systemic hypotension (SBP < 85 mmHg), admission for further pharmacologic and/or left ventricular assist device (LVAD) therapies may be considered. In those patients who demonstrate pulmonary vasoreactivity, that is in those who are able to satisfactorily improve their PVR and/or PASP with provocation, their predicted survival post-transplant is unclear with some studies showing worsened survival post-transplant [12] and others showing outcomes similar to those with more normal PVR pre-transplant [13, 14].

Advanced Age

When evaluating a patient for cardiac transplantation, advanced age is a relative contraindication to cardiac transplantation. In 2011, the median age of the cardiac transplant recipient was 54 years of age—a number which has not varied much over the years. However, the age distribution of transplant recipients has changed significantly in the last decade with older patients now being transplanted more frequently. From 1982 to 1991, approximately 38 % of cardiac transplant recipients were between the ages of 50 and 59 and 12 % were between the ages of 60 and 69. In contrast, from 2002 to 2010, the former group received 35 % of the available hearts, while the oldest group received 27 % of all implants [2]. This trend is a reflection of the growing

experience that carefully selected patients with end-stage HF and advance age may do well with cardiac transplantation.

The previously mentioned supply and demand mismatch in regard to donor hearts and potential recipients has certainly led to many ethical discussions centered on advanced age when determining recipient candidacy. Having said that, instead of asking whether a patient is "too old" for transplant, the better question is "What is the likelihood that the patient will live the average 12.1 years post-transplant in light of their age and other co-morbidities?". In the early years of cardiac transplantation, age > 55 years old was considered a contraindication to cardiac transplantation due to concerns for decreased survival post-transplant. Over the last two decades, however, numerous single center studies have demonstrated similar outcomes in patients > 60 years of age when compared to younger patients [15–17]. In addition, several other centers have reported individual experiences suggesting that carefully selected patients > 70 years of age may still do well with cardiac transplantation [18–21]. To the contrary, other single-center studies have demonstrated decreased post-transplant survival in patients > 60 years of age. In one of the largest retrospective studies to date, Weiss et al. looked at over 14,000 patients transplanted between 1999 and 2006. In patients ≥ 60 years of age, 30 day, 1 year and 5 year survival was 93 %, 84 %, and 69 % respectively compared to 94 %, 87 %, and 75 % in those < 60 years of age. Despite this survival difference, the authors concluded that results were still encouraging in those ≥ 60 years of age and, therefore, cardiac transplantation should be extended to this age group [22].

Based on the works noted above and other similar single center experiences, the 2016 ISHLT guidelines modified the listing criteria to address the issue of advanced age in assessing recipient candidacy. These guidelines state that patients should be considered for cardiac transplantation if they are ≤ 70 years of age (Class I recommendation). These guidelines further state that carefully selected patients >70 years of age may also be considered for cardiac transplantation (Class IIb) [6].

Malignancy

In determining a patient's candidacy for cardiac transplantation, appropriate cancer screening is crucial. All patients should undergo age and gender appropriate screening which may include colonoscopy, mammography, Pap smear, pelvic examination and assessment of prostate-specific antigen levels. Based on patient comorbidities and/or family history, additional imaging of the chest, abdomen and pelvis and other tumor markers may also be considered.

In addition to appropriate cancer screening, patients with a known malignancy should undergo careful evaluation and risk stratification. Historically, most centers have required that a potential recipient be in remission for at least 5 years prior to transplantation due to the necessary immunosuppression and incumbent risk of provoking previously treated malignancies. This approach is somewhat supported by recent evidence suggesting that the risk of recurrence is directly related to cancer-free

duration prior to transplantation, with those patients being in remission for ≥ 5 years having the lowest risk of recurrence post-transplant [23]. Along similar lines, smaller single center studies have shown no significant difference in regard to survival or the development of a malignancy after transplant in those with an appropriate interval free of malignancy prior to transplantation [24]. This delineation however is somewhat arbitrary, as pre-existing neoplasms are quite diverse in regard to response to treatment, risk of recurrence and metastatic potential. Numerous studies have demonstrated that patients with pre-existing malignancies have undergone cardiac transplantation without recurrence of their primary tumor after transplantation [25–28]. Realizing that a single, defined cancer-free period prior to cardiac transplantation is arbitrary, the 2016 ISHLT guidelines maintained the following Class I recommendation: "Cardiac transplantation should be considered when tumor recurrence is low based on tumor type, response to therapy and negative metastatic work-up. The specific amount of time to wait to transplant after neoplasm remission will depend on the aforementioned factors and no arbitrary time period for observation should be used" [6].

Obesity

Morbid obesity has long been considered a relative contraindication to cardiac transplantation. Numerous trials have demonstrated a direct relationship between obesity and morbidity and mortality after cardiac surgery. Using various methods to measure obesity, several single-center studies have shown a similar correlation between pre-transplant obesity and unfavorable outcomes after cardiac transplantation. These outcomes included increased risk of primary graft failure, mortality, infection, frequency of high-grade rejection and decreased time to first high-grade rejection [29–32]. Other small studies have shown no difference in similar meaningful outcomes, such as survival, rejection or infection, after cardiac transplantation [29, 31]. Although this data is conflicting, the weight of the evidence supports the notion that pre-transplant obesity is associated with worse outcomes after cardiac transplantation. As a result, the 2016 ISHLT guidelines issued a Class IIa recommendation stating that patients with a body mass index > 35 kg/m^2 are at a greater risk of poor outcomes after cardiac transplantation and, therefore, it is reasonable to recommend weight loss to a target BMI below 35 kg/m^2 prior to listing [6].

Diabetes Mellitus

Diabetes mellitus (DM) and its associated end-organ damage should be carefully analyzed in patients undergoing evaluation for cardiac transplantation. One must also consider the potential adverse effects of corticosteroids on glycemic control, and the potential need for insulin post-transplant in patients previously treated with

oral hypoglycemics. Given the complexities of these assessments, consultation with an endocrinologist should be considered.

Several studies have shown that patients with pre-existing DM may do well after cardiac transplantation with similar survival, transplant coronary artery disease, rejection and infection [33, 34]. Other single-center studies have shown less favorable outcomes in patients with pre-existing DM citing worse mortality, transplant coronary artery disease, infections and ejection fraction [33, 35–38]. In the largest evaluation of patients with and without DM undergoing cardiac transplantation, Russo et al. reviewed over 20,000 patients undergoing first-time cardiac transplant between 1995 and 2005. The authors concluded that there was no significant difference in post-transplant survival between the group with uncomplicated, pre-existing DM and the group without DM. However, when comparing those with pre-existing DM and evidence of end-organ disease to the group without DM, mortality and post-transplant renal failure and infections were worse in the former group. In the 2016 ISHLT guidelines on the listing criteria for heart transplantation a Class IIa recommendation was given stating that DM with end-organ damage, other than poor glycemic control (glycosylated hemoglobin > 7.5) or non-proliferative retinopathy, was a relative contraindication to cardiac transplantation.

Chronic Kidney Disease

Because of the potentially detrimental effects of the long-term use of immunosuppressants on renal function, as well as the common comorbidities that often afflict the patient being considered for cardiac transplantation, evaluation of renal function prior to transplantation is critical. Numerous risk factors for the development of significant renal disease after cardiac transplantation have been identified and include age, male gender, hypertension, diabetes mellitus, impaired creatinine clearance/estimated glomerular filtration rate (GFR) prior to transplantation, and the number of episodes of rejection after transplantation [39–44]. During the early years of cardiac transplantation, irreversible renal dysfunction, defined as a serum creatinine > 2 mg/dl, was considered a contraindication to cardiac transplantation [45]. However, no specific level of creatinine has been previously identified that confers an unacceptable risk for cardiac transplantation. Nonetheless, the majority of transplant centers have defined some cut-off for either serum creatinine, creatinine clearance or estimated GFR above which is considered a relative contraindication for cardiac transplantation in the absence of concomitant renal transplantation. In addition to measures of renal function, the use of renal ultrasound, to assess kidney size and evaluate for evidence of medical renal disease, and renal arterial ultrasound, to assess for renovascular disease, may also aid in risk stratification. In the 2016 ISHLT guidelines a Class IIa recommendation was made in regard to renal dysfunction stating that estimated GFR or creatinine clearance should be measured and, in those with evidence of abnormal renal function, renal ultrasound, renal arterial ultrasound and estimation of proteinuria should be considered. Furthermore, the

presence of irreversible renal dysfunction, defined as an estimated GFR < 30 ml/min/1.73 m^2, may be considered a relative contraindication to cardiac transplantation alone [6].

Peripheral Vascular Disease

The presence and severity of cerebrovascular and peripheral vascular disease (PVD) should also be considered prior to cardiac transplantation. In small, single-center studies, the development of PVD post-transplant occurred in approximately 10 % of patients. Pre-transplant ischemic heart disease, smoking, post-transplant hypertension, and hypertriglyceridemia were identified as risk factors for the development of PVD after heart transplantation [46, 47]. The approach to evaluation, as well as the degree of PVD deemed unacceptable for transplantation, varies widely among transplant centers worldwide. In the 2016 ISHLT guidelines a Class IIb recommendation was made in regard to vascular disease stating that clinically severe, symptomatic cerebrovascular disease not amenable to revascularization, as well peripheral vascular disease that is not revascularizable and will likely limit rehabilitation, may be considered a contraindication to cardiac transplantation [6].

Tobacco Abuse

The effects of smoking on the cardiovascular system in the general population, as well as the oncogenic effects of tobacco exposure, have been well described. In addition, smoking after cardiac transplantation has been shown to accelerate allograft vasculopathy as well as the development of malignancy [48]. Unfortunately, approximately 20 % of patients who are abstinent from tobacco at the time of transplant start smoking again after cardiac transplantation [49, 50]. Furthermore, although second-hand tobacco exposure has been correlated with the development of coronary artery disease, it is often difficult to convey this important relationship to patients and families [51, 52]. It is paramount, therefore, that the patient, as well as their caregivers, be educated on the importance of tobacco cessation and the importance of avoiding second-hand smoke during the evaluation process as well as during the post-transplant period—a Class I recommendation in the 2016 ISHLT guidelines. Given the poor outcomes that are associated with tobacco use in the months preceding heart transplantation, abstinence should be assessed at least 6 months prior to transplantation and potentially monthly in those with a perceived high risk of recidivism. Assessment of urine markers of tobacco exposure, such as nicotine and cotinine, may also be considered given the imprecise assessment of second-hand tobacco exposure. Recent studies have suggested that individuals self-identified as non-smokers with a serum cotinine > 0.7 ng/ml had an increased risk of coronary artery disease [53]. The 2016 ISHLT guidelines go on to state that

active tobacco abuse may be considered a relative contraindication to cardiac transplantation (Class IIa/Level of Evidence C) [6].

Substance Abuse

Although there is evidence that consumption of moderate amounts of alcohol may have protective effects on the cardiovascular system [54], the toxic effect of excessive alcohol consumption have been well described. In men and women who consume more than four and three drinks per occasion respectively, there is an increased risk of alcohol abuse [55]. In addition, there is evidence that chronic, excessive alcohol consumption may impair memory [56]. Although little is known about recidivism in patients with a history of alcoholism who have undergone cardiac transplantation, in such patients who have undergone liver transplantation, as many as 50 % begin return to alcohol consumption in the first 5 years post-transplant [57]. In this same population, a family history of alcoholism, lack of social support and < 6 months abstinence prior to transplantation have been identified as risk factors for relapse [58]. Most programs require a period of abstinence prior to listing for transplant. The 2016 ISHLT guidelines suggest that a structured rehabilitation program be considered for patients with a history of alcohol abuse in the last 24 months prior to listing for transplant (Class IIb/Level of Evidence C). In addition, patients who are actively abusing alcohol or other substances of abuse should not undergo cardiac transplantation (Class III/Level of Evidence C) [6].

Psychosocial Status

An exhaustive psychosocial assessment of the patient and their caregivers is critical in the transplant evaluation process. There must be confidence that the patient is able to comprehend his or her current disease state, prognosis, and the risks and benefits of cardiac transplantation, as well as understand alternative therapies including LVADs and palliative care. In addition, there should be a track record of compliance given the complex drug regimens, frequent clinic visits and procedures, and lifestyle changes that are incumbent with cardiac transplantation. The evaluation should also include an assessment of the patient's perception of their current quality of life, as well as their long-term goals. Lastly, adequate caregivers must be identified who are willing, able and committed to supporting the patient perioperatively as well as long-term. The 2016 ISHLT guidelines state that social supports deemed insufficient to achieve compliant care in the outpatient setting is a relative contraindication to heart transplantation. Further, the benefit of heart transplantation in patients with severe cognitive-behavioral disabilities or dementia has not been established, may cause harm and cannot be recommended in this sub-group of patients (Class IIa/Level of Evidence C).

Maintaining objectivity when discussing these assessments can be difficult. The transplant team must be careful not to confuse potential psychosocial predictors of poor outcome with their own perceptions of the patient's quality of life or value to society.

Listing and Donor-Recipient Matching

Once a patient has gone through the evaluation process and has been deemed an appropriate candidate for cardiac transplantation, he or she is placed on a waiting list and is given a listing status which is determined by their severity of illness. Patients who are in the hospital receiving mechanical circulatory support (i.e. left and/or right ventricular assist device, total artificial heart, intra-aortic balloon pump, extracorporeal membrane oxygenation) for acute hemodynamic decompensation and/or multiple inotropic drugs along with continuous hemodynamic monitoring of left ventricular filling pressures are designated Status IA. Patients on single or multiple low dose inotropes and those with a durable left ventricular assist device in place are designated Status IB. Patients not meeting these criteria are designated Status 2. In patients who have been previously listed but are not currently transplantable due to a potentially reversible reason (i.e. infection, end-organ dysfunction, etc.) a Status 7 (temporarily inactive) designation is used.

The United Network for Organ Sharing (UNOS) is a private, non-profit organization that is contracted by the federal government to manage the organ transplant system within the United States. An organ procurement organization (OPO) is a private, non-profit organization which is certified by the Centers for Medicare and Medicaid Services and is responsible for donor management within a given geographic area. Once a donor becomes available, the local OPO offers the donor heart to all potential candidates via a centralized computer network that is maintained by UNOS. UNOS makes offers to transplant programs based on ABO blood typing and acceptable donor weight ranges that have been submitted by all transplant programs for their potential recipients. Within the group of potential recipients with an acceptable blood type and weight, donor hearts are allocated to recipients based on severity of illness and time on the list. The algorithm used by UNOS to allocate donor hearts is complex and ultimately attempts to ensure the most appropriate allocation of a precious resource to the sickest patients.

Pre-transplant Longitudinal Care

While awaiting transplantation, listed patients should undergo periodic assessment to ensure continued candidacy. Patients should be seen in follow-up at least every 3 months with assessment of weight/BMI and routine laboratory testing to assess

blood counts, coagulation and end-organ function. PRA testing should be performed after sensitizing events (i.e. blood transfusion, LVAD implantation, etc.) or on a regular basis in patients with a PRA > 10 % at baseline. In regard to HF severity, cardiopulmonary stress testing should be repeated at least yearly—right heart catheterization should be performed every 6 months and considered more frequently in patients with pulmonary hypertension. Age appropriate cancer screening to include Pap smear, mammogram and assessment of prostate-specific antigen levels should also be performed.

References

1. Go AS, Mozaffarian D, Roger VL, Benjamin EJ, Berry JD, Borden WB, et al. Heart disease and stroke statistics – 2013 update: a report from the American Heart Association. Circulation. 2013;127(1):e6–e245. Epub 2012/12/15.
2. Stehlik J, Edwards LB, Kucheryavaya AY, Benden C, Christie JD, Dobbels F, et al. The Registry of the International Society for Heart and Lung Transplantation: twenty-eighth adult heart transplant report – 2011. J Heart Lung Transplant. 2011;30(10):1078–94. Epub 2011/10/04.
3. Butler J, Khadim G, Paul KM, Davis SF, Kronenberg MW, Chomsky DB, et al. Selection of patients for heart transplantation in the current era of heart failure therapy. J Am Coll Cardiol. 2004;43(5):787–93. Epub 2004/03/05.
4. O'Neill JO, Young JB, Pothier CE, Lauer MS. Peak oxygen consumption as a predictor of death in patients with heart failure receiving beta-blockers. Circulation. 2005;111(18):2313–8. Epub 2005/05/04.
5. Goda A, Lund LH, Mancini D. The heart failure survival score outperforms the peak oxygen consumption for heart transplantation selection in the era of device therapy. J Heart Lung Transplant. 2011;30(3):315–25. Epub 2010/11/26.
6. Mehra MR, CE C, MM H, MJ S, Pa U, et al. The 2016 International Society for Heart and Lung Transplantation listing criteria for heart transplantation: a 10-year update. J Heart Lung Transplant. 2016;35:1–23.
7. Aaronson KD, Schwartz JS, Chen TM, Wong KL, Goin JE, Mancini DM. Development and prospective validation of a clinical index to predict survival in ambulatory patients referred for cardiac transplant evaluation. Circulation. 1997;95(12):2660–7. Epub 1997/06/17.
8. Koelling TM, Joseph S, Aaronson KD. Heart failure survival score continues to predict clinical outcomes in patients with heart failure receiving beta-blockers. J Heart Lung Transplant. 2004;23(12):1414–22. Epub 2004/12/21.
9. Levy WC, Mozaffarian D, Linker DT, Sutradhar SC, Anker SD, Cropp AB, et al. The seattle heart failure model: prediction of survival in heart failure. Circulation. 2006;113(11):1424–33. Epub 2006/03/15.
10. Stobierska-Dzierzek B, Awad H, Michler RE. The evolving management of acute right-sided heart failure in cardiac transplant recipients. J Am Coll Cardiol. 2001;38(4):923–31. Epub 2001/10/05.
11. Kirklin JK, Naftel DC, Kirklin JW, Blackstone EH, White-Williams C, Bourge RC. Pulmonary vascular resistance and the risk of heart transplantation. J Heart Transplant. 1988;7(5):331–6. Epub 1988/09/01.
12. Butler J, Stankewicz MA, Wu J, Chomsky DB, Howser RL, Khadim G, et al. Pre-transplant reversible pulmonary hypertension predicts higher risk for mortality after cardiac transplantation. J Heart Lung Transplant. 2005;24(2):170–7. Epub 2005/02/11.

13. Drakos SG, Kfoury AG, Gilbert EM, Horne BD, Long JW, Stringham JC, et al. Effect of reversible pulmonary hypertension on outcomes after heart transplantation. J Heart Lung Transplant. 2007;26(4):319–23. Epub 2007/04/04.
14. Goland S, Czer LS, Kass RM, De Robertis MA, Mirocha J, Coleman B, et al. Pre-existing pulmonary hypertension in patients with end-stage heart failure: impact on clinical outcome and hemodynamic follow-up after orthotopic heart transplantation. J Heart Lung Transplant. 2007;26(4):312–8. Epub 2007/04/04.
15. Forni A, Faggian G, Chiominto B, Iafrancesco M, Patelli F, Innocente F, et al. Heart transplantation in older candidates. Transplant Proc. 2007;39(6):1963–6. Epub 2007/08/19.
16. Crespo-Leiro MG, Paniagua-Martin MJ, Muniz J, Marzoa R, Pinon P, Rodriguez JA, et al. Long-term results of heart transplant in recipients older and younger than 65 years: a comparative study of mortality, rejections, and neoplasia in a cohort of 445 patients. Transplant Proc. 2005;37(9):4031–2. Epub 2006/01/03.
17. Nagendran J, Wildhirt SM, Modry D, Mullen J, Koshal A, Wang SH. A comparative analysis of outcome after heart transplantation in patients aged 60 years and older: the University of Alberta experience. J Card Surg. 2004;19(6):559–62. Epub 2004/11/19.
18. Blanche C, Matloff JM, Denton TA, Czer LS, Fishbein MC, Takkenberg JJ, et al. Heart transplantation in patients 70 years of age and older: initial experience. Ann Thorac Surg. 1996;62(6):1731–6. Epub 1996/12/01.
19. Blanche C, Blanche DA, Kearney B, Sandhu M, Czer LS, Kamlot A, et al. Heart transplantation in patients seventy years of age and older: a comparative analysis of outcome. J Thorac Cardiovasc Surg. 2001;121(3):532–41. Epub 2001/03/10.
20. Morgan JA, John R, Mancini DM, Edwards NM. Should heart transplantation be considered as a treatment option for patients aged 70 years and older? J Thorac Cardiovasc Surg. 2004;127(6):1817–9. Epub 2004/06/03.
21. Daneshvar D, Czer LS, Phan A, Schwarz ER, De Robertis M, Mirocha J, et al. Heart transplantation in patients aged 70 years and older: a two-decade experience. Transplant Proc. 2011;43(10):3851–6. Epub 2011/12/17.
22. Weiss ES, Nwakanma LU, Patel ND, Yuh DD. Outcomes in patients older than 60 years of age undergoing orthotopic heart transplantation: an analysis of the UNOS database. J Heart Lung Transplant. 2008;27(2):184–91. Epub 2008/02/13.
23. Sigurdardottir V, Bjortuft O, Eiskjaer H, Ekmehag B, Gude E, Gustafsson F, et al. Long-term follow-up of lung and heart transplant recipients with pre-transplant malignancies. J Heart Lung Transplant. 2012;31(12):1276–80. Epub 2012/10/24.
24. Fernandez-Vivancos C, Paniagua-Martin MJ, Marzoa-Rivas R, Barge-Caballero E, Grile-Cancela Z, Recio-Mayoral A, et al. Long-term outcome in heart transplant patients with pre-transplant malignancies. Transplant Proc. 2010;42(8):3006–10. Epub 2010/10/26.
25. Koerner MM, Tenderich G, Minami K, Mannebach H, Koertke H, zu Knyphausen E, et al. Results of heart transplantation in patients with preexisting malignancies. Am J Cardiol. 1997;79(7):988–91. Epub 1997/04/01.
26. Oechslin E, Kiowski W, Schneider J, Follath F, Turina M, Gallino A. Pretransplant malignancy in candidates and posttransplant malignancy in recipients of cardiac transplantation. Ann Oncol. 1996;7(10):1059–63. Epub 1996/12/01.
27. Dillon TA, Sullivan M, Schatzlein MH, Peterson AC, Scheeringa RH, Clark Jr WR, et al. Cardiac transplantation in patients with preexisting malignancies. Transplantation. 1991;52(1):82–5. Epub 1991/07/11.
28. Hinkamp T, Sullivan H, Bakhos M, Grieco J, Pifarre R. Orthotopic cardiac transplantation in two patients with previous malignancy. Ann Thorac Surg. 1991;51(6):1004–6. Epub 1991/06/01.
29. Macha M, Molina EJ, Franco M, Luyun L, Gaughan JP, McClurken JB, et al. Pre-transplant obesity in heart transplantation: are there predictors of worse outcomes? Scand Cardiovasc J. 2009;43(5):304–10. Epub 2009/03/18.
30. Grady KL, White-Williams C, Naftel D, Costanzo MR, Pitts D, Rayburn B, et al. Are preoperative obesity and cachexia risk factors for post heart transplant morbidity and mortality: a

multi-institutional study of preoperative weight-height indices. Cardiac Transplant Research Database (CTRD) Group. J Heart Lung Transplant. 1999;18(8):750–63. Epub 1999/10/08.
31. Grady KL, Costanzo MR, Fisher S, Koch D. Preoperative obesity is associated with decreased survival after heart transplantation. J Heart Lung Transplant. 1996;15(9):863–71. Epub 1996/09/01.
32. Guisado Rasco A, Sobrino Marquez JM, Nevado Portero J, Romero Rodriguez N, Ballesteros Prada S, Lage Galle E, et al. Impact of overweight on survival and primary graft failure after heart transplantation. Transplant Proc. 2010;42(8):3178–80. Epub 2010/10/26.
33. Higgins J, Pflugfelder PW, Kostuk WJ. Increased morbidity in diabetic cardiac transplant recipients. Can J Cardiol. 2009;25(4):e125–9. Epub 2009/04/03.
34. Morgan JA, John R, Weinberg AD, Colletti NJ, Mancini DM, Edwards NM. Heart transplantation in diabetic recipients: a decade review of 161 patients at Columbia Presbyterian. J Thorac Cardiovasc Surg. 2004;127(5):1486–92. Epub 2004/04/30.
35. Saraiva J, Sola E, Prieto D, Antunes MJ. Diabetes as an outcome predictor after heart transplantation. Interactive Cardiovasc Thoracic Surg. 2011;13(5):499–504; discussion Epub 2011/08/13.
36. Marelli D, Laks H, Patel B, Kermani R, Marmureanu A, Patel J, et al. Heart transplantation in patients with diabetes mellitus in the current era. J Heart Lung Transplant. 2003;22(10):1091–7. Epub 2003/10/11.
37. Meyer SR, Modry DL, Norris CM, Pearson GJ, Bentley MJ, Koshal A, et al. Pretransplant diabetes, not donor age, predicts long-term outcomes in cardiac transplantation. J Card Surg. 2006;21(2):117–24. Epub 2006/02/24.
38. Klingenberg R, Gleissner C, Koch A, Schnabel PA, Sack FU, Zimmermann R, et al. Impact of pre-operative diabetes mellitus upon early and late survival after heart transplantation: a possible era effect. J Heart Lung Transplant. 2005;24(9):1239–46. Epub 2005/09/07.
39. Ishani A, Erturk S, Hertz MI, Matas AJ, Savik K, Rosenberg ME. Predictors of renal function following lung or heart-lung transplantation. Kidney Int. 2002;61(6):2228–34. Epub 2002/05/25.
40. Esposito C, Semeraro L, Bellotti N, Fasoli G, Fornoni A, Rampino T, et al. Risk factors for chronic renal dysfunction in cardiac allograft recipients. Nephron. 2000;84(1):21–8. Epub 2000/01/25.
41. Vossler MR, Ni H, Toy W, Hershberger RE. Pre-operative renal function predicts development of chronic renal insufficiency after orthotopic heart transplantation. J Heart Lung Transplant. 2002;21(8):874–81. Epub 2002/08/07.
42. Van Buren DH, Burke JF, Lewis RM. Renal function in patients receiving long-term cyclosporine therapy. J Am Soc Nephrol. 1994;4(8 Suppl):S17–22. Epub 1994/02/01.
43. Garrido IP, Crespo-Leiro MG, Paniagua MJ, Muniz J, Vazquez-Rey E, Perez-Fernandez R, et al. Independent predictors of renal dysfunction after heart transplantation in patients with normal pretransplant renal function. J Heart Lung Transplant. 2005;24(9):1226–30. Epub 2005/09/07.
44. Odim J, Wheat J, Laks H, Kobashigawa J, Gjertson D, Osugi A, et al. Peri-operative renal function and outcome after orthotopic heart transplantation. J Heart Lung Transplant. 2006;25(2):162–6. Epub 2006/02/01.
45. Mudge GH, Goldstein S, Addonizio LJ, Caplan A, Mancini D, Levine TB, et al. 24th Bethesda conference: cardiac transplant. Task force 3: recipient guidelines/prioritization. J Am Coll Cardiol. 1993;22(1):21–31. Epub 1993/07/01.
46. Erdoes LS, Hunter GC, Venerus BJ, Hall KA, Bull DA, Berman SS, et al. Prospective evaluation of peripheral vascular disease in heart transplant recipients. J Vasc Surg. 1995;22(4):434–40; discussion 40–2. Epub 1995/10/01.
47. Bull DA, Hunter GC, Copeland JG, Bernhard VM, Rosado LJ, McIntyre KE, et al. Peripheral vascular disease in heart transplant recipients. J Vasc Surg. 1992;16(4):546–53; discussion 53–4. Epub 1992/10/01.
48. Botha P, Peaston R, White K, Forty J, Dark JH, Parry G. Smoking after cardiac transplantation. Am J Transplant. 2008;8(4):866–71. Epub 2008/03/08.

49. Basile A, Bernazzali S, Diciolla F, Lenzini F, Lisi G, Maccherini M, et al. Risk factors for smoking abuse after heart transplantation. Transplant Proc. 2004;36(3):641–2. Epub 2004/04/28.
50. Mehra MR, Uber PA, Prasad A, Scott RL, Park MH. Recrudescent tobacco exposure following heart transplantation: clinical profiles and relationship with athero-thrombosis risk markers. Am J Transplant. 2005;5(5):1137–40. Epub 2005/04/09.
51. Lightwood JM, Coxson PG, Bibbins-Domingo K, Williams LW, Goldman L. Coronary heart disease attributable to passive smoking: CHD policy model. Am J Prev Med. 2009;36(1):13–20. Epub 2008/12/20.
52. He J, Vupputuri S, Allen K, Prerost MR, Hughes J, Whelton PK. Passive smoking and the risk of coronary heart disease – a meta-analysis of epidemiologic studies. N Engl J Med. 1999;340(12):920–6. Epub 1999/03/25.
53. Whincup PH, Gilg JA, Emberson JR, Jarvis MJ, Feyerabend C, Bryant A, et al. Passive smoking and risk of coronary heart disease and stroke: prospective study with cotinine measurement. BMJ. 2004;329(7459):200–5. Epub 2004/07/02.
54. Ronksley PE, Brien SE, Turner BJ, Mukamal KJ, Ghali WA. Association of alcohol consumption with selected cardiovascular disease outcomes: a systematic review and meta-analysis. BMJ. 2011;342:d671. Epub 2011/02/24.
55. Gunzerath L, Faden V, Zakhari S, Warren K. National Institute on alcohol abuse and alcoholism report on moderate drinking. Alcohol Clin Exp Res. 2004;28(6):829–47. Epub 2004/06/18.
56. Heffernan TM. The impact of excessive alcohol use on prospective memory: a brief review. Curr Drug Abuse Rev. 2008;1(1):36–41. Epub 2008/01/01.
57. Weinrieb RM, Van Horn DH, Lynch KG, Lucey MR. A randomized, controlled study of treatment for alcohol dependence in patients awaiting liver transplantation. Liver Transpl. 2011;17(5):539–47. Epub 2011/04/21.
58. Dew MA, DiMartini AF, Steel J, De Vito DA, Myaskovsky L, Unruh M, et al. Meta-analysis of risk for relapse to substance use after transplantation of the liver or other solid organs. Liver Transpl. 2008;14(2):159–72. Epub 2008/02/01.

Chapter 21
Pathophysiology of the Alloimmune Response and Immunosuppression

Michael X. Pham

The Alloimmune Response to Foreign Antigen

Introduction

Alloimmunity is defined as the body's immune response to foreign antigens found on the cells of organs transplanted between genetically nonidentical members of the same species (allografts). In organ transplantation, alloimmunity is primarily directed toward Major Histocompatability Complex (MHC) molecules expressed on the surface of donor organs. The alloimmune response can be broadly classified into two arms. Cell-mediated immunity involves the activation and recruitment of antigen-specific cytotoxic T-lymphocytes, macrophages, and natural killer cells in response to a foreign graft. In contrast, humoral immunity is primarily mediated by B-lymphocytes, antibodies, and complement. Both processes, if left unmodulated after organ transplantation, can lead to organ rejection.

Components of the Alloimmune Response

- **MHC molecules** are called **Human leukocyte antigens (HLA)** in humans. They are cell surface antigen-presenting proteins that are encoded by the MHC complex, a large group of highly polymorphic genes located on chromosome 6. These proteins are used by the immune system to differentiate between cells of self and non-self origin and to recognize foreign invaders such as bacteria and viruses. The MHC molecules are divided into two classes. Class I molecules are

M.X. Pham, MD, MPH
Barry S. Levin Department of Transplantation, Sutter Health California Pacific Medical Center, 2340 Clay Street, San Francisco, CA 94115, USA
e-mail: phamMX@sutterhealth.org

H. Eisen (ed.), *Heart Failure*, DOI 10.1007/978-1-4471-4219-5_21

encoded by three major HLA genes (HLA-A, B, and C). They are expressed on the surface of all nucleated cells and present endogenous antigen (proteins derived from within the cell such as viral peptides and tumor antigens) to the immune system. Class II molecules are encoded by three additional HLA genes (HLA-DP, DQ, DR) and are only expressed on the surface of specialized cells, called antigen presenting cells (APC). APCs have the ability to process and present exogenous antigen, such as bacteria, that has been uptaken and digested by the cell. The HLA genes are co-dominantly expressed. Therefore, each individual will inherit and express one allele from each parent for each of the six major MHC genes.

- **Antigen presenting cells** include dendritic cells, macrophages, B lymphocytes, and activated vascular endothelial cells. Their primary role is to present foreign antigen to T lymphocytes. Because T lymphocytes are unable to recognize intact or free antigen, APC's must internalize and process any soluble donor antigen and must subsequently present them as donor antigen fragments bound to MHC molecules on their surfaces. APC's can be of both donor and recipient origin.
- Two major populations of **T lymphocytes** are involved in the alloresponse to a transplanted organ. Cytotoxic T lymphocytes, also known as CD8+ T cells because they express the CD8 glycoprotein on their surfaces, have T cell receptors that recognize foreign antigen fragments bound to MHC Class I proteins on the surface of donor cells, and, in response, induce cell death via direct cytotoxicity or by inducing apoptosis. They play a major role in cell-mediated immunity. In contrast, helper T lymphocytes, or CD4+ T cells, contain T receptors that recognize MHC Class II complexes on the surface of APCs, and in turn stimulate antibody-producing B-cells that generate antibodies specific to the recognized antigen. Helper T lymphocytes also stimulate macrophages and natural killer cells that are involved in cell-mediated immunity.
- **B lymphocytes** are involved in the humoral response to alloantigens. B lymphocytes contain immunoglobulin receptors on their surface that recognize foreign antigen. Once activated, B lymphocytes differentiate into antibody-secreting plasma cells that generate antibodies with specificities against specific MHC Class I or II molecules. These antibodies bind to the surface of their target donor cells, activate complement, and induce cell lysis. Additionally, alloantibodies coat the surface of donor cells and target them for destruction by macrophages and natural killer cells.
- **Natural killer cells** are a small subset of lymphocytes that lack both T-cell and B-cell surface receptors to directly recognize foreign antigen. Instead, they are recruited by activated T helper lymphocytes through the secretion of cytokines such as interleukin-2 (IL-2) and interferon-gamma (IFN-gamma) to kill foreign cells.
- **Macrophages** are differentiated monocytes that reside within tissues. They function as APCs by presenting processed alloantigen fragments in combination with MHC Class II molecules to CD4+ T lymphocytes. Additionally, macrophages play a similar effector role as natural killer cells.

Mechanisms of Transplant Rejection

Allorecognition

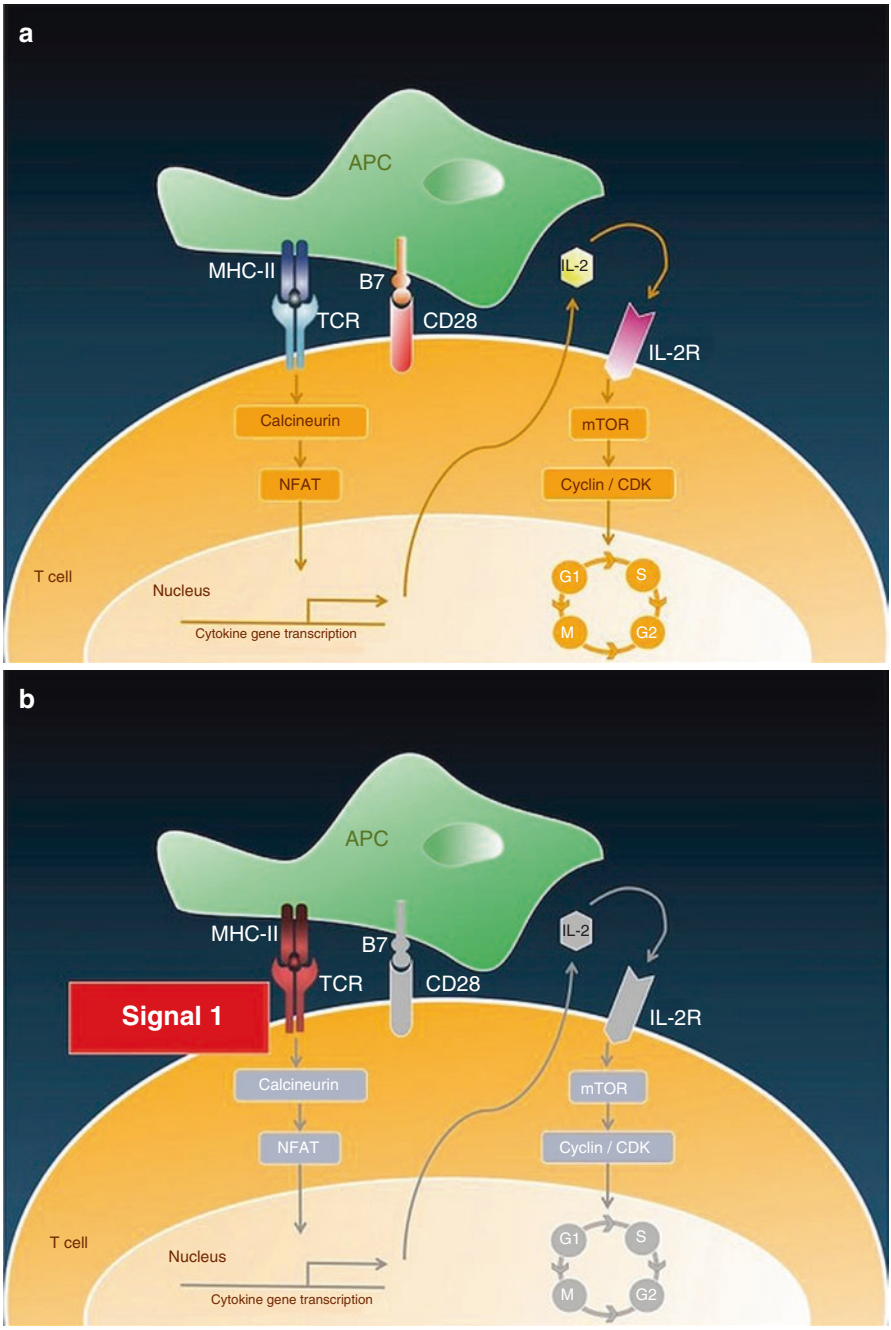
The initial step in mounting an alloimmune response to a transplanted organ occurs in the recipient's lymph nodes and involves recognition of the transplanted tissue as non-self, or foreign. The recipient's immune response recognizes the presence of donor (foreign) antigen through one of two pathways. In the **direct pathway**, donor dendritic cells present within the transplanted organ migrate from the graft to the recipient's lymph nodes, where intact, foreign MHC class I and II proteins expressed on their surfaces are recognized by recipient CD8+ and CD4+ T cells, respectively. This pathway is thought to play a major role in acute rejection. In the **indirect pathway**, recipient APCs (both dendritic cells and B lymphocytes) enter the graft, where they internalize and process soluble MHC molecules shed by the graft, and subsequently migrate back to the draining lymph nodes. There, foreign MHC proteins are recognized by recipient CD4+ T cells as processed peptides complexed with self MHC class II molecules.

Lymphocyte Activation and Proliferation

In the lymph nodes, naïve and memory T lymphocytes interact with APCs of both donor and host origin. Individual T lymphocytes are only able to recognize a single, specific antigen presented in the context of MHC. A T lymphocyte with a specificity for a particular MHC-peptide complex is activated and undergoes clonal expansion once it recognizes its unique ligand on the surface of APCs. T lymphocyte activation requires two specific signals (Fig. 21.1a–d). Signal 1 occurs when the T cell receptor (TCR) on the surface of T lymphocytes recognizes and binds to the peptide-MHC complex on the surface of APCs. This is followed by a second, costimulatory signal which involves interaction between the B7 ligand on the APC with CD28 on the surface of T lymphocytes. Signals 1 and 2 initiate a series of signal transduction pathways that result in the expression of the interleukin-2 (IL-2) gene. IL-2 and other cytokines, in turn, bind to the IL-2 receptor on the surface of the original T lymphocyte and on nearby activated T lymphocytes to provide a third signal that triggers cell division, clonal expansion, and differentiation to express effector functions.

Effector Mechanisms Leading to Tissue Injury

Allograft rejection is mediated through both cellular and humoral effector mechanisms (Fig. 21.2). Activated, antigen-specific CD8+ T lymphocytes directly affect donor cell death via releasing a number of cytotoxic proteins that result in cell lysis and that induce apoptosis within the target cell. Similarly, activated CD4+ helper T


a
APC
MHC-II
B7
TCR
CD28
IL-2
IL-2R
Calcineurin
mTOR
NFAT
Cyclin / CDK
T cell
Nucleus
Cytokine gene transcription
G1
S
M
G2
b
APC
MHC-II
B7
TCR
CD28
IL-2
IL-2R
Signal 1
Calcineurin
mTOR
NFAT
Cyclin / CDK
T cell
Nucleus
Cytokine gene transcription
G1
S
M
G2

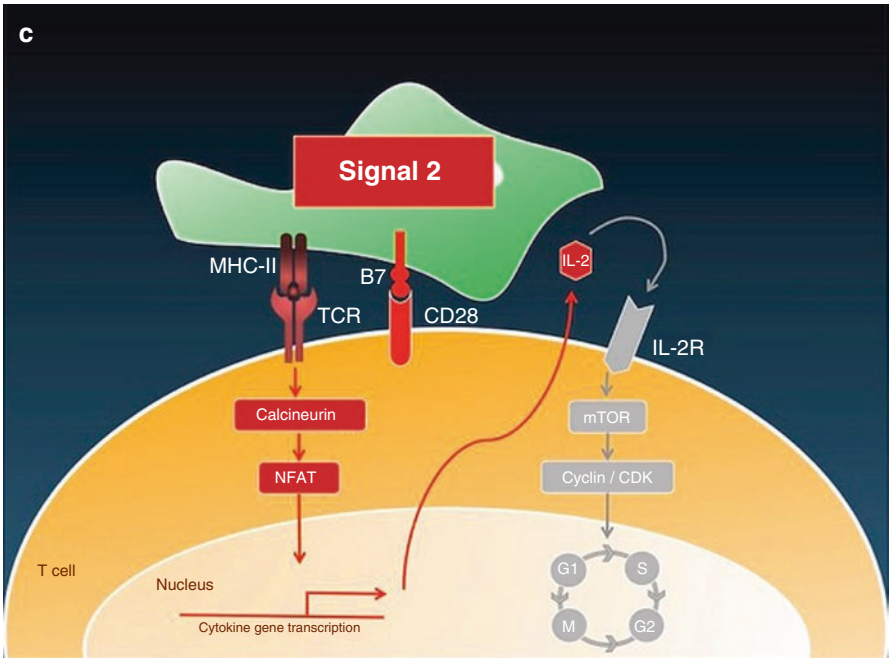


Fig. 21.1 (continued)

Fig. 21.1 Steps in T lymphocyte activation and proliferation. Panel **a** Multiple signals are required for T cell activation and proliferation in response to alloantigen recognition. Panel **b** Donor antigens on the surface of antigen presenting cells (*APC*) are recognized by the T cell receptor (*TCR*) on the surface of T lymphocytes (*signal 1*). Panel **c** A second signal, involving binding of the B7 molecules on the APC to CD28 on the surface of T lymphocytes is required for T lymphocyte activation to occur (*signal 2*). Signals 1 and 2 trigger an increase in the cytoplasmic levels of calcium, which in turn activates the cytoplasmic protein phosphatase calcineurin. Calcineurin dephosphorylates a transcription factor called nuclear factor of activated T cells (*NFAT*), allowing it to enter the nucleus, where it promotes the expression of interleukin 2 (*IL-2*). Panel **d** Secreted IL-2 binds to the IL-2 receptor (*IL-2R*) on the surface of activated T lymphocytes (*signal 3*), providing the stimulus needed for cell growth and proliferation through the mammalian target of rapamycin (mTOR) pathway

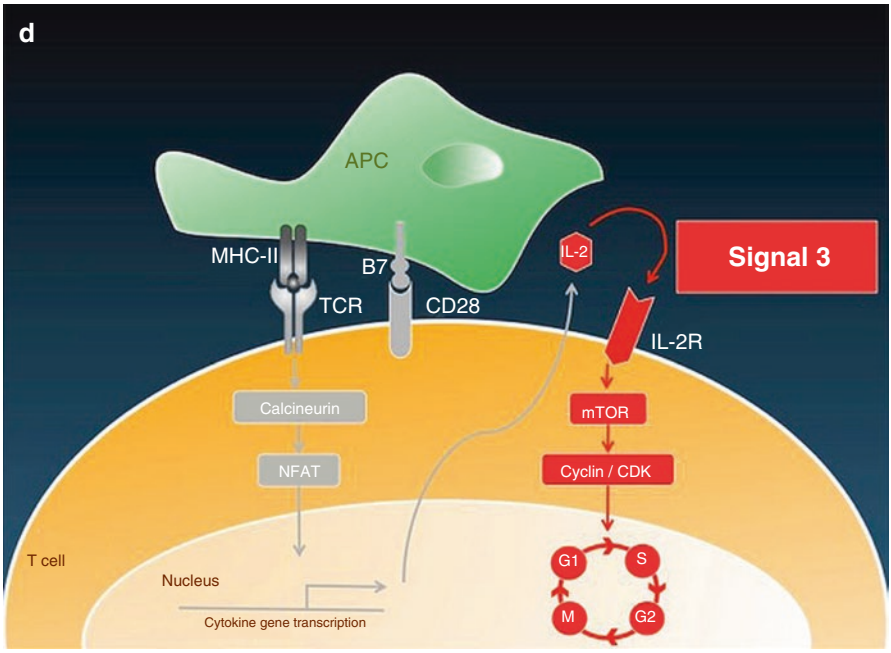


Fig. 21.1 (continued)

lymphocytes secrete a variety of cytokines, including interleukin-4 and interleukin-5 that promote the maturation of B-lymphocytes and the production of donor-specific alloantibodies. Alloantibodies bind to their specific MHC targets on the surface of vascular endothelial cells within the allograft, where they cause active damage to the graft by activating the complement cascade and by targeting cells for destruction by natural killer cells and macrophages in a process called antibody-dependent cell-mediated cytotoxicity (ADCC). The later cells have specific receptors on their surfaces that recognize tissue-bound antibody and kill targeted cells through the release of pore-forming proteins and proteolytic enzymes. Additionally, CD4+ T lymphocytes initiate a nonspecific delayed-type hypersensitivity (DTH) response whereby non-antigen-specific cells such as macrophages, natural killer cells, and monocytes are recruited into the graft to enhance the inflammatory response.

Principles of Immunosuppression

The goal of immunosuppression is to blunt the alloimmune response to prevent or treat cardiac allograft rejection while minimizing both drug toxicities as well as the major sequella of immune suppression, namely infection and malignancy. Most

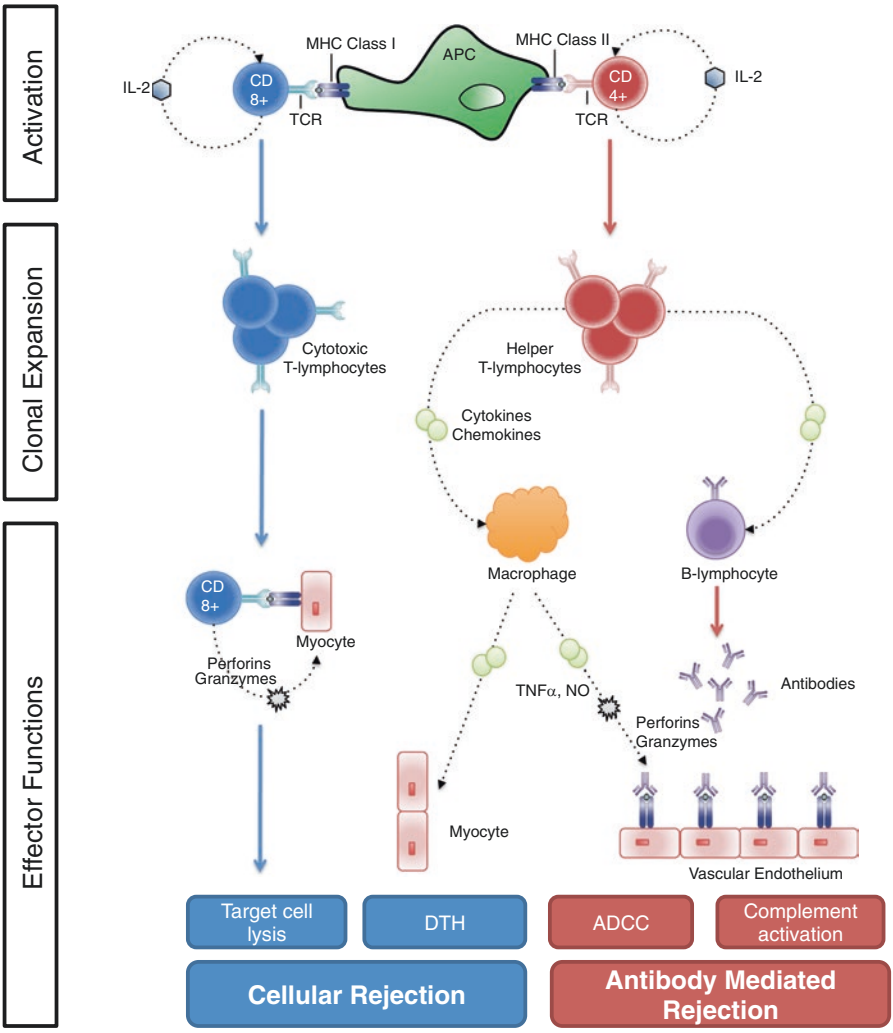


Fig. 21.2 Effector mechanisms leading to allograft rejection. Activated T lymphocytes undergo clonal expansion and differentiation into effector cells. CD8+ cytotoxic T lymphocytes directly affect donor cell death by causing cell lysis and inducing apoptosis. In contrast, CD4+ helper T cells secrete cytokines and chemokines that stimulate B lymphocyte maturation and alloantibody production and that help macrophages, natural killer cells, and monocytes to induce a delayed-type hypersensitivity response

clinically used immunosuppressive regimens consist of a combination of several agents used concurrently and follow several general principles. The first principle is that immune reactivity and tendency toward graft rejection are highest early (within the first 3–6 months) after graft implantation and decrease with time. Thus, most

regimens employ the highest intensity of immunosuppression immediately after surgery and decrease the intensity over the first year, eventually settling on the lowest maintenance levels of immunosuppression that are compatible with preventing graft rejection and minimizing drug toxicities. The second general principle is to use low doses of several drugs without overlapping toxicities in preference over higher (and more toxic) doses of a single drug whenever feasible. The third principle is that too intense immunosuppression is undesirable because it leads to undesirable effects such as susceptibility to infection and malignancy.

Immunosuppressive regimens can be classified as induction, maintenance, or anti-rejection. Induction regimens provide intense early post-operative immune suppression while maintenance regimens are used throughout the patient's life to prevent both acute and chronic rejection. This chapter will review the induction and maintenance immunosuppressive regimens used in heart transplantation. The treatment of acute rejection will be discussed in subsequent chapters.

Induction Therapy

Currently, slightly fewer than 50 % of heart transplant programs employ a strategy of augmented immunosuppression, or *induction* therapy, during the early post-operative period [1]. The goal of induction therapy is to provide intense immunosuppression when the risk of allograft rejection is highest. From a clinical perspective, the main advantages of induction therapy are to allow delayed initiation of nephrotoxic immunosuppressive drugs in patients with compromised renal function prior to or following surgery and to provide some flexibility with respect to early corticosteroid weaning or use of corticosteroid-sparing maintenance immunosuppressive regimens after transplantation [2–4]. Several anti-lymphocyte antibodies that target specific epitopes on the surface of both B and T cells have been used as part of induction therapy. However, the overall strategy of universal induction therapy and the optimal drugs to achieve a state of early intense immunosuppression remain controversial. The decreased early rejection observed with induction therapy may be negated by an increase in late rejection after induction therapy is completed and by the potential for increased rates of infection and malignancy associated with such therapy [5–11]. However, patients at highest risk for fatal rejection, including younger patients, African American patients, patients with high levels of pre-formed antibodies against HLA epitopes, and patients supported on ventricular assist devices may derive a benefit from induction therapy [12].

Muromonab-CD3 (OKT3)

OKT3 is a murine monoclonal antibody that binds to the T cell receptor-CD3 complex on the surface of circulating T cells. It exerts its immunosuppressive effects via a variety of mechanisms, including rapid T cell depletion from the peripheral

circulation as a result of opsonization in the liver and spleen, and modulation of the T cell receptor-CD3 antigen recognition complex, thereby blocking the immunologic function of these cells [13, 14].

OKT3 administration is associated with a number of important acute and long-term side effects. The first or second drug dose is typically associated with a *cytokine release syndrome* characterized by fevers, rigors, nausea, vomiting, diarrhea, hypotension, chest pain, dyspnea or wheezing, arthralgias, and myalgias. This syndrome is caused by initial activation of T cells and release of multiple cytokines. It can be attenuated by pre-medication with intravenous steroids, antihistamines, antipyretics, and H2-blockers. Rare life-threatening complications have included pulmonary edema, aseptic meningitis, and encephalopathy. Long-term adverse reactions include an increased risk of life-threatening opportunistic infections, particularly with cytomegalovirus, and post-transplant lymphoproliferative disorders. Finally, prolonged use of OKT3 can elicit a host anti-mouse antibody response that can blunt future drug efficacy and increase the risk of antibody-mediated rejection [15–17]. Due to these adverse effects and the availability of alternate agents, the use of OKT3 has been abandoned.

Polyclonal Anti-thymocyte Antibodies

Polyclonal antibodies are derived by immunization of horses (**ATGAM**) or rabbits (**Thymoglobulin**) with human thymocytes. These preparations contain antibodies directed against a wide variety of human T-cell antigens and cause rapid depletion of T-lymphocytes by inducing complement-mediated cytolysis and cell-mediated opsonization in the spleen and liver. There are no head-to-head comparison trials of ATGAM and Thymoglobulin in heart transplantation, but data from the kidney transplant literature suggests that thymoglobulin may result in a lower incidence of both short and long-term acute rejection compared to ATGAM, possibly because of more profound and durable lymphopenia after Thymoglobulin administration [18, 19]. These agents combined are currently employed in 20 % of heart transplant recipients based upon the most recent international transplant registry data [1].

The major acute side effects associated with this class of drugs include a serum sickness reaction characterized by fevers, chills, tachycardia, hypertension or hypotension, myalgias, and rash. The reaction is typically noticed during the first or second drug infusion and can be treated by temporarily stopping the drug infusion and restarting at a lower infusion rate. Pre-medication with intravenous steroids, antihistamines, antipyretics, and H2 blockers can prevent or reduce the severity of symptoms. Dose-dependent leukopenia (30–50 %) and thrombocytopenia (30–40 %) have also been observed and typically respond to dose reduction or drug discontinuation for severe cases (WBC < 2000 cells/mm^3 or platelet count < 50,000 cells/mm^3). These agents do not induce a host antibody response to horse or rabbit sera and can be re-used for the treatment of allograft rejection. Long-term side effects include a pre-disposition to opportunistic infections, particularly with cytomegalovirus, and a possible increase in the incidence and aggressiveness of post-transplant malignancies [11, 20, 21].

Interleukin-2 Receptor Antagonists

In recent years, the use of interleukin-2 (IL-2) receptor antagonists for induction therapy has increased, and these drugs are now used in 28 % of patients undergoing heart transplantation [1]. Compared to OKT3 and anti-thymocyte antibodies, this class of drugs has a significantly lower incidence of drug-related adverse reactions [22, 23]. The currently available agent, **Basiliximab** (Simulect), is an anti-IL-2 receptor monoclonal antibodies that selectively binds to the IL-2 receptor of T-lymphocytes, blocks binding of IL-2 to the receptor complex, and exhibits its immunosuppressive effects by inhibiting IL-2 mediated T-lymphocyte proliferation.

Basiliximab was studied in a pilot multicenter, placebo-controlled randomized study of 56 de novo heart transplant recipients designed to assess the safety, tolerability, and pharmacokinetics of the drug. Patients were randomized to two doses of either basiliximab or to placebo in addition to a background immunosuppressive regimen that included cyclosporine, mycophenolate mofetil, and corticosteroids. There were no significant differences between treatment groups with respect to drug-related adverse events or infections. At 6 months, a non-statistically significant trend toward a decrease in the mean number of days to a first biopsy-proven acute rejection episode of ISHLT Grade $\geq$ 2R or to a rejection episode with hemodynamic compromise was observed in the basiliximab group compared to placebo (74 versus 41 days) [24].

Alemtuzumab

Alemtuzumab (Campath-1H) is a humanized rat monoclonal antibody that targets the CD52 antigen expressed on both T and B cells. This powerful cytolytic agent produces a profound lymphopenia that lasts for approximately 6 months and that may persist for up to 3 years in some individuals [25]. The agent was originally developed to treat chronic lymphocytic leukemia but has also been used as induction therapy in kidney and heart transplantation, where it has permitted use of lower intensity maintenance immunosuppression [26, 27]. Currently, the use of alemtuzumab as induction therapy is limited to only 2 % of heart transplant recipients [28].

Maintenance Immunosuppressive Regimens

The strategies and drugs used for immune suppression have advanced considerably since the first heart transplant was performed in 1967. Beginning with the introduction of cyclosporine in 1983, significant advances have been made in moving from drugs that provide broad and non-specific immunosuppression to newer agents that

provide more targeted immunosuppression through selective inhibition of lymphocyte activation and proliferation. Drug selectivity has resulted in a marked increase in patient survival due to a decrease in the incidence of both life-threatening opportunistic infections and rejection episodes. Most maintenance immunosuppressive protocols employ a three-drug regimen consisting of a calcineurin-inhibitor (cyclosporine or tacrolimus), an antimetabolite agent (mycophenolate mofetil or less commonly azathioprine), and tapering doses of corticosteroids over the first year post-transplantation. The commonly used drugs in heart transplantation and their toxicities are outlined in Table 21.1 [29].

Calcineurin-Inhibitors

Since the introduction of cyclosporine in the early 1980's, the calcineurin inhibitors have remained the cornerstone of maintenance immunosuppressive therapy in heart and other solid organ transplantation. These drugs exert their immunosuppressive effects by inhibiting calcineurin, which is normally responsible for the transcription of IL-2 and several other cytokines, including TNF-α, granulocyte-macrophage colony-stimulating factor, and interferon-gamma (Fig. 21.1). The end result is blunting of T-lymphocyte activation and proliferation in response to alloantigens. The two available calcineurin inhibitors, **cyclosporine** and **tacrolimus**, form complexes with different intracellular binding proteins, and these drug-protein complexes subsequently bind to and inhibit calcineurin. The drugs differ with respect to both efficacy and side effect profile.

Cyclosporine

Cyclosporine is a peptide derived from the fungus *Tolypocladium inflatum* that has powerful immunosuppressive properties. It binds to the cytoplasmic protein cyclophilin to inhibit calcineurin. The drug is available in several formulations. The older oil-based formulation, called Sandimmune®, was characterized by variable and incomplete absorption. The newer modified formulations, including Gengraf® and Neoral®, are microemulsion formulations that result in improved and more reproducible drug absorption. Due to their improved pharmacokinetic profile, the microemulsion preparations are generally preferred over the oil-based formulation. The two formulations are not considered bioequivalent, and patients should not be routinely switched from one to the other without close monitoring of drug levels.

Dosing and Therapeutic Drug Monitoring Cyclosporine is available as oil-based or microemulsion capsules, as an oral microemulsion solution, and as a concentrate for injection. When given intravenously, approximately one third of the daily oral dose should be given as a continuous infusion over 24 h. The drug is typically titrated to achieve therapeutic 12-h trough levels. In general, cyclosporine levels are

Table 21.1 Immunosuppressive agents used in heart transplantation [29]

Drug	Dosing	Target levels	Major toxicities
Calcineurin inhibitors			
Cyclosporine	4–8 mg/kg/day in 2 divided doses, titrated to keep target 12-h trough levels	0–6 months: 250–350 ng/mL 6–12 months: 200–250 ng/mL >12 months: 100–200 ng/mL	Renal insufficiency Hypertension Dyslipidemia Hypokalemia and hypomagnesemia Hyperurecemia Neurotoxicity (encephalopathy, seizures, tremors, neuropathy) Gingival hyperplasia Hirsutism
Tacrolimus	0.05–0.1 mg/kg/day in 2 divided doses, titrated to keep target 12-hr. trough levels	0–6 months: 10–15 ng/mL 6–12 months: 5–10 ng/mL >12 months: 5–10 ng/mL	Renal dysfunction Hypertension Hyperglycemia and diabetes mellitus Dyslipidemia Hyperkalemia Hypomagnesemia Neurotoxicity (tremors, headaches)
Cell cycle agents			
Azathioprine	1.5–3.0 mg/kg/day, titrated to keep WBC ~ 3 K	None	Bone marrow suppression Hepatitis (rare) Pancreatitis Malignancy
Mycophenolate mofetil	2000–3000 mg/day in 2 divided doses	Mycophenolic acid (MPA): 2–5 mcg/ml	Gastrointestinal disturbances (nausea, gastritis, and diarrhea) Leukopenia
Mycophenolic acid	1440 mg/day in 2 divided doses	None	Less gastrointestinal disturbances compared to mycophenolate mofetil Leukopenia
Proliferation signal inhibitors			
Sirolimus	1–3 mg/day, titrated to keep therapeutic 24-h trough levels	5–10 ng/mL	Oral ulcerations Hypercholesterolemia and hypertriglyceridemia Poor wound healing Lower extremity edema Pulmonary toxicities (pneumonitis, alveolar hemorrhage) Leukopenia, anemia, and thrombocytopenia Potentiation of CNI nephrotoxicity Proteinuria

Table 21.1 (continued)

Drug	Dosing	Target levels	Major toxicities
Everolimus	1–1.5 mg/day, titrated to keep therapeutic 12-h trough levels	3–8 ng/mL	Similar to sirolimus
Corticosteroids			
Prednisone	0.5–1 mg/kg/day in 2 divided doses, tapered to 0.05 mg/kg/day by 6–12 month	None	Weight gain Hypertension Hyperlipidemia Osteopenia Hyperglycemia Poor wound healing Salt and water retention Proximal myopathy Cataracts Peptic ulcer disease Growth retardation

Reproduced with permission from McGraw Hill, Pham et al. [29], with permission from McGraw-Hill

kept highest in the first year post-transplantation (200–350 ng/mL) and lowered in subsequent periods (100–200 ng/mL). However, target drug levels should be individualized according to a patient's risk of rejection, renal function, and susceptibility to drug toxicities and infection.

Major Toxicities The major toxicities of cyclosporine include renal insufficiency, hypertension, dyslipidemia, hypokalemia and hypomagnesemia, and neurotoxicity (see Table 21.1). Gingival hyperplasia and hirsutism are two additional side effects that are unique to cyclosporine.

Tacrolimus

Tacrolimus (Prograf®), previously known as FK-506, is a macrolide compound derived from the fungus *Streptomyces tsukubaensis*. It binds to a cytoplasmic protein called FK binding protein and inhibits calcineurin via a similar pathway to that of cyclosporine. In recent years, the use of tacrolimus in heart transplantation has increased, and it is currently the most widely used calcineurin-inhibitor.

Multiple single-center and multi-center randomized comparisons between de novo use of tacrolimus and cyclosporine after heart transplantation have been reported [30–37]. As a whole, these trials have shown similar survival between patients treated with the two agents but fewer episodes of biopsy-proven or drug-treated acute rejection among patients treated with tacrolimus. Additionally, tacrolimus is associated with a more favorable side effect profile compared to cyclosporine. Compared to patients treated with cyclosporine, patients on tacrolimus had less

hypertension, less hyperlipidemia, but a higher incidence of post-transplant diabetes mellitus.

Dosing and Therapeutic Drug Monitoring Tacrolimus is available as oral capsules and as an injectable solution. The drug is typically given orally. When intravenous administration is required, approximately one third of the daily oral dose should be given as a continuous infusion over 24 h. Drug dosing is titrated to achieve therapeutic 12-h trough levels. In general, target levels are typically highest in the first 6 months (10–15 ng/mL) and lower thereafter (5–10 ng/mL).

Major Toxicities Compared to cyclosporine, the use of tacrolimus is associated with less hypertension and dyslipidemia. However, an increased frequency of new-onset diabetes mellitus has been observed in patients on tacrolimus compared with cyclosporine.

Antimetabolites

The antimetabolites, or antiproliferative agents, interfere with the synthesis of nucleic acids and exert their immunosuppressive effects by inhibiting the proliferation of both T and B lymphocytes.

Azathioprine

Azathioprine (Imuran®) is a prodrug that is first rapidly hydrolyzed in the blood to its active form, 6-mercaptopurine, and subsequently converted to a purine analogue, thio-inosine-monophosphate. This antimetabolite is incorporated into DNA and inhibits further nucleotide synthesis, thereby preventing mitosis and proliferation of rapidly dividing cells such as activated T and B lymphocytes. This drug is typically used as an adjunctive immunosuppressive agent with either corticosteroids or more commonly in conjunction with a calcineurin inhibitor. The major side effects include dose-dependent myelosuppression, particularly leukopenia. Azathioprine should be temporarily withheld if the white cell count falls below 3000/mm^2 or drops by 50 % compared to the previous value. Other potentially serious side effects include hepatotoxicity and pancreatitis.

Mycophenolate Mofetil

Mycophenolate mofetil (Cellcept®) has replaced azathioprine as the preferred antimetabolite agent in recent years. It is also prodrug that is rapidly hydrolyzed to its active form, mycophenolic acid (MPA). MPA is a reversible inhibitor of inosine monophosphate dehydrogenease, a critical enzyme for the de-novo synthesis of guanine nucleotides. Lymphocytes lack a key enzyme in the guanine salvage

pathway and are dependent upon the de novo pathway for the production of purines necessary for RNA and DNA synthesis. Therefore both T- and B-lymphocytes proliferation are selectively inhibited.

In a multi-center, active-controlled, randomized trial, mycophenolate mofetil was compared with azathioprine when used in conjunction with cyclosporine and corticosteroids in 650 de novo heart transplant recipients. Because an intravenous form of the study drug (mycophenolate mofetil) was not available at the time of the trial, 11 % of the patients withdrew before receiving the drug. Survival and rejection were similar in both groups when analyzed in an intention-to-treatment manner. However, among treated patients, mycophenolate mofetil was associated with a significant reduction in both mortality (6 % versus 11 %, p=0.031) and in the incidence of treatable rejection (66 % versus 74 %, p=0.026) at 1 year [38].

Dosing and Therapeutic Drug Monitoring Mycophenolate mofetil is available as an oral tablet or capsule and as a powder for injection. The intravenous solution is given at the same oral dose as a 2 h infusion every 12 h. The drug is typically administered at a starting dose of 1000–1500 mg twice daily and subsequently decreased as needed in response to leukopenia or gastrointestinal intolerance. While drug monitoring is not routinely performed, some centers target MPA trough levels between 2 and 5 ng/mL.

Major Toxicities Mycophenolate mofetil is not nephrotoxic and causes less bone marrow suppression compared to azathioprine. The main side effects include dose related leukopenia and gastrointestinal toxicities such as nausea, gastritis, and diarrhea. A possible association between mycophenolate mofetil and Progressive Multifocal Leukoencephalopathy (PML) has been reported [39].

Mycophenolic Acid

Mycophenolate sodium (Myfortic®) is an enteric coated, delayed release salt of mycophenolic acid, developed to improve the upper gastrointestinal tolerability of mycophenolate. Mycophenolic acid is available in 180 mg and 360 mg enteric coated tablets. Because of this coating, the tablet should *not* be crushed. The following conversions between mycophenolate mofetil (MMF) and mycophenolate sodium should provide equimolar amounts of MPA:

- 1000 mg MMF = 720 mg mycophenolate sodium
- 1500 mg MMF = 1080 mg mycophenolate sodium

Single and multi-center studies in de novo heart transplant recipients have shown that EC-MPS is therapeutically similar to MMF with respect to prevention of both biopsy-proven and treated acute rejection episodes, graft loss, or death. However, significantly fewer patients in the EC-MPS group required dose reductions during treatment [40, 41].

Proliferation Signal Inhibitors

In recent years, a new class of drugs called proliferation signal inhibitors, or mammalian target of rapamycin (mTOR) inhibitors, has been used in selected patients with renal insufficiency, cardiac allograft vasculopathy, or malignancies, in an attempt to reverse or slow progression of these conditions. However, the high incidence of drug-related adverse effects, including pericardial effusions, delayed sternal wound healing after transplantation, and the potential for enhanced nephrotoxicity when used with standard-dose cyclosporine, may limit the widespread use of these agents as de-novo therapy following transplantation [36, 42–44]. The two drugs in this class, **Sirolimus** and **Everolimus**, have similar mechanisms of action. They are structurally similar to **Tacrolimus** and also bind to the FK binding protein; however, they exert their immunosuppressive effects via a calcineurin-independent mechanism. The drug-immunophilin complex inhibits a protein kinase in the cytoplasm called mammalian target of rapamycin (mTOR) (Fig. 21.1d). mTOR is involved in the transduction signals from the IL-2 receptor to the nucleus. The consequence of mTOR inhibition is cell cycle arrest at the G1 to S phase, preventing both T- and B-cell proliferation in response to cytokine signals.

Sirolimus

Sirolimus (Rapamune®) is a macrolide antibiotic derived from the fungus *Streptomyces hygroscopicus*. The efficacy of sirolimus as an alternative to azathioprine was evaluated in a prospective, open-label, randomized trial of 136 de novo heart transplant recipients. Patients were randomized 2:1 to receive one of two sirolimus doses (3 or 5 mg) or to azathioprine. Sirolimus doses were subsequently adjusted in both groups to achieve similar target blood levels. All patients received concurrent immunosuppression with cyclosporine and corticosteroids. Compared with azathioprine, the use of either dose of sirolimus was associated with fewer biopsy-proven acute cellular rejection episodes at 6 months. Additionally, the development of cardiac allograft vasculopathy, as defined by intravascular ultrasound, was significantly reduced in the sirolimus groups at both 6 months and 2 years. Patient survival at 12 months was comparable among groups [43]. The combination of sirolimus with tacrolimus was also compared against mycophenolate mofetil with tacrolimus and mycophenolate mofetil with cyclosporine in a multi-center randomized trial involving 343 de novo heart transplant recipients. In this study, there was no statistically significant difference in the incidence of acute cellular rejection or hemodynamically compromising rejection among the three groups, but patients in both the sirolimus plus tacrolimus group and in the mycophenolate mofetil plus tacrolimus group experienced fewer treated rejection episodes compared to patients in the mycophenolate mofetil plus cyclosporine group. However, patients in the sirolimus plus tacrolimus group experienced an increased

incidence of renal dysfunction and wound healing complications compared to the other two groups [36].

Dosing and Therapeutic Drug Monitoring Sirolimus is available in a liquid or tablet formulation. When used in conjunction with cyclosporine-modified capsules (Gengraf or Neoral), Sirolimus should be given 4 h after cyclosporine administration to minimize the pharmacokinetic interaction between the two drugs. Dosing is typically adjusted to achieve serum trough levels of 5–10 ng/mL. However, target ranges may vary depending upon the assay (immunoassay versus chromatographic) used, and clinicians should be familiar with the reference range for the assay used at their institutions.

Major Toxicities Sirolimus has no inherent nephrotoxic effects but can potentiate the efficacy and nephrotoxic effects of the calcineurin inhibitors. Therefore, when these agents are used together, the dosage of the calcineurin inhibitor should be reduced by approximately 25 %, and reduced calcineurin-inhibitor drug therapeutic drug levels should be targeted. The most common drug-related toxicities include hyperlipidemia, oral ulcerations, lower extremity edema, and bone marrow suppression with leukopenia, thrombocytopenia, and anemia [43]. Post-surgical wound healing complications, as well as an increase in the incidence of pleural and pericardial effusions requiring drainage, have also been reported when the drug is used immediately after transplantation [42, 45]. Proteinuria has also been reported among patients converted to sirolimus, although its incidence and clinical significance are not well understood [46]. Finally, rare but serious cases of sirolimus-related pulmonary toxicities have been described [47–49].

Everolimus

Everolimus (Zortress®, Certican®) is an analog of Sirolimus that has weaker binding affinity to the FK binding protein and subsequently has a shorter drug half-life (30 h) compared to that of sirolimus (60 h). Everolimus was studied in a 24-month, multi-center, randomized, open-label non-inferiority study involving 721 de novo heart transplant recipients. Patients were randomized to one of two everolimus drug exposures (1.5 mg/day or 3.0 mg/day in divided doses) with reduced-dose cyclosporine, or to mycophenolate mofetil with standard-dose cyclosporine. Patients received corticosteroids with or without induction therapy according to individual transplant center protocols. Enrollment into the higher dose (3.0 mg/day) everolimus arm was stopped prematurely due to a higher incidence of early mortality in this group. Everolimus was found to be non-inferior to mycophenolate mofetil with respect to the primary efficacy endpoint of biopsy-proven acute cellular rejection, acute rejection with hemodynamic compromise, graft loss or retransplantation, death, or loss to follow-up. As reported with previous studies [50], patients on everolimus had reduced intimal proliferation on intravascular ultrasound at 12 months post-transplantation. More nonfatal serious adverse events, particularly pericardial

effusions, and a higher rate of drug discontinuations due to adverse events were reported in the everolimus group compared to the mycophenolate mofetil group. Finally, everolimus was noted to be inferior to mycophenolate mofetil with respect to renal function, but a post-hoc analysis indicated that this finding was largely driven by a subset of study centers that were not successful in reducing the cyclosporine exposure in the everolimus group [43].

Major Toxicities The side effect profile for everolimus is similar to that of sirolimus, although it has been reported in clinical practice that the frequency and severity of adverse events may be attenulated with everolimus. When everolimus is used in conjunction with a calcineurin inhibitor, the calcineurin inhibitor dosage should be reduced by approximately 25 % to minimize the risk of potentiated nephrotoxicity. Finally, the use of everolimus during the first 3 months after heart transplantation is not recommended due to concerns regarding the risk of increased mortality due to serious opportunistic infections.

Corticosteroids

Corticosteroids are non-specific anti-inflammatory agents that interrupt multiple steps in immune activation, including antigen presentation, cytokine production, and proliferation of lymphocytes. Although steroids are highly effective for the prevention and treatment of acute rejection, their long-term use is associated with a number of adverse effects including new onset or worsening diabetes mellitus, hyperlipidemia, hypertension, fluid retention, myopathy, osteoporosis, and a predisposition toward opportunistic infections. Thus, while most programs employ corticosteroids as one of the three maintenance immunosuppressive agents, they are used in relatively high doses in the early postoperative period but then tapered to low doses or discontinued altogether after the first 6–12 months [51–54]. Certain low-risk patients may tolerate earlier (within 1–2 months post-transplantation) steroid withdrawal without long-term adverse consequences [55, 56].

Trends in Immunosuppression Use

Recent international trends in the use of maintenance immunosuppressive agents at 1 and 5 years post-transplantation are presented in Fig. 21.3. Tacrolimus use has steadily increased since 2000 and is currently the most widely used calcineurin inhibitor in heart transplantation. Mycophenolate mofetil and mycophenolic acid remain the predominant antimetabolite agents. Use of the proliferation signal inhibitors sirolimus or everolimus is infrequent (9 %) during the first year but has steadily increased in recent years, such that 20 % of patients are on either agent by 5 years post-transplantation. Finally, the use of long-term corticosteroids has continued to

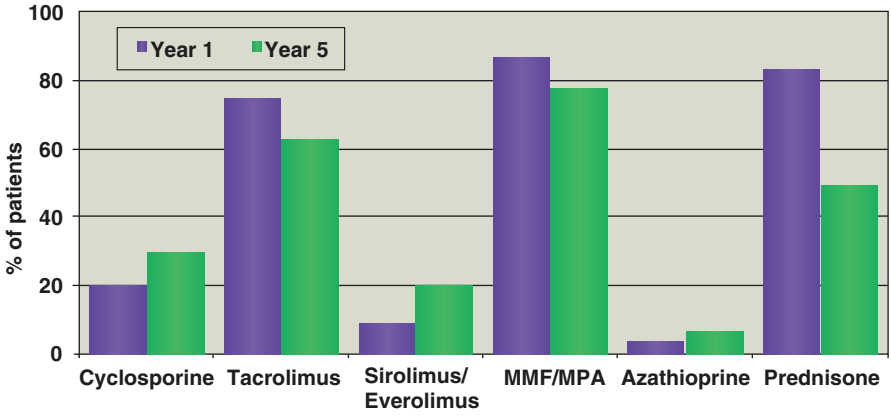


Fig. 21.3 Maintenance immunosuppression after heart transplantation [1]. The histogram shows the proportion of heart transplant recipients who were maintained on each immunosuppressive agent at the time of their 1-year and 5-year follow-up appointments between January 2007 to June 2011. Different patient cohorts are represented in the 1-year and 5-year histograms. *MMF* mycophenolate mofetil. *MPA* mycophenolic acid [1] (Adapted from Stehlik et al. [1], © 2012, with permission from Elsevier)

decline steadily, with fewer than 50 % of patients remaining on some amount of corticosteroids by 5 years post-transplantation [1] .

Special Considerations

Most programs employ a standard *de-novo* immunosuppressive regimen immediately after transplantation. Once stabilized on a particular regimen, immunosuppressive agents are not routinely altered except in response to significant drug toxicities or post-transplant complications. The most common changes in drug regimens and their rationale are described below.

Refractory or Recurrent Rejection

Following one or more episodes of acute rejection, many centers will attempt to optimize a patient's baseline immunosuppression. Some programs that routinely utilize cyclosporine as the de-no calcineurin-inhibitor of choice will switch patients to tacrolimus. Patients previously on azathioprine may be converted to the newer and more effective antimetabolite agents, mycophenolate mofetil or mycophenolic acid. Finally, patients on either azathioprine or mycophenolate mofetil may be converted to one of the proliferation signal inhibitors, either sirolimus or everolimus.

Renal Insufficiency

Several renal sparing protocols are employed to slow or reverse the progression of calcineurin inhibitor-mediated nephrotoxicity. Strategies include calcineurin-inhibitor dosage reduction in conjunction with either an antimetabolite agent or a proliferation signal inhibitor, or complete withdrawal of the calcineurin-inhibitor in favor of using the combination of a proliferation signal inhibitor and mycophenolate mofetil (CNI-free regimens). All three strategies have resulted in significant improvements in renal function without a significant increase in the rate of acute rejection or graft dysfunction [57–65]. The use of CNI-free regimens may provide additional improvements in renal function compared to low-dose CNI strategies in carefully selected patients who are at low risk of rejection [66, 67]. Of important note, use of a calcineurin-free regimen as de-novo immunosuppression, in the early (within 12 weeks) post-operative period, or in patients at higher risk for rejection, should be done with caution due to the observed increased incidence of biopsy-proven rejection in these settings [68, 69]. Additionally, the use of proliferation signal inhibitors should be avoided in patients with pre-existing proteinturia ($\geq$150 mg/day) as renal function has been reported to further diminish in these patients after exposure to a proliferation signal inhibitor [65].

Cardiac Allograft Vasculopathy

Because mTOR also signals smooth muscle and endothelial cell proliferation in response to growth factors, the proliferation signal inhibitors have been used to prevent allograft vasculopathy when used in a de-novo setting after heart transplantation, or to slow disease progression and to reduce the incidence of clinically significant cardiac events in patients with established disease [43, 50, 70, 71].

Malignancies

Observational data, mostly from the kidney transplant literature, suggest that the proliferation signal inhibitors sirolimus and everolimus may reduce the incidence of post-transplant malignancies [72–74]. Limited data also suggests that sirolimus monotherapy may cause regression of certain skin tumors, such as Kaposi sarcoma, in kidney transplant recipients [75]. Postulated mechanisms responsible for this anti-tumor effect include direct antiproliferative actions of these drugs on tumor growth and angiogenesis as well as facilitation of CNI dose reduction or withdrawal [76]. Randomized, controlled clinical trials, adequately powered within each organ group, will be required to determine if the proliferation signal inhibitors are effective for prevention and treatment of post-transplant malignancies.

Side Effects

Certain side effects, such as hirsutism or gingival hyperplasia, are unique to cyclosporine. Therefore, individuals who develop severe forms of these complications on cyclosporine may be converted to tacrolimus. Patients with persistent upper gastrointestinal symptoms on mycophenolate mofetil despite an initial dose reduction may better tolerate enteric coated mycophenolate sodium. Severe cases of sirolimus-related lower extremity edema and rare but potentially life-threatening episodes of sirolimus-related interstitial pneumonitis will prompt most centers to discontinue the drug.

Drug Interactions

Clinicians involved in the care of heart transplant recipients should be aware of the potential for drug interactions when other agents are added to or deleted from a patient's medical regimen [77]. A list of the most common and clinically important drug interactions is presented in Table 21.2 [29].

Pharmacokinetic drug interactions occur when a new drug changes immunosuppressive drug levels, either by interfering with the absorption, distribution, metabolism, or elimination of the immunosuppressive agent. Most clinically important pharmacokinetic drug interactions occur due to altered drug metabolism. The calcineurin inhibitors and proliferation signal inhibitors are extensively metabolized by the cytochrome P-450 3 A4 enzyme pathway in the liver. Drugs that *induce* the P-450 3 A4 pathway result in enhanced metabolism of the calcineurin inhibitors and proliferation signal inhibitors, thus *lowering* their blood levels and clinical effectiveness. The most common P-450 3 A4 inducers include the anti-seizure medication **phenytoin**, the anti-tubercular drug **rifampin**, and the herbal agent **St. John's Wort**. Conversely, drugs that *inhibit* the enzyme pathway result in decreased metabolism of the calcineurin inhibitors and proliferation signal inhibitors, thereby *increasing* their blood levels and potentiating their toxicities. The most common P-450 3 A4 inhibitors include the calcium channel blockers, antifungal drugs, macrolide antibiotics, HIV protease inhibitors, the anti-arrhythmic agent **amiodarone**, and grapefruit juice. Finally, the immunosuppressive agents themselves can affect the metabolism of other drugs. For example, patients taking many HMG Co-A reductase inhibitors (statins) in conjunction with cyclosporine, tacrolimus, or sirolimus have an increased risk of myopathy and/or rhabdomyolysis due to increased statin drug levels.

Drugs with potential immunosuppressive interactions are not contra-indicated in heart transplant recipients but should be used cautiously with close monitoring of immunosuppressive drug levels and toxicities. One important exception is the combination of azathioprine and **allopurinol**. Allopurinol inhibits the activity of xanthine oxidase, which is involved in the metabolism of azathioprine, resulting in high levels of the active metabolite 6-mercaptopurine and subsequent severe bone

Table 21.2 Important drug interactions [29]

Drugs that increase levels of cyclosporine, tacrolimus, and sirolimus	
Calcium channel blockers	Diltiazem Nifedipine Nicardipine Verapamil
Antifungal drugs	Itraconazole Fluconazole Ketoconazole Voriconazole Posaconazole
Macrolide antibiotics	All
Fluoroquinolone antibiotics	Ciprofloxacin
HIV-protease inhibitors	All
Antiarrhythmic agents	Amiodarone
Gastrointestinal agents	Metoclopramide
Miscellaneous	Grapefruit juice
Drugs that decrease levels of cyclosporine, tacrolimus, and sirolimus	
Anti-tubercular drugs	Rifampin
Anti-seizure drugs	Phenytoin Phenobarbital
Gastrointestinal drugs	Octreotide
Miscellaneous	St. John's Wort
Drugs with synergistic nephrotoxicity when used with cyclosporine or tacrolimus	
Aminoglycoside antibiotics Amphotericin B Colchicine Non-steroidal anti-inflammatory agents (NSAIDs)	
Drugs whose concentrations are increased when used with cyclosporine or tacrolimus	
Lovastatin Simvastatin Atorvastatin Ezetimibe	

Reproduced with permission from McGraw Hill, Pham et al. [29], with permission from McGraw-Hill

marrow suppression. This combination should be avoided, particularly given the availability of alternate immunosuppressive agents such as mycophonolate mofetil and mycophenolic acid.

Pharmacodynamic drug interactions occur when a drug modulates an immunosuppressive agent's effect at a given blood concentration, either increasing or diminishing the immunosuppressive drug's physiologic effect. For example, concurrent use of ganciclovir, valganciclovir, or trimetroprim-sulfamethoxazole can potentiate the myelosuppressive effects of the antimetabolite agents and proliferation signal inhibitors. Additionally, additive nephrotoxicity is observed when amphotericin B, aminoglycosides, foscarnet, or nonsteroidal anti-inflammatory agents are used with the calcineurin inhibitors.

References

1. Stehlik J, Edwards LB, Kucheryavaya AY, Benden C, Christie JD, Dipchand AI, et al. The registry of the international society for heart and lung transplantation: 29th official adult heart transplant report--2012. J Heart Lung Transplant. 2012;31(10):1052–64.
2. Rosenberg PB, Vriesendorp AE, Drazner MH, Dries DL, Kaiser PA, Hynan LS, et al. Induction therapy with basiliximab allows delayed initiation of cyclosporine and preserves renal function after cardiac transplantation. J Heart Lung Transplant. 2005;24(9):1327–31.
3. Yamani MH, Taylor DO, Czerr J, Haire C, Kring R, Zhou L, et al. Thymoglobulin induction and steroid avoidance in cardiac transplantation: results of a prospective, randomized, controlled study. Clin Transplant. 2008;22(1):76–81.
4. Cantarovich M, Giannetti N, Barkun J, Cecere R. Antithymocyte globulin induction allows a prolonged delay in the initiation of cyclosporine in heart transplant patients with postoperative renal dysfunction. Transplantation. 2004;78(5):779–81.
5. Adamson R, Obispo E, Dychter S, Dembitsky W, Moreno-Cabral R, Jaski B, et al. Long-term outcome with the use of OKT3 induction therapy in heart transplant patients: a single-center experience. Transplant Proc. 1998;30(4):1107–9.
6. Johnson MR, Mullen GM, O'Sullivan EJ, Liao Y, Heroux AL, Kao WG, et al. Risk/benefit ratio of perioperative OKT3 in cardiac transplantation. Am J Cardiol. 1994;74(3):261–6.
7. Swinnen LJ, Costanzo-Nordin MR, Fisher SG, O'Sullivan EJ, Johnson MR, Heroux AL, et al. Increased incidence of lymphoproliferative disorder after immunosuppression with the monoclonal antibody OKT3 in cardiac-transplant recipients. N Engl J Med. 1990;323(25):1723–8.
8. Opelz G, Dohler B. Lymphomas after solid organ transplantation: a collaborative transplant study report. Am J Transplant. 2004;4(2):222–30.
9. Beniaminovitz A, Itescu S, Lietz K, Donovan M, Burke EM, Groff BD, et al. Prevention of rejection in cardiac transplantation by blockade of the interleukin-2 receptor with a monoclonal antibody. N Engl J Med. 2000;342(9):613–9.
10. Prieto M, Lake KD, Pritzker MR, Jorgensen CR, Arom KV, Love KR, et al. OKT3 induction and steroid-free maintenance immunosuppression for treatment of high-risk heart transplant recipients. J Heart Lung Transplant. 1991;10(6):901–11.
11. Rinaldi M, Pellegrini C, D'Armini AM, Aiello M, Negri M, Arbustini E, et al. Neoplastic disease after heart transplantation: single center experience. Eur J Cardiothorac Surg. 2001;19(5):696–701.
12. Higgins R, Kirklin JK, Brown RN, Rayburn BK, Wagoner L, Oren R, et al. To induce or not to induce: do patients at greatest risk for fatal rejection benefit from cytolytic induction therapy? J Heart Lung Transplant. 2005;24(4):392–400.
13. Caillat-Zucman S, Blumenfeld N, Legendre C, Noel LH, Bach JF, Kreis H, et al. The OKT3 immunosuppressive effect. In situ antigenic modulation of human graft-infiltrating T cells. Transplantation. 1990;49(1):156–60.
14. Norman DJ. Mechanisms of action and overview of OKT3. Ther Drug Monit. 1995;17(6):615–20.
15. Michaels PJ, Espejo ML, Kobashigawa J, Alejos JC, Burch C, Takemoto S, et al. Humoral rejection in cardiac transplantation: risk factors, hemodynamic consequences and relationship to transplant coronary artery disease. J Heart Lung Transplant. 2003;22(1):58–69.
16. Jensen PB, Birkeland SA, Rohrp N, Elbirk A, Jorgensen KA. Development of anti-OKT3 antibodies after OKT3 treatment. Scand J Urol Nephrol. 1996;30(3):227–30.
17. Hammond EH, Wittwer CT, Greenwood J, Knape WA, Yowell RL, Menlove RL, et al. Relationship of OKT3 sensitization and vascular rejection in cardiac transplant patients receiving OKT3 rejection prophylaxis. Transplantation. 1990;50(5):776–82.
18. Hardinger KL, Rhee S, Buchanan P, Koch M, Miller B, Enkvetchakul D, et al. A prospective, randomized, double-blinded comparison of thymoglobulin versus Atgam for induction immunosuppressive therapy: 10-year results. Transplantation. 2008;86(7):947–52.

19. Brennan DC, Flavin K, Lowell JA, Howard TK, Shenoy S, Burgess S, et al. A randomized, double-blinded comparison of Thymoglobulin versus Atgam for induction immunosuppressive therapy in adult renal transplant recipients. Transplantation. 1999;67(7): 1011–8.
20. El-Hamamsy I, Stevens LM, Carrier M, Pelletier G, White M, Tremblay F, et al. Incidence and prognosis of cancer following heart transplantation using RATG induction therapy. Transpl Int. 2005;18(11):1280–5.
21. Carrier M, Leblanc MH, Perrault LP, White M, Doyle D, Beaudoin D, et al. Basiliximab and rabbit anti-thymocyte globulin for prophylaxis of acute rejection after heart transplantation: a non-inferiority trial. J Heart Lung Transplant. 2007;26(3):258–63.
22. Segovia J, Rodriguez-Lambert JL, Crespo-Leiro MG, Almenar L, Roig E, Gomez-Sanchez MA, et al. A randomized multicenter comparison of basiliximab and muromonab (OKT3) in heart transplantation: SIMCOR study. Transplantation. 2006;81(11):1542–8.
23. Mattei MF, Redonnet M, Gandjbakhch I, Bandini AM, Billes A, Epailly E, et al. Lower risk of infectious deaths in cardiac transplant patients receiving basiliximab versus anti-thymocyte globulin as induction therapy. J Heart Lung Transplant. 2007;26(7):693–9.
24. Mehra MR, Zucker MJ, Wagoner L, Michler R, Boehmer J, Kovarik J, et al. A multicenter, prospective, randomized, double-blind trial of basiliximab in heart transplantation. J Heart Lung Transplant. 2005;24(9):1297–304.
25. Bloom DD, Hu H, Fechner JH, Knechtle SJ. T-lymphocyte alloresponses of Campath-1H-treated kidney transplant patients. Transplantation. 2006;81(1):81–7.
26. Morris PJ, Russell NK. Alemtuzumab (Campath-1H): a systematic review in organ transplantation. Transplantation. 2006;81(10):1361–7.
27. Teuteberg JJ, Shullo MA, Zomak R, Toyoda Y, McNamara DM, Bermudez C, et al. Alemtuzumab induction prior to cardiac transplantation with lower intensity maintenance immunosuppression: one-year outcomes. Am J Transplant. 2010;10(2):382–8.
28. Stehlik J, Edwards LB, Kucheryavaya AY, Benden C, Christie JD, Dobbels F, et al. The registry of the international society for heart and lung transplantation: twenty-eighth adult heart transplant report – 2011. J Heart Lung Transplant. 2011;30(10):1078–94.
29. Pham MX, Chen JM, Berry GJ, Hunt SA. Cardiac transplantation. In: Fuster V, Walsh RA, RA H, editors. Hurst's the heart. 13 ed. New York: McGraw-Hill; 2011.
30. Grimm M, Rinaldi M, Yonan NA, Arpesella G, Arizon Del Prado JM, Pulpon LA, et al. Superior prevention of acute rejection by tacrolimus vs. cyclosporine in heart transplant recipients – a large European trial. Am J Transplant. 2006;6(6):1387–97.
31. Groetzner J, Meiser BM, Schirmer J, Koglin J, vScheidt W, Klauss V, et al. Tacrolimus or cyclosporine for immunosuppression after cardiac transplantation: which treatment reveals more side effects during long-term follow-up? Transplant Proc. 2001;33(1–2):1461–4.
32. Meiser BM, Uberfuhr P, Fuchs A, Schmidt D, Pfeiffer M, Paulus D, et al. Single-center randomized trial comparing tacrolimus (FK506) and cyclosporine in the prevention of acute myocardial rejection. J Heart Lung Transplant. 1998;17(8):782–8.
33. Rinaldi M, Pellegrini C, Martinelli L, Goggi C, Gavazzi A, Campana C, et al. FK506 effectiveness in reducing acute rejection after heart transplantation: a prospective randomized study. J Heart Lung Transplant. 1997;16(10):1001–10.
34. Reichart B, Meiser B, Vigano M, Rinaldi M, Martinelli L, Yacoub M, et al. European multicenter tacrolimus (FK506) heart pilot study: one-year results – European tacrolimus multicenter heart study group. J Heart Lung Transplant. 1998;17(8):775–81.
35. Taylor DO, Barr ML, Radovancevic B, Renlund DG, Mentzer Jr RM, Smart FW, et al. A randomized, multicenter comparison of tacrolimus and cyclosporine immunosuppressive regimens in cardiac transplantation: decreased hyperlipidemia and hypertension with tacrolimus. J Heart Lung Transplant. 1999;18(4):336–45.
36. Kobashigawa JA, Miller LW, Russell SD, Ewald GA, Zucker MJ, Goldberg LR, et al. Tacrolimus with mycophenolate mofetil (MMF) or sirolimus vs. cyclosporine with MMF in cardiac transplant patients: 1-year report. Am J Transplant. 2006;6(6):1377–86.

37. Kobashigawa JA, Patel J, Furukawa H, Moriguchi JD, Yeatman L, Takemoto S, et al. Five-year results of a randomized, single-center study of tacrolimus vs microemulsion cyclosporine in heart transplant patients. J Heart Lung Transplant. 2006;25(4):434–9.
38. Kobashigawa J, Miller L, Renlund D, Mentzer R, Alderman E, Bourge R, et al. A randomized active-controlled trial of mycophenolate mofetil in heart transplant recipients. Mycophenolate Mofetil Investigators. Transplantation. 1998;66(4):507–15.
39. Communication about an ongoing safety review of Cellcept (mycophenolate mofetil) and Myfortic (mycophenolic acid). 2008 [updated 4 June 2008, 1 Jan 2009]. Available from: http://www.fda.gov/cder/drug/early_comm/mycophenolate.htm.
40. Kobashigawa JA, Renlund DG, Gerosa G, Almenar L, Eisen HJ, Keogh AM, et al. Similar efficacy and safety of enteric-coated mycophenolate sodium (EC-MPS, myfortic) compared with mycophenolate mofetil (MMF) in de novo heart transplant recipients: results of a 12-month, single-blind, randomized, parallel-group, multicenter study. J Heart Lung Transplant. 2006;25(8):935–41.
41. Lehmkuhl H, Hummel M, Kobashigawa J, Ladenburger S, Rothenburger M, Sack F, et al. Enteric-coated mycophenolate-sodium in heart transplantation: efficacy, safety, and pharmacokinetic compared with mycophenolate mofetil. Transplant Proc. 2008;40(4):953–5.
42. Kuppahally S, Al-Khaldi A, Weisshaar D, Valantine HA, Oyer P, Robbins RC, et al. Wound healing complications with de novo sirolimus versus mycophenolate mofetil-based regimen in cardiac transplant recipients. Am J Transplant. 2006;6(5 Pt 1):986–92.
43. Keogh A, Richardson M, Ruygrok P, Spratt P, Galbraith A, O'Driscoll G, et al. Sirolimus in de novo heart transplant recipients reduces acute rejection and prevents coronary artery disease at 2 years: a randomized clinical trial. Circulation. 2004;110(17):2694–700.
44. Eisen HJ, Kobashigawa J, Starling RC, Pauly DF, Kfoury A, Ross H, et al. Everolimus versus mycophenolate mofetil in heart transplantation: a randomized, multicenter trial. Am J Transplant. 2013;22.
45. Zakliczynski M, Nozynski J, Kocher A, Lizak MK, Zakliczynska H, Przybylski R, et al. Surgical wound-healing complications in heart transplant recipients treated with rapamycin. Wound Repair Regen. 2007;15(3):316–21.
46. Zuckermann A, Manito N, Epailly E, Fiane A, Bara C, Delgado JF, et al. Multidisciplinary insights on clinical guidance for the use of proliferation signal inhibitors in heart transplantation. J Heart Lung Transplant. 2008;27(2):141–9.
47. Garcia-Luque A, Cordero E, Torello J, Lage E, Juan JM, Cisneros JM, et al. Sirolimus-associated pneumonitis in heart transplant recipients. Ann Pharmacother. 2008;42(7):1143–5.
48. Khalife WI, Kogoj P, Kar B. Sirolimus-induced alveolar hemorrhage. J Heart Lung Transplant. 2007;26(6):652–7.
49. Delgado JF, Torres J, Jose Ruiz-Cano M, Sanchez V, Escribano P, Borruel S, et al. Sirolimus-associated interstitial pneumonitis in 3 heart transplant recipients. J Heart Lung Transplant. 2006;25(9):1171–4.
50. Eisen HJ, Tuzcu EM, Dorent R, Kobashigawa J, Mancini D, Valantine-von Kaeppler HA, et al. Everolimus for the prevention of allograft rejection and vasculopathy in cardiac-transplant recipients. N Engl J Med. 2003;349(9):847–58.
51. Miller LW, Wolford T, McBride LR, Peigh P, Pennington DG. Successful withdrawal of corticosteroids in heart transplantation. J Heart Lung Transplant. 1992;11(2 Pt 2):431–4.
52. Olivari MT, Jessen ME, Baldwin BJ, Horn VP, Yancy CW, Ring WS, et al. Triple-drug immunosuppression with steroid discontinuation by six months after heart transplantation. J Heart Lung Transplant. 1995;14(1 Pt 1):127–35.
53. Kobashigawa JA, Stevenson LW, Brownfield ED, Moriguchi JD, Kawata N, Fandrich R, et al. Initial success of steroid weaning late after heart transplantation. J Heart Lung Transplant. 1992;11(2 Pt 2):428–30.
54. Teuteberg JJ, Shullo M, Zomak R, McNamara D, McCurry K, Kormos RL. Aggressive steroid weaning after cardiac transplantation is possible without the additional risk of significant rejection. Clin Transplant. 2008;22(6):730–7.

55. Taylor DO, Bristow MR, O'Connell JB, Price GD, Hammond EH, Doty DB, et al. Improved long-term survival after heart transplantation predicted by successful early withdrawal from maintenance corticosteroid therapy. J Heart Lung Transplant. 1996;15(10):1039–46.
56. Renlund DG, O'Connell JB, Gilbert EM, Watson FS, Bristow MR. Feasibility of discontinuation of corticosteroid maintenance therapy in heart transplantation. J Heart Transplant. 1987;6(2):71–8.
57. Gustafsson F, Ross HJ, Delgado MS, Bernabeo G, Delgado DH. Sirolimus-based immunosuppression after cardiac transplantation: predictors of recovery from calcineurin inhibitor-induced renal dysfunction. J Heart Lung Transplant. 2007;26(10):998–1003.
58. Raichlin E, Khalpey Z, Kremers W, Frantz RP, Rodeheffer RJ, Clavell AL, et al. Replacement of calcineurin-inhibitors with sirolimus as primary immunosuppression in stable cardiac transplant recipients. Transplantation. 2007;84(4):467–74.
59. Rothenburger M, Teerling E, Bruch C, Lehmkuhl H, Suwelack B, Bara C, et al. Calcineurin inhibitor-free immunosuppression using everolimus Certican in maintenance heart transplant recipients: 6 months follow-up. J Heart Lung Transplant. 2007;26(3):250–7.
60. Bestetti R, Theodoropoulos TA, Burdmann EA, Filho MA, Cordeiro JA, Villafanha D. Switch from calcineurin inhibitors to sirolimus-induced renal recovery in heart transplant recipients in the midterm follow-up. Transplantation. 2006;81(5):692–6.
61. Fernandez-Valls M, Gonzalez-Vilchez F, de Prada JA, Ruano J, Ruisanchez C, Martin-Duran R. Sirolimus as an alternative to anticalcineurin therapy in heart transplantation: experience of a single center. Transplant Proc. 2005;37(9):4021–3.
62. Kushwaha SS, Khalpey Z, Frantz RP, Rodeheffer RJ, Clavell AL, Daly RC, et al. Sirolimus in cardiac transplantation: use as a primary immunosuppressant in calcineurin inhibitor-induced nephrotoxicity. J Heart Lung Transplant. 2005;24(12):2129–36.
63. Hunt J, Lerman M, Magee MJ, Dewey TM, Herbert M, Mack MJ. Improvement of renal dysfunction by conversion from calcineurin inhibitors to sirolimus after heart transplantation. J Heart Lung Transplant. 2005;24(11):1863–7.
64. Groetzner J, Kaczmarek I, Landwehr P, Mueller M, Daebritz S, Lamm P, et al. Renal recovery after conversion to a calcineurin inhibitor-free immunosuppression in late cardiac transplant recipients. Eur J Cardiothorac Surg. 2004;25(3):333–41.
65. Potena L, Prestinenzi P, Bianchi IG, Masetti M, Romani P, Magnani G, et al. Cyclosporine lowering with everolimus versus mycophenolate mofetil in heart transplant recipients: long-term follow-up of the SHIRAKISS randomized, prospective study. J Heart Lung Transplant. 2012;31(6):565–70.
66. Gleissner CA, Doesch A, Ehlermann P, Koch A, Sack FU, Katus HA, et al. Cyclosporine withdrawal improves renal function in heart transplant patients on reduced-dose cyclosporine therapy. Am J Transplant. 2006;6(11):2750–8.
67. Potter BJ, Giannetti N, Edwardes MD, Cecere R, Cantarovich M. Calcineurin inhibitor substitution with sirolimus vs. reduced-dose calcineurin inhibitor plus sirolimus is associated with improved renal dysfunction in heart transplant patients. Clin Transplant. 2007;21(3):305–8.
68. Gonzalez-Vilchez F, de Prada JA, Exposito V, Garcia-Camarero T, Fernandez-Friera L, Llano M, et al. Avoidance of calcineurin inhibitors with use of proliferation signal inhibitors in de novo heart transplantation with renal failure. J Heart Lung Transplant. 2008;27(10):1135–41.
69. Roche. Higher than expected incidence of acute rejection in cardiac transplant patients switched from calcineurin inhibitors in combination with CellCept (mycophenolate mofetil) to Rapamune (sirolimus) in combination with CellCept at 12 weeks post heart transplantation. 2007.
70. Mancini D, Pinney S, Burkhoff D, LaManca J, Itescu S, Burke E, et al. Use of rapamycin slows progression of cardiac transplantation vasculopathy. Circulation. 2003;108(1):48–53.
71. Raichlin E, Bae JH, Khalpey Z, Edwards BS, Kremers WK, Clavell AL, et al. Conversion to sirolimus as primary immunosuppression attenuates the progression of allograft vasculopathy after cardiac transplantation. Circulation. 2007;116(23):2726–33.

72. Mathew T, Kreis H, Friend P. Two-year incidence of malignancy in sirolimus-treated renal transplant recipients: results from five multicenter studies. Clin Transplant. 2004;18(4): 446–9.
73. Campistol JM, Eris J, Oberbauer R, Friend P, Hutchison B, Morales JM, et al. Sirolimus therapy after early cyclosporine withdrawal reduces the risk for cancer in adult renal transplantation. J Am Soc Nephrol. 2006;17(2):581–9.
74. Kauffman HM, Cherikh WS, Cheng Y, Hanto DW, Kahan BD. Maintenance immunosuppression with target-of-rapamycin inhibitors is associated with a reduced incidence of de novo malignancies. Transplantation. 2005;80(7):883–9.
75. Stallone G, Schena A, Infante B, Di Paolo S, Loverre A, Maggio G, et al. Sirolimus for Kaposi's sarcoma in renal-transplant recipients. N Engl J Med. 2005;352(13):1317–23.
76. Guba M, von Breitenbuch P, Steinbauer M, Koehl G, Flegel S, Hornung M, et al. Rapamycin inhibits primary and metastatic tumor growth by antiangiogenesis: involvement of vascular endothelial growth factor. Nat Med. 2002;8(2):128–35.
77. Page 2nd RL, Miller GG, Lindenfeld J. Drug therapy in the heart transplant recipient: part IV: drug-drug interactions. Circulation. 2005;111(2):230–9.

Chapter 22
Antibody-Mediated Rejection

Abdallah Georges Kfoury, Deborah Budge, Kimberly D. Brunisholz, and M. Elizabeth H. Hammond

Introduction

Antibody-mediated rejection (AMR) of the cardiac allograft, formerly also termed *vascular* or *humoral* rejection, typically occurs in the absence of interstitial lymphocytic infiltrates that are characteristic of acute cellular rejection. Its pathological hallmarks include capillary endothelial activation and macrophage infiltration, as well as vascular immunofluorescent deposition of immunoglobulin and complement. Clinically, AMR occurs early post heart transplant and tends to recur, is harder to treat, and is associated with poor outcomes [1–6].

The concept that acute and chronic rejection in heart transplantation may be mediated by alloantibodies has only been recently accepted. In some recipients, a humoral immune response triggered by antibody-antigen engagement may ultimately result in graft injury and dysfunction through the interplay of various cellular and non-cellular pathways [7–11].

Prior to 2005, cardiac AMR was loosely defined and not uniformly accepted even when clinically manifest. As a result, its true incidence and breadth from

A.G. Kfoury, MD, FACC (✉) • M.E.H. Hammond, MD
Intermountain Medical Center (UTAH Cardiac Transplant Program), Intermountain Heart Institute, 5121 South Cottonwood Street, Salt Lake City, USA

University of Utah School of Medicine, Salt Lake City, USA
e-mail: akfoury@imail.org; liz.hammond@hotmail.com

D. Budge, MD
Intermountain Medical Center (UTAH Cardiac Transplant Program), Intermountain Heart Institute, 5121 South Cottonwood Street, Salt Lake City, USA
e-mail: deborah.budge@imail.org

K.D. Brunisholz, PhDc, MST
Intermountain Healthcare, Primary Care Clinical Program, Institute for Health Care Delivery Research, 36 South State Street, Salt Lake City, UT 84111, USA
e-mail: kim.brunisholz@imail.org

H. Eisen (ed.), *Heart Failure*, DOI 10.1007/978-1-4471-4219-5_22

subclinical to symptomatic states were not fully appreciated. Likewise, treatment strategies could neither be standardized nor tested effectively on a large scale [1–3, 7, 12–14].

Recent years have seen a rising interest and awareness of the clinical significance of cardiac AMR for a number of reasons. Among them, its formal recognition by the International Society for Heart and Lung Transplantation (ISHLT), general consensus on its defining pathologic criteria, and a growing body of clinical experience [15–18]. Additionally, new advances in solid-phase assays have allowed a more accurate and discriminate appraisal of preformed or de novo antibodies [19, 20] that are usually implicated in its pathophysiology. Emerging animal models of cardiac AMR will become important platforms to further elucidate its mechanisms and to test candidate therapies.

Predisposing Risk Factors

Recipient Demographics

AMR is more likely to be found in females, patients with congenital heart disease, and those of younger age among an adult population [1–4]. Recent findings suggest that pathologic AMR is also clinically relevant in the pediatric cardiac transplant population even in the absence of pre-formed antibodies [5].

Preformed Antibodies

While AMR has been found to occur both early and late after transplantation, presensitization remains one of its main risk factors. From mainly observational studies, situations associated with preformed antibodies include previous transplantation, transfusion, and pregnancy [1, 3, 21]. Patients implanted with cardiac assist or replacement devices can also develop alloantibodies, the extent of which may vary with the type of support. It appears that continuous-flow left ventricular assist devices (LVAD) are associated with lower PRA levels than are pulsatile-flow LVADs [22, 23]. Platelet transfusions during LVAD implantation have been shown to be a risk factor associated with the development of human leukocyte antigen (HLA) class I immunoglobulin G (IgG) antibodies [24]. Furthermore, LVAD recipients develop prominent B-cell activation as evidenced by increased production of anti-HLA class I and class II antibodies [24].

Positive Post-operative Donor-Recipient Crossmatch

A positive post-operative donor-recipient crossmatch is highly associated with histologic evidence of AMR, again suggesting a strong etiologic role of pre-formed alloantibodies in AMR [6, 12, 25, 26]. In a small group of 44 patients, Michaels et al. demonstrated that a positive flow cytometry T-cell crossmatch was significantly observed in 32 % of AMR-positive recipients compared with 12 % of controls without AMR on endomyocardial biopsy (EMB) [3].

Nowadays with better antibody detection assays and virtual crossmatching, a situation where a highly-sensitized patient is transplanted and allowed to have a positive final crossmatch is usually avoided.

Ischemia

The exact mechanism for cardiac dysfunction and poor survival after prolonged allograft ischemic time remains unclear, but it is in part likely due to triggering of the innate immune response within the allograft [27]. These hearts may display histologic findings similar to those observed during AMR, suggesting that ischemic graft injury resulting from delayed ischemic time may predispose cardiac transplant recipients to AMR by triggering the host adaptive immune responses as well [28, 29]. However, several studies have shown no difference in graft ischemic time when comparing patients diagnosed with AMR to those with the histopathologic diagnosis of acute cellular rejection [3, 25]. This has recently been substantiated by Singhal et al. demonstrating that increased ischemic time is not associated with higher incidence or frequency of AMR post-transplant [30].

Muromonab-CD3 Sensitization

The use of muromonab-CD3 (Orthoclone OKT3®), a murine monoclonal antibody, post-transplant for induction or for rejection treatment is a significant risk factor for AMR. This is especially true in patients who become sensitized and develop human anti-mouse antibody. In our experience, these patients uniformly exhibited immunohistologic changes on EMB which were indistinguishable from those seen in AMR, and suffered poor outcomes [31, 32]. OKT3 was voluntarily discontinued a few years ago because of safety issues. Yet, the use of this drug contributed much to our early description and understanding of cardiac AMR.

Viral Infection

Preoperative seropositive status for cytomegalovirus (CMV), grafting of organs from seropositive donors or a postoperative CMV infection, are associated with an increased risk of AMR and chronic rejection. These same factors are associated with chronic rejection in kidney, lung, and liver transplant recipients [33, 34]. Complex interplay between immunological and non-immunological factors such as CMV infection, HLA mismatch, and AMR after transplant can ultimately lead to endothelial injury and exaggerated repair response which leads to the development of cardiac allograft vasculopathy (CAV), a major cause of late graft failure and subsequent poor survival in patients following heart transplantation [35, 36].

De-novo Donor-Specific Antibodies Post-transplantation

Recent data suggest that cardiac AMR is strongly correlated with the development of anti-HLA antibodies post-transplantation [7, 37]. Detection or absence of donor-specific antibodies (DSA) does not, however, confirm or exclude the diagnosis of AMR. As demonstrated by Bocrie et al. in a study of renal transplant recipients, DSA were present in 58.3 % of renal allografts with chronic allograft nephropathy but were detectable in the peripheral blood in only 16.6 % of cases [38]. Also, DSA may be entirely bound to the allograft and undetectable in peripheral blood even after a biopsy-proven AMR episode. The precise role of non-HLA antibodies post-transplant in AMR occurrence remains unclear. Recently, Nath et al. showed that non-HLA antibodies directed against cardiac myosin and vimentin were elevated in recipients who subsequently developed AMR [39]. However, antibodies to major histocompatability class I-related chain A (MICA) have not been shown to correlate with rejection episodes, survival, and CAV following heart transplantation [40]. Therefore, current 2013 ISHLT guidelines focus on pathologic features of AMR with DSA detection supportive of a rejection episode, but are not essential for diagnosis [15, 16].

Immunology/Pathways of Cardiac AMR

New information about the human immune responses has emerged which is highly relevant to the pathogenesis of AMR in allografts. The innate immune response system, which evolved to defend humans against foreign invaders, is also activated by other injuries deemed dangerous to the organism, such as medical device implantation, brain death, or ischemia-reperfusion injury (IRI). It has been recently emphasized that both the innate and adaptive immune responses are important in mediating allograft injury after transplantation [27, 28, 41, 42].

Innate immunity refers to the non-specific immune system originally described by Janeway, whose elements include macrophages, neutrophils, natural killer cells, platelets, endothelial cells, cytokines, coagulation proteins and complement components [28, 43, 44]. The system involves pattern recognition receptors (Toll like receptors, TLR) on these cells that respond to specific pathogens or injury associated molecular profiles [28, 41, 43–45].

The innate system can initiate an adaptive immune response in transplanted patients because alloantigens are always presented in the context of allograft tissue injury. A variety of injury related molecules are released during IRI and these molecules are recognized by TLR receptors on dendritic cells, vascular endothelial cells and lymphocytes leading to dendritic cell activation and antigen recognition. Inflammatory responses include cytokine storms, complement activation and leukocyte chemotaxis that further accelerate and modify the allograft immune response.

By contrast, adaptive immunity is highly specific and is triggered by the recognition of specific antigen and can be reprised because of the specific memory function of its elements, the T and B lymphocytes [11, 46–48]. T cells recognize antigen as peptides bound to Major Histocompatibility Complex (MHC) proteins and proliferate in response; B cells proliferate in response to T-cell antigenic recognition and also can recognize antigen themselves through their immunoglobulin receptors. These specific responses generate specific effector mechanisms including antibody production, complement activation, coagulation, and CD8 mediated cytotoxicity. These effector mechanisms functions trigger innate immune responses of further coagulation, kinin, and complement activation and injury [47, 49–51] (Fig. 22.1). Details of the allo-immune response are covered elsewhere in this textbook.

B cells are critical players in the pathogenesis of the antibody mediated immune response. B-cell immunoglobulin protein receptors are uniquely coded to a specific antigen. When the antigen is encountered in its native form (not in association with MHC antigens as required by T cells), the B cell can undergo activation to specific plasma cells and memory cells. T-cell dependent activation requires a co-stimulatory signal from a corresponding specific Th2 cell, a T helper cell, that secretes cytokines leading to clonal expansion and differentiation into plasma cells and memory cells. With T-cell independent antigens, the activation signals of antigen recognition and co-stimulation are both provided by the antigen. In some cases the co-stimulatory signal is supplied by TLR receptors on cells such as endothelial cells. T-cell independent antigen stimulation results in differentiation of B cells into Immunoglobulin M producing plasma cells, exclusively. Fully activated B lymphocytes of either type possess surface markers CD 19, part of the antigen receptor, and CD 20, a marker of complete activation, particularly important in T-cell independent antigen recognition. Activated B cells can produce small quantities of specific immunoglobulin and those responding to T-cell dependent antigens can undergo immunoglobulin class switching [52–54].

Plasma cells are end stage cells that produce large quantities of an antigen specific antibody of a defined immunoglobulin class. They are incapable of antigen recognition and do not possess the usual B-cell markers CD19 and CD20. They do

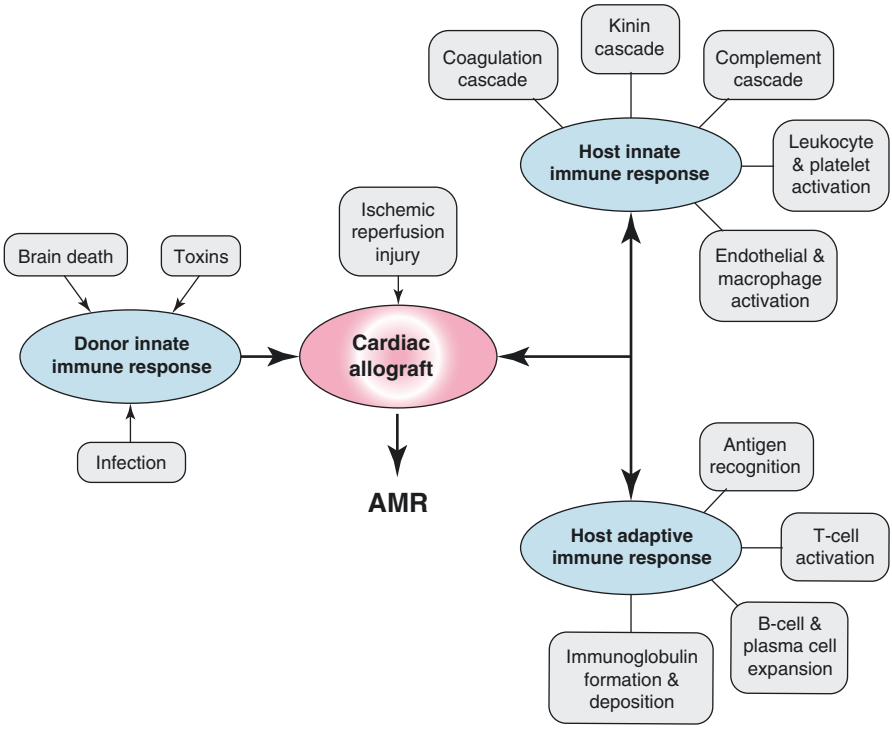


Fig. 22.1 Interplay of Donor and host immune responses in cardiac AMR

possess other surface markers including CD27, CD 38 and CD 78 and IL-6 receptor. They lack the common leukocyte antigen, CD45 [55–57].

The other important effector cells of the antibody adaptive immune response are macrophages, neutrophils, platelets and NK Cells, which possess Fc receptors for immunoglobulin as well as TLR receptors and complement receptors. These effector cells, while not possessing specific antigen recognition properties, are stimulated through these cell surface receptors to produce specific proteins that act as effectors of the innate immune response, chiefly through the coagulation, kinin and complement cascades [41, 44, 47, 58, 59].

In AMR, the principal site of immune interaction is the vascular endothelium. Endothelial cells function to present antigen and act as co-stimulatory cells to T cells. They possess TLR receptors that allow them to respond to injury associated molecular profiles created during allograft injury or ischemia. This interaction leads to endothelial activation and cytokine release which triggers inflammation, dendritic cell activation, and also lymphocyte activation. Endothelial cells express CD40 and other molecules which can contribute to T-cell activation (CD58; CD134 ligand, ICOS ligand). CD 40 is critical in providing cognate T-cell help for B-cell Ig production and class switching. CD 40 and its ligand have been demonstrated in cardiac allografts undergoing rejection [59–61].

Antibodies produced against MHC and other antigens released during tissue injury bind to MHC antigens on the vascular endothelium. These antibodies may or may not fix complement which can accelerate the level of injury of the endothelium. Importantly, the antibodies also can bind immune cells with receptors for the Fc portion of the immunoglobulin molecule, including macrophages, NK cells, B lymphocytes, neutrophils, and platelets, which further accelerate allograft injury [62–65].

In summary, the reaction of the host to an allograft is a complex interplay of factors involving both the innate and adaptive immune responses. The centerpiece of these reactions is the endothelium of the microvasculature which acts both as an active participant and the target of the destructive elements of this response. If the vascular endothelium is repeatedly injured by these processes, the graft will experience ischemic damage that either eventuates in global myocardial damage and heart failure or allograft coronary artery disease and graft loss [66, 67].

Pathology of Cardiac AMR

In 2005, a consensus conference was held at the National Institutes of Health concerning AMR in solid organ allografts, which led to a concerted effort to standardize the definition of AMR in hearts and the approach to diagnosis [8, 29].The ISHLT 2005 guidelines recommended diagnosis of AMR based on interpretation of pathologic changes in conjunction with cardiac allograft dysfunction and/or hemodynamic compromise and the presence of DSA [29]. AMR has since been recognized to exist along a spectrum from an asymptomatic phase with occurrence of DSA in isolation to a symptomatic phase with allograft dysfunction and hemodynamic compromise. This is a clinically useful distinction as asymptomatic AMR has been shown to be associated with poorer outcomes [1, 3, 17, 18, 68, 69]. Furthermore, a universally accepted definition for allograft dysfunction does not exist. The ISHLT 2005 working formulation for cardiac AMR was further refined in 2013. For the remainder of this section, the pathologic features published in 2013 will be described and illustrated. Table 22.1 contrasts the recommendations across the three versions of the ISHLT guidelines. A key difference between the 2005 and 2013 ISHLT guidelines is the proposed shift from a clinical to pathologic diagnosis [15, 16].

Specimen Handling Considerations

Specimen requirements for cardiac biopsy interpretation were standardized in the first ISHLT grading schema. At least four biopsy fragments of viable non-scarred myocardium are necessary to ensure an adequate sample for interpretation. Early studies of AMR in cardiac allografts used frozen tissue samples obtained at the time of routine endomyocardial biopsy. Such samples were considered highly desirable

Table 22.1 Comparison of antibody-mediated rejection grading across ISHLT schemata [16, 29, 70]

	1990 grading schema [70]	2005 grading schema [29]	2013 grading schema [16]
Required samples	Four pieces of myocardium	Three pieces of myocardium	Three pieces of myocardium
Sample type to be used for IHC	Frozen tissue should be saved for potential IF to detect 'vascular' rejection	Frozen tissue or tissue fixed for routine processing could be used for detection	Same as 2005
IHC surveillance	Optional	Only in biopsies suspected histologically to be positive	2 biopsies in first month; then at 1, 3, 6 and 12 months
Histopathology of AMR	Vasculitis, edema without cellular infiltrate	Edema, capillary swelling, intravascular macrophages or neutrophils, interstitial edema	Same as 2005
IHC, IF method	IF optional with IgG, IgM, C3 scoring as additional information	IgG, IgM, IgA, C3d and/or C4d or C1q, fibrin	C4d and/or C3d required; IgG, IgM, fibrin optional; HLA for capillary integrity assessment
IHC, IP method	None	IP for CD68 or C4d and CD34 or CD31 to define capillaries	IP for CD68 and C4d; CD31, CD 34 optional to define capillaries; C3d optional
AMR scoring	Humoral Rejection	AMR positive (AMR1) if positive histology, IHC, graft dysfunction, and DSA	pAMR 1–3 based only on histology and IHC
DSA	None required	Required for AMR positive (AMR1)	Should be checked with biopsy, but not required for pAMR diagnosis
Follow up of AMR	None required	None required	After 2 weeks until negative by IHC

ISHLT international society for heart and lung transplantation, *IHC* immunohistochemistry, *IF* immunofluorescence, *IP* immunoperoxidase, *AMR* antibody-mediated rejection, *HLA* human leukocyte antigen, *DSA* donor-specific antibodies

for this purpose in the original ISHLT grading schema because they obviate the artifacts associated with routine formalin fixed paraffin embedded (FFPE) tissue processing which includes tissue fixation, dehydration and lipid extraction associated with xylene infiltration prior to paraffinization. Newer experience suggests that these processing issues can be surmounted by using other fixatives and different immunohistochemical methods. The recent updating of the ISHLT schema for cardiac allografts allows for either frozen or FFPE samples to be used. Reagents and procedures vary depending on the sample type [70] (Table 22.2).

Table 22.2 2013 ISHLT pAMR criteria [16]

	Histologic features	IF features	IP features	Comments
pAMR 0	No suspicious findings	No findings	No findings	No findings
pAMR 1 (H+)	Capillary endothelial swelling or denudation; intravascular accumulation of macrophages or neutrophils; interstitial edema	Negative	Negative	May see weak IF or IP staining that does not qualify as positive
pAMR 1 (I+)	None or focal features as above	Diffuse or multifocal intense staining with C4d or C3d in capillaries	Diffuse or multifocal intense staining of capillaries with C4d and CD 68 if used	Either IF or IP features qualify as positive; Intensity is similar to controls
pAMR 2	Capillary endothelial swelling or denudation; intravascular accumulation of macrophages or neutrophils; interstitial edema	Diffuse or multifocal intense staining with C4d or C3d in capillaries; strong HLA staining of capillaries	Diffuse or multifocal intense staining of capillaries with C4d and CD 68 if used	Either IF or IP features qualify as positive
pAMR 3	Capillary endothelial swelling or denudation; intravascular accumulation of macrophages or neutrophils; interstitial edema; intravascular thrombi; myocyte necrosis without cellular rejection; interstitial tissue debris	Diffuse or multifocal interrupted staining with C4d or C3d in capillaries; weak staining of HLA ; fibrin accumulation; C3d or C4d autostaining of necrotic myocytes	Diffuse or multifocal intense staining of capillaries with C4d and CD 68 if used; CD31 or CD34 staining of capillaries demonstrates damaged walls or capillary loss	Histologic features hard to distinguish from severe rejection (ISHLT 3R)

ISHLT international society for heart and lung transplantation, *IF* immunofluorescence, *IP* immunoperoxidase, *H* histopathology, *I* immunopathology, *HLA* human leukocyte antigen

Histopathologic Features of Cardiac AMR

In acute AMR, there are well defined histopathologic features predominantly involving the capillaries (Fig. 22.2a–c). The capillaries are swollen with enlarged endothelial cells possessing obvious features of activation by electron microscopy [32]. The endothelial cells can occlude the lumina. Often there are also adherent

macrophages and/or neutrophils in the capillaries that cause the vessels to have a cellular, rope like character. In later biopsies of AMR when capillary damage has been prolonged, the capillaries may appear discontinuous or even absent, giving a faulty innocuous appearance. In such cases, there is often significant interstitial edema manifested as widening of interstitial spaces, often with a bluish color. As this process continues unabated, the capillaries disappear, the edema dissipates and the process becomes very difficult to distinguish from a negative biopsy without evidence of any acute rejection. Two groups have documented that the histopathologic features do not correlate well with the immunopathologic features [71, 72].

When AMR becomes severe, there may be associated necrotic debris in the interstitial spaces and extravasated leukocytes and platelets, providing the obvious appearance of severe injury [17, 32, 73, 74].

Immunopathologic Features of Cardiac AMR

To diagnose AMR, biopsies must be subjected to immunohistochemical (IHC) or immunofluorescence (IF) staining to detect immune reactants of AMR, especially complement components. By immunohistochemistry on FFPE prepared samples, macrophages are detected by CD 68 staining, capillary damage is defined using CD 34 or CD 31, and C4d is detected in capillaries [73] (Fig. 22.2g–i).

There is less agreement about the significance of the distribution of the C4d staining (all capillaries or just focal areas) and the intensity of C4d staining provided on a semi-quantitative scale. More studies must be done to correlate various patterns of staining with patient outcomes in order to see what patterns are most significant. C3d can be sought by immunohistochemistry, but no large studies have been published on the value of this staining method.

By IF staining, C4d and/or C3d can be detected in capillaries and issues of distribution and intensity are significant (Fig. 22.2d, e). One group has published that both C3d and C4d are needed to accurately diagnose AMR by IF. This result is controversial. Other IF reactants which can expand the diagnostic accuracy include IgG or IgM and HLA-DR which is upregulated on capillaries in acute AMR and downregulated when AMR becomes severe and longstanding. Detection of HLA DR by IF is optional. Evaluation of IF staining for fibrin is also optional. Fibrin staining has been shown by at least two groups to correlate with severity of AMR and with poor outcome [75–78] (Fig. 22.2f).

Outstanding Pathology Controversies

The most vexing issue of cardiac transplant pathology interpretation is the interplay of factors which can affect the histologic and immunopathologic findings as previously described. Pathologic examination relies on the expression of proteins and

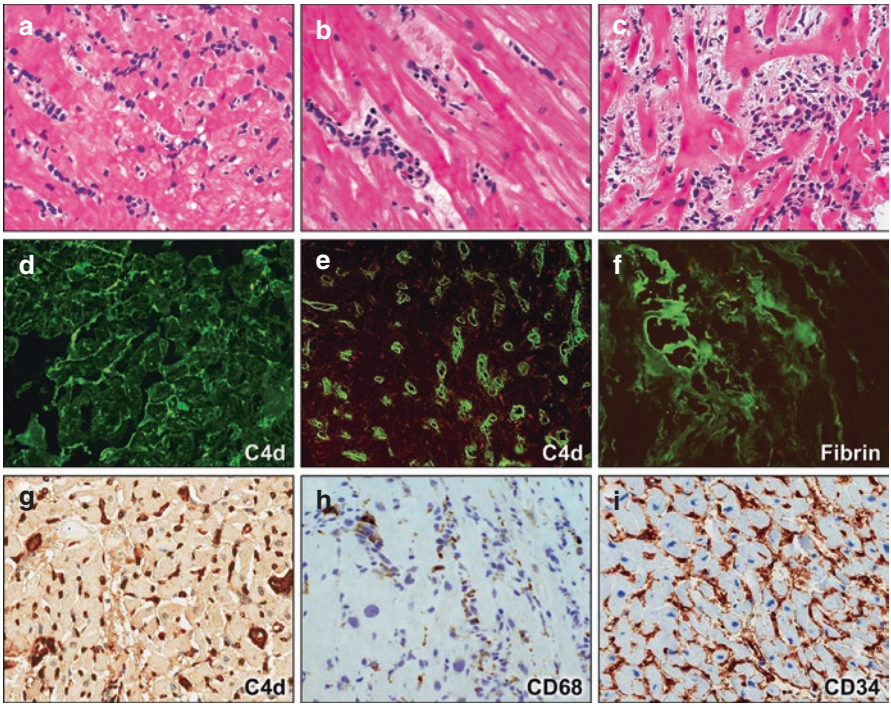


Fig. 22.2 Pathology of Cardiac AMR. (**a**) Endomyocardial biopsy showing obvious adherence of macrophages to swollen endothelial cells throughout the fragment (hematoxylin and eosin (H&E) stain, 10×). Immunofluorescent (IF) staining for C4d was negative. Diagnosis: pAMR 1 (H+). (**b**) Endomyocardial biopsy shows prominent intravascular macrophages, neutrophils and prominent endothelial cells (H&E stain, 20×). IF staining was strongly positive for C4d (panel **e**). Diagnosis: pAMR 2. (**c**) Endomyocardial biopsy from patient with persistent AMR over several weeks. Capillaries are swollen with adherent macrophages. Interstial regions are edematous and contain cellular debris as well as more macrophages (H&E stain, 20×). IF staining was positive for C4d and fibrin (panel **f**). Diagnosis: pAMR 3. (**d**) C4d on frozen section of endomyocardial biopsy from patient without significant histologic features of AMR on the current biopsy, but obvious AMR on previous biopsies. Strong linear stained capillaries are seen throughout the section (IF stain, 10×). Diagnosis: pAMR 1 (I+). (**e**) C4d on frozen section of endomyocardial biopsy from patient with obvious histologic evidence of AMR (panel **b**). Round capillary profiles show intense staining (IF stain, 10×). Diagnosis: pAMR 2. (**f**) Endomyocardial biopsy (same patient, panel C) showing fibrin intensely stains swollen capillary profiles and extends into the neighboring interstitium (IF stain, 20×). Diagnosis: pAMR 3. (**g**) Immunohistochemical (IHC) stain for C4d from patient suspected of having AMR on the basis of prior history of AMR. Tissue previously fixed in formalin was used and shows strong brown outlining of capillaries. Staining of similar intensity was found in the control biopsy (immunoperoxidase (IP) stain, 10×). Diagnosis: pAMR 1 (I+). (**h**) IHC stain for CD68 to highlight macrophages from the biopsy shown in panel G. Strongly stained brown macrophages are scattered throughout the capillaries (IP stain, 20×). Diagnosis: pAMR 1 (I+). (**i**) IHC stain for CD34, a marker of activated endothelial cells and platelets. Capillaries have ragged profiles which extend into the interstitial spaces suggesting neovascularization. Patient had three previous episodes of AMR during the first year post-transplant (IP stain, 10×). Diagnosis: pAMR 1 (I+)

cells in a tiny sample of the heart transplant tissue. Traditional pathologic monitoring relies on interval biopsies which are morbid and prone to artifacts of sampling, interpretation, sample handling, and test method selection.

Fortunately, the genes and proteins involved in these complex interactions have been defined in experimental systems and molecular and proteomic methods are emerging to allow monitoring in vivo. The interplay between serum and tissue sampling will also require definition [79–82].

Molecular profiling using non overlapping pathogenesis based transcripts (PBT) have been successfully used to complement pathologic assessment of renal transplant biopsies and certain transcripts have shown high correlation with histopathology, DSA activity and poor outcome in renal AMR patients [79]. The transcript sets each define relevant biologic events in transplantation such as parenchymal injury, endothelial activation, infiltration by T cells or macrophages, and gamma interferon induced inflammatory events. The transcript sets were independently developed in experimental systems and tested in human transplant renal biopsy tissue. When the same approach was applied to cardiac transplant biopsies, expression of transcript sets reflecting T-cell and macrophage infiltration, and y -interferon effects correlated strongly with each other and with transcripts indicating tissue/myocardium injury. This molecular phenotype correlated with Quilty ($p < 0.005$), capillaritis ($p < 0.05$) and decreased left ventricular ejection fraction (LVEF) ($p < 0.007$), but not with the histologic diagnosis of acute cellular rejection. The study was done prior to the ISHLT grading schema characterizing AMR but capillaritis is a reasonable correlate of AMR. Further work is needed to validate this interesting study [79, 82].

A recent pilot study using plasma proteomics has also been reported in renal transplant patients, providing evidence that protein concentrations in plasma may provide a relevant measure for the occurrence of biopsy-proven acute rejection and offers a potential tool for immunologic monitoring [83].

Until markers of these diverse processes are available, we will have to rely on careful clinical-pathologic correlation among providers. Hopefully, molecular profiling based on discrete transcript sets and proteomic monitoring will eventually solve this conundrum.

Clinical Features of Cardiac AMR

Incidence/Prevalence

The true incidence of cardiac AMR has not been well documented in the absence of routine screening in asymptomatic patients. It is therefore likely that it had been underreported prior to 2011. Much of the literature instead describes the prevalence of symptomatic AMR. The prevalence of lone symptomatic AMR ranges between 10 and 15 %, whereas the prevalence of AMR when routinely surveilled (symptomatic and asymptomatic) or when diagnosed concurrently with acute cellular rejection (mixed rejection) may surpass 40 % [10, 84–86]. This wide range is also the result of the lack of prior standardized diagnostic criteria as well as the diversity of the populations studied in their predisposition to AMR.

Time to Occurrence

Observational studies indicate that cardiac AMR tends to become manifest early after transplantation [2, 3, 77, 84, 87]. Additionally, the risk of recurrence is higher in heart transplant recipients who have three or more episodes of AMR in the first 3 months post-transplant, and repeat episodes of AMR are usually clustered soon after the first episode occurs. AMR can occur late after heart transplantation, though less commonly, and is usually associated with de novo DSA and poor outcomes [67, 88]. It is difficult sometimes to separate early from late AMR since most reports of late symptomatic AMR come from transplant programs that do not routinely screen asymptomatic patients earlier on.

Presentation

Most episodes of cardiac AMR are mild in severity and perhaps silent [87]. When clinically manifest, there are no signs or symptoms specific to AMR. Instead, patients typically present with congestive (shortness of breath, dyspnea on exertion, cough) or low-flow (fatigue, exercise intolerance) symptoms that are common to overt heart failure from any cause. Signs on physical exam will vary depending on the patient's acuity and whether a single or both ventricles are involved. A lower than usual blood pressure, an elevated central venous pressure, or a new S3 gallop are all warning signs that mandate immediate attention and further diagnostic investigation, preferably in the hospital. Signs and symptoms can be subtle and mild in a stable outpatient or severe and catastrophic in another with cardiogenic shock. Unlike for acute cellular rejection, patients with AMR are more likely to present with allograft dysfunction, hemodynamic compromise, or heart failure [1, 2, 4, 6, 13, 14, 89, 90].

On echocardiogram, besides systolic dysfunction, AMR may be associated with abnormal diastolic function (Fig. 22.3), increased left ventricular mass [91]. Findings on 12-lead electrocardiogram are also non-specific but we have found

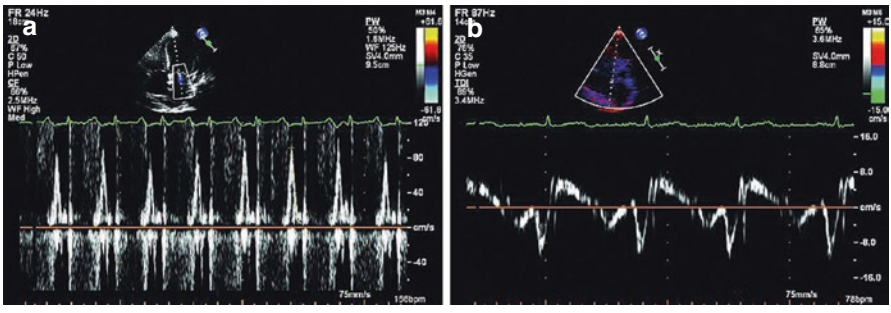


Fig. 22.3 Diastolic abnormalities on echocardiogram. (**a**) Pulse wave Doppler of the mitral valve inflow in a patient with acute AMR. Increased E/A ratio. The Mitral Valve Deceleration Time measures 61 msec. (**b**) Tissue Doppler of the septal mitral valve annulus showing reduced e' velocity and reversal of e'/a' ratio

diffuse low QRS voltage on presentation to be invariably associated with fatal acute AMR. Blood tests abnormalities are typically related to the patient's other co-morbidities and circulatory stability in general. Non-invasive methods including biomarkers to detect rejection may be abnormal with acute AMR, but to date none can exclusively be used to reliably diagnose it or rule it out. As such, cardiac AMR remains a pathological diagnosis on endomyocardial biopsy.

Outcomes

The chances of *pathological* resolution of asymptomatic cardiac AMR when left untreated are related to its severity and time of occurrence since transplant (Fig. 22.4). Milder AMR episodes and those taking place beyond 12 months post-transplant are more likely to resolve or improve on follow up biopsies [87]. Even then, asymptomatic cardiac AMR tends to recur and has been linked to a higher risk of CAV [18] and cardiovascular mortality [92] (Fig. 22.5).

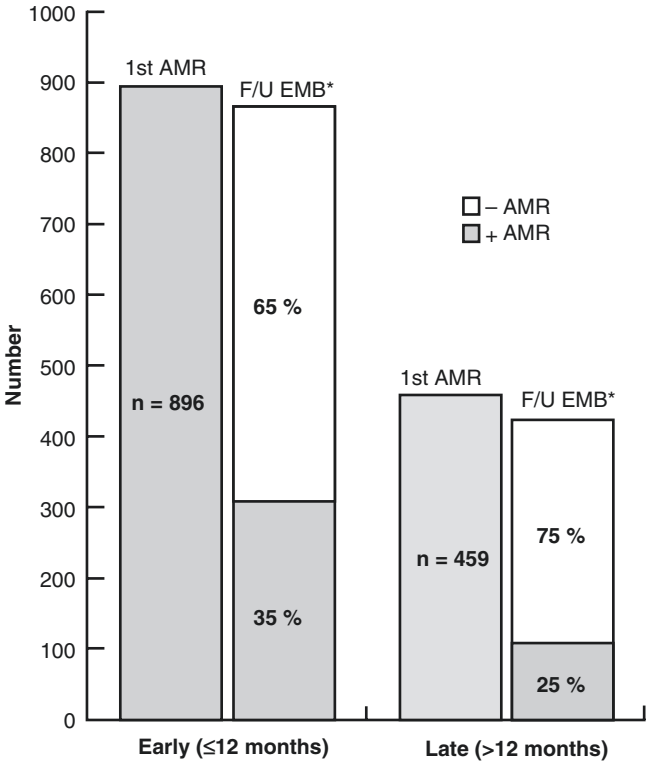


Fig. 22.4 Outcome of the Initial Antibody-mediated Rejection (AMR) on Next Follow up. (F/U) Endomyocardial Biopsy (EMB) (Reprinted from the Kfoury et al. [87], with permission from Elsevier) *AMR status was not checked for or reported in a few follow-up EMBs hence the small differences in totals

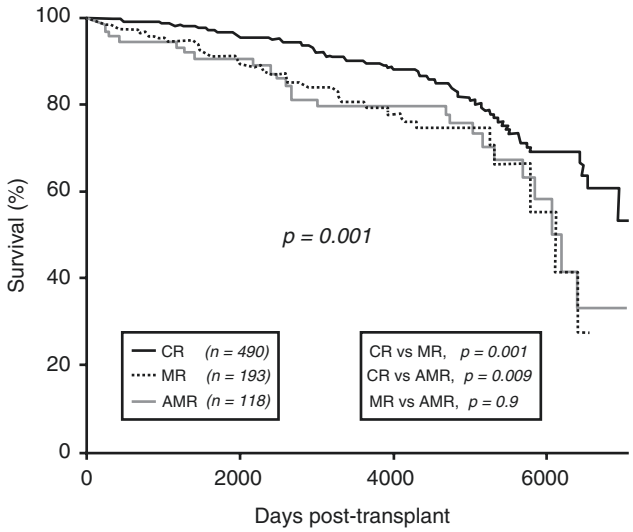


Fig. 22.5 Kaplan-Meier survival curves by rejection pattern (Reprinted from the Kfoury et al. [92], with permission from Elsevier) *CR* cellular rejection, *MR* mixed rejection, *AMR* antibody-mediated rejection

Definitive therapeutic success with acute cardiac AMR is difficult to gauge given the limited experience and the lack of standardized approach. Better odds of recovery appear to be related to timely and aggressive intervention. The availability of newer agents specifically targeting various steps of the humoral immunologic response allows for a multi-target approach that may be both more effective and safer.

Besides the immediate clinical challenges that acute AMR poses, patients who develop a pattern of repeated AMR have a many fold higher risk of cardiac allograft vasculopathy, chronic cardiac dysfunction, and mortality [3, 7, 9, 17, 68, 89]. An accelerated form of diffuse coronary artery disease developing over weeks has been associated with AMR and notoriously portends very poor outcomes [93]. The nature of the mechanistic link between *microscopic* AMR and *macroscopic* CAV remains to be fully elucidated. It is also conceivable that AMR and CAV are part of one pathological-clinical continuum.

Treatment of Cardiac AMR

The diagnosis of AMR is made by pathological findings. The decision of whether to treat and with what requires careful consideration and will take into account the patient's clinical presentation, biopsy grade, allograft function, and the presence of donor-specific antibodies (Fig. 22.6). General recommendations for the treatment of AMR were published by the ISHLT in 2010 [94]. As more is learned about the pathophysiology and consequences of AMR, additional therapeutic strategies are being tried. The alloantibody response is complex, however, and caution needs to be

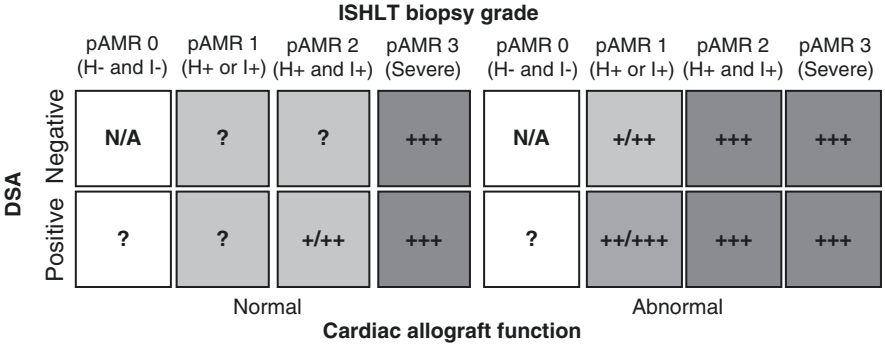


Fig. 22.6 Determinants of the likelihood to treat cardiac AMR [87]. + likely, ++ more likely, +++ yes, *ISHLT* international society for heart and lung transplantation, *H* histopathology, *I* immunopathology, *DSA* donor-specific antibodies, *N/A* not applicable

taken as these new treatments have potential toxicities and disruptive effects on the modulating action of the immune response [95]. Ultimately, there is great need for randomized controlled trials in the prevention and treatment of AMR.

ISHLT Guidelines[1] *[94]*

Class IIa

1. The following treatments can be used to disrupt the immune-mediated injury of the heart allograft in AMR: (1) high-dose intravenous (IV) corticosteroids; (2) cytolytic immunosuppressive therapy.
2. The following treatments may be used to remove circulating anti-HLA antibodies or decrease their reactivity: (1) plasmapheresis; (2) immune apheresis (immunoadsorption); (3) IVIg.
3. The following treatments are used to maintain adequate cardiac output and systemic blood pressure: (1) IV inotropes and vasopressors; (2) mechanical circulatory support.
4. When AMR is suspected, EMB examination should be expanded to include immunohistochemistry stains for complement split products and possible antibody.
5. Recipient serum should be screened for presence, quantity and specificity of anti-donor (HLA) antibodies.
6. Follow-up EMB should be performed 1–4 weeks after initiation of therapy and include immunohistochemistry examination.
7. Adjustment of maintenance immunosuppressive therapy may be considered. This can include increase in the dose of current immunosuppressive agent(s), addition of new agent(s) or conversion to different agent(s).

[1] All recommendations are Level of Evidence C.

Class IIb

1. Systemic anticoagulation may decrease intravascular thrombosis in the heart allograft.
2. Emergent retransplantation may be considered if the above measures do not restore acceptable heart allograft function, but outcomes in this situation are unfavorable.

Therapeutic Targets: Current and Future

T-Cell Inhibition

B-cell activity, including activation, isotype switching, and antibody production, is tightly regulated by T cells, therefore therapy targeting T-cell activity is an important aspect of treatment for AMR. Antithymocyte globulin (ATG) is prepared by immunizing rabbits or horses to macerated human thymus which contains predominately T cells, but also B cells, plasma cells, and dendritic cells, resulting in multiple antilymphocyte immunoglobulins. Various preparations are available and include rabbit antithymocyte globulin (rAThG), rabbit anti-T cell globulin (rATcG), equine antithymocyte globulin (eAThG), and equine antilymphocyte globulin (eALG). rAThG is the most commonly used preparation in the United States. ATG is very effective at killing or modulating T cells and is used as an induction agent and for treatment of cellular rejection [94, 96–100]. In addition to T-cell targets (CD3, CD4, CD8, and T-cell receptors), ATG contains antibodies to B-cell and plasma cell antigens and antigens expressed on both T and B cells, including CD20, CD30, FcR, CD126, and CD138 [101–103]. ATG may therefore be effective in the treatment of AMR beyond its inhibition of T cells via B-cell apoptosis, blockade of cytokine receptors, and binding of inhibitory receptors. It is generally used in moderate to severe cases of AMR associated with graft dysfunction and/or hemodynamic compromise. A usual course of treatment is between 3 and 7 days, and a CD3-count guided strategy may result in lower adverse events [103, 104].

The primary effect of calcineurin inhibitors (tacrolimus, cyclosporine) is inhibition of T-cell activation; there is no conclusive evidence for activity on T-cell-independent B-cell antibody production. Based on data showing less rejection in patients treated with tacrolimus/mycophenolate mofetil (MMF) versus cyclosporine/MMF, some advocate changing from cyclosporine to tacrolimus in a patient with AMR [105]. Rapamycin is an mTOR inhibitor that inhibits T-cell activity by blocking transcription of IL-2. Unlike the CNIs, rapamycin may also inhibit B-cell antibody production and proliferation via T-cell independent mechanisms [106, 107]. In clinical studies, rapamycin has been associated with decreased incidence and slower progression of cardiac allograft vasculopathy [108–110], a process likely related to AMR-mediated mechanisms. Changing from MMF to rapamycin or the addition of rapamycin is a reasonable strategy in a patient with AMR.

B-Cell Depletion/Inhibition

The spleen is the largest lymphoid organ in the body and houses antibody-producing memory B cells and plasma cells [111]. Splenectomy has been successfully used as a rescue therapy in cases of severe AMR in kidney transplant recipients refractory to standard therapy [112–114], however data for its use in heart transplant patients is lacking. When used, it is often combined with other B-cell targeted therapies to achieve maximal response.

B-cell depletion is also achieved with the administration of antibodies which bind antigens expressed on the surface of B cells. Agents used include the anti-CD52 antibody alemtuzumab as well as antithymocyte globulin, both of which deplete T cells in addition to B cells [100, 115–118]. Recently, the anti-CD20 antibody rituximab has been increasingly used. CD20 is not present on pro-B cells or mature plasma cells, thus it effectively eliminates peripheral B cells, but does not prevent the regeneration of B cells from precursors and may not directly decrease immunoglobulin levels. Research and therapeutic interest in rituximab has been greatest in the kidney transplant field [119–121]. A few case reports and series describe the use of rituximab in the treatment of AMR in cardiac transplant recipients, always as part of a multi-therapy regimen; therefore it is difficult to determine the exact efficacy of rituximab [90, 122–125].

Additional B-cell depleting agents developed for the treatment of lymphoma and autoimmune diseases and which may be useful in transplantation include the anti-CD20 antibodies ofatumumab and ocrelizumab, which are potentially more potent, have a lower risk for immunogenicity, and have less complement activation [126–130] CD22 is an inhibitory receptor that remains present as B cells mature and after expression of CD20 is lost. Epratuzumab is an anti-CD22 antibody shown to reduce B-cell numbers as well as inhibit their activation and proliferation [131]. Anti-CD19 antibodies are being developed and have the added advantage of acting against B cells and plasma cells [132].

Agents that target co-stimulatory receptors on the surface of B cells may also have therapeutic benefit in AMR. BAFF is a costimulator critical for B-cell differentiation, survival and expansion; naive B cells in particular are sensitive to BAFF depletion. Belimumab and atacicept target BAFF and have shown potential in the treatment of systemic lupus erythmatosus [133, 134]. Co-stimulation ligand receptor pairs, such as CD40-CD154, present on T and B cells are essential for activation. Anti-CD154 antibodies were promising but failed in clinical trials due to thrombotic complication [135–137]. Unlike CD154, CD40 is not expressed on platelets and may not have the same thrombotic risk. Anti-CD40 antibodies are being tested in autoimmune diseases and transplantation [137].

B-cell depletion may have adverse effects [95]. Regulatory B cells inhibit effector T cells and facilitate the expansion of regulatory T cells, thereby potentially promoting tolerance. Therapies that target B cells may also deplete these important regulatory B cells. Further research is needed to identify the optimal agents and timing of administration that balance the effects of B cell depletion on rejection and graft survival.

Plasma Cell Depletion

Plasma cells produce large amounts of IgG, a proportion of which will be misfolded and require degradation by the proteasome. Bortezomib acts as a proteasome inhibitor and therefore results in accumulation of misfolded proteins and apoptosis of plasma cells. Developed for the treatment of multiple myeloma, bortezomib has been used in the treatment of AMR in transplant recipients, and may be particularly useful by preferentially targeting alloantibody-producing cells [138–142]. Toxicities with bortezomib have been reported, and randomized controlled trials are needed to formally evaluate this therapy prior to widespread adoption.

Antibody Removal

Immunoadsorption (IA), plasmapheresis (PP), and therapeutic plasma exchange (TPE) effectively and quickly remove circulating antibodies and have been used for desensitization and treatment of AMR [14, 56, 143–145]. A single exchange of one plasma volume with PP or TPE removes approximately two-thirds of all solutes in the plasma; therefore multiple sessions are required for adequate antibody removal. According to ISHLT guidelines, common protocols consist of 1–5 sessions of PP per week for 1–4 weeks [94]. The plasma volume is usually replaced with albumin or fresh frozen plasma. IA uses regenerable adsorbers that are able to process high volumes of plasma and remove antibody through affinity adsorption. It is more effective and specific at antibody removal, generally achieving >90 % antibody reduction with two sessions, but does not remove circulating cytokines. It is less likely to cause hemodynamic instability, however it is less widely available. Additional therapies targeting antibody activity or production should be combined with these methods of antibody removal to minimize the rapid rebound in antibody titers that occurs following treatment.

Antibody Inhibition

The activity of circulating antibodies can also be targeted, most commonly with intravenous immunoglobulin (IVIg). IVIg contains polyclonal IgG obtained from pooled plasma samples. There are multiple potential mechanisms by which IVIg may be effective in the treatment of AMR, including the expansion of regulatory T cells, up-regulation of the inhibitory FcyRIIB receptor on B cells, and the suppression of complement activation [146–148]. Although there is very little data from clinical trials examining the use of IVIg in transplant, it is commonly used for desensitization and for treatment of rejection, often in combination with PP and/or agents that target antibody production such as rituximab [149, 150]. Future use of

IVIg may include IgG that has been engineered to have greater affinity for the MHC class I receptor FcRn, in which binding would compete with endogenous IgG and lead to a reduction in IgG titers [151].

Many of the changes seen in AMR are mediated through the complement cascade, and there is recent interest in use of agents that target this pathway. Small animal studies showed improved graft survival, decreased incidence of AMR, and reduced inflammatory infiltration following treatment with an anti-C5 monoclonal antibody or C5aR antagonist [152–154]. Eculizumab, an antibody directed against the complement component C5, has been successfully used in the treatment of AMR in renal transplant recipients [155–157]. Additional data is needed prior to routine use.

Other Measures

Glucocorticoids bind to glucocorticoid receptors on T cells, antigen presenting cells, and endothelial cells and modify gene regulation via the glucocorticoid response elements. Immunosuppressive effects include decreased production of multiple pro-inflammatory cytokines and interference with cytokine receptor signaling [159–161]. For AMR associated with hemodynamic abnormalities, high-dose corticosteroids (methylprednisolone 1000 mg IV daily for 3 consecutive days) should be used. In less severe cases, an oral bolus dose may be used. Table 22.3 summarizes the dose, frequency, duration, and most common side effects of these various drugs/interventions used for cardiac AMR.

In AMR, platelets and other components of the coagulation cascade are activated and microthrombi may develop in the small vessels of the allograft, potentially leading to ischemia and further graft dysfunction [32, 89]. When treating a patient for AMR, it is reasonable to administer systemic anticoagulation to decrease the risk of intravascular thrombosis [94].

Potential future therapies for the treatment of AMR include anti-interleukins, agents that inhibit more proximal components of the complement cascade, and strategies aimed at inducing tolerance [162–165].

Desensitization

Patients with pre-transplant sensitization have increased wait times to transplant, as well as increased rejection, higher rates of cardiac allograft vasculopathy, and decreased survival following transplant [3, 166–168]. Desensitization therapy may be performed in order to minimize these risks, and utilizes many of the same therapies used in the treatment of AMR [169]. Protocols vary by transplant center and may also be individualized for each patient. In 2009, the ISHLT published a report from a consensus conference on the management of sensitized patients which contains a description of desensitization protocols from six transplant centers [170]. Most programs treated patients with pre-transplant PRAs >50 % and used a

Table 22.3 Drugs and interventions in cardiac AMR [94, 139–141, 156–158]

	Dose	Frequency	Duration	Side effects
Plasmapheresis (PP) [94]	1–2 plasma exchanges	Daily Every other day 3 times per week Once weekly	3–5 days 1–2 weeks 1–4 weeks 2–4 weeks	Hypotension, bleeding, blood-borne infection
IV immunoglobulin [94]	100–1000 mg/kg	1–3 times per week, often after PP	1–4 weeks	Headache, fever, chills, thrombosis, volume overload, aseptic meningitis, acute renal failure
Rituximab [94]	375 mg/m^2	Once weekly	1–4 weeks	Fever, hives, chills, leukopenia, infection, nausea
Bortezomib [139–141]	1.3 mg/m^2	Every 3–5 days	4 doses (2–4 weeks)	GI toxicity, thrombocytopenia, neutropenia, peripheral neuropathy
Eculizumab [156–159]	600–900 mg	Once weekly	1–4 weeks	GI toxicity, nasopharyngitis, anemia, headache, leukopenia,
Corticosteroids Methylprednisolone Prednisone	250–1000 mg 1–3 mg/kg	Daily Daily	3 days 3–5 days	Fluid retention, hyperglycemia, osteoporosis, hypertension
Antithymocyte Globulin (rabbit)	0.75–1.5 mg/kg	Daily or every other day	5–14 days	Fever, chills, hypotension, shortness of breath, thrombocytopenia

combination of plasmapheresis, IVIg and rituximab. Bortezemib has also been successfully utilized, generally if initial treatments failed to adequately reduce PRA levels [171, 172]. Clinical trials are needed and are being organized around protocols for desensitization and prevention.

Animal Models of AMR

Experiments using animal models have led to advancements in the understanding and treatment of rejection in heart transplantation. Early studies emphasized the important role of T cells in rejection. In these studies, the passive transfer of antibodies to rodent allograft recipients failed to accelerate rejection, whereas the transfer of sensitized lymphocytes led to prompt rejection [173–176]. Although it would later be shown the lack of rejection with early antibody transfer was due to a lack of

graft perfusion [177–179], research was directed away from the role of antibodies in rejection for many years and instead focused on the importance of T cells and cellular rejection in graft survival.

Two significant findings reignited the interest in AMR: the ability to identify C4d deposition in graft microvasculature and the recognition that C4d is often associated with circulating donor-specific antibodies [179, 180]. Since then, research using small animal models has led to insights in acute and chronic AMR, but there is great need for better animal models to fill existing gaps in our knowledge of and ability to treat AMR.

Acute AMR

Acute AMR is characterized pathologically by endothelial activation, inflammatory infiltration, and parenchymal injury. In mouse models of rejection, C3d and C4d deposition have been associated with circulating alloantibodies; grafted immunoglobulin knockout mice lacking alloantibody do not show C3d and C4d deposition and early endothelial injury [181–183]. The passive transfer of complement activating antibodies to these knockout mice leads to complement deposition and allograft rejection [184, 185]. An adequate antibody titer is necessary to produce the pathologic changes of AMR [186]. Future research that manipulates the antibody titer used in transfer experiments may allow the creation of models of subclinical AMR [187].

Complement activation can lead to the production of split products such as C5a and C5b, pro-inflammatory proteins that attract macrophages, neutrophils, and platelets. In allograft mouse models in which monoclonal antibodies to C5 or C5a receptor antagonists were administered, chemokine up-regulation and macrophage infiltration were inhibited [152–154]. These models allow the opportunity to understand the role of complement in AMR and to test new therapeutic targets.

Non-complement mediated pathways also contribute to acute AMR. Antibody-binding to MHC class I antigens on endothelial cells in the absence of complement and leukocytes leads to the release of growth factors and cytokines and to cell proliferation [188, 189]. Antibody binding to endothelial cells and vimentin stimulates the expression of P-selectin, which leads to leukocyte and platelet adherence and accelerated rejection [190–192]. Findings such as these may help explain and characterize the changes of AMR that are sometimes seen in the absence of C4d deposition.

Chronic AMR

Chronic AMR is an established consequence of cumulative and repetitive episodes of AMR and is characterized most commonly in cardiac allografts by vasculopathy. Colvin et al. demonstrated that chronic arteriopathy can be induced by the passive

transfer of donor specific antibodies to knockout mice devoid of T and B cells [193]. The arteriopathy could persist and progress even following clearance of antibody and C4d deposition. Similarly, the transfer of polyclonal antibodies to transplanted SCID mice leads to extensive graft arteriopathy; an adequate antibody titer is necessary to cause vasculopathy [194].

Reed and colleagues have shown that antibody binding to endothelial cell surface molecules leads to changes in signal transduction of pro-inflammatory and pro-proliferative pathways. One example is mammalian target of rapamycin complex 1 (mTORC1)-mediated activation of cell survival and proliferation signaling pathways following anti-HLA antibody binding [189]. These findings provide the rationale for using rapamycin, an mTORC1 inhibitor, to prevent or halt the progression of vasculopathy [195]. Anti-HLA antibody binding has also been shown to stimulate Rho and its target protein Rho kinase, initiating pathways of cell proliferation [196]. Treatment with a Rho-kinase inhibitor suppressed vasculopathy development in a mouse model [197]. Additional animal models are needed to further elucidate the pathways linking antibody-binding, signaling cascades, and chronic rejection and to test potential new therapies.

Accommodation and Tolerance

Accommodation is defined as the resistance of a graft to the effects of graft-specific antibodies and complement fixation [198, 199]. Complete inhibition of complement activation is one potential mechanism in cardiac xenografts that show accommodation [200]. These grafts demonstrate deposition of C4d and C3d but not C5b and MAC, the late components of the complement cascade. Other accommodated xenograft models show increased expression of cytoprotective proteins that have anti-apoptotic activities [201–204].

Exposure to low levels of donor-specific antibodies may lead to accommodation [203]. In one model, repeated injection of low-dose donor-specific antibodies led to increased expression of complement regulatory proteins such as decay accelerating factor [204]. Reed and colleagues have shown that the signaling events which regulate accommodation versus cell proliferation are dependent on the specificity and the concentration of the antibody [205].

In need of better understanding is whether long-term exposure to donor-specific antibodies, even at low levels, would eventually lead to chronic rejection or if accommodation could persist. Colvin has suggested that accommodation may not be an all-or-none phenomenon, but rather a spectrum exists along which acute rejection, accommodation, and chronic rejection can develop following antibody binding [206]. Animal models provide the opportunity to gain an understanding of the mechanisms and natural history of accommodation which could lead to new therapeutic strategies.

References

1. Hammond EH, Yowell RL, Nunoda S, Menlove RL, Renlund DG, Bristow MR, et al. Vascular (humoral) rejection in heart transplantation: pathologic observations and clinical implications. J Heart Transplan. 1989;8(6):430–43.
2. Lones MA, Czer LS, Trento A, Harasty D, Miller JM, Fishbein MC. Clinical-pathologic features of humoral rejection in cardiac allografts: a study in 81 consecutive patients. J Heart Lung Transplant. 1995;14(1 Pt 1):151–62.
3. Michaels PJ, Espejo ML, Kobashigawa J, Alejos JC, Burch C, Takemoto S, et al. Humoral rejection in cardiac transplantation: risk factors, hemodynamic consequences and relationship to transplant coronary artery disease. J Heart Lung Transplant. 2003;22(1):58–69.
4. Casarez TW, Perens G, Williams RJ, Kutay E, Fishbein MC, Reed EF, et al. Humoral rejection in pediatric orthotopic heart transplantation. J Heart Lung Transplant. 2007;26(2):114–9.
5. Everitt MD, Hammond ME, Snow GL, Stehlik J, Revelo MP, Miller DV, et al. Biopsy-diagnosed antibody-mediated rejection based on the proposed International Society for Heart and Lung Transplantation working formulation is associated with adverse cardiovascular outcomes after pediatric heart transplant. J Heart Lung Transplant. 2012;31(7):686–93.
6. Ensley RD, Hammond EH, Renlund DG, Yowell RL, Bristow MR, DeWitt CW, et al. Clinical manifestations of vascular rejection in cardiac transplantation. Transplant Proc. 1991;23(1 Pt 2):1130–2.
7. Cherry R, Nielsen H, Reed E, Reemtsma K, Suciu-Foca N, Marboe CC. Vascular (humoral) rejection in human cardiac allograft biopsies: relation to circulating anti-HLA antibodies. J Heart Lung Transplant 1992;11(1 Pt 1):24–9; discussion 30.
8. Reed EF, Demetris AJ, Hammond E, Itescu S, Kobashigawa JA, Reinsmoen NL, et al. Acute antibody-mediated rejection of cardiac transplants. J Heart Lung Transplant. 2006;25(2):153–9.
9. Tambur AR, Pamboukian SV, Costanzo MR, Herrera ND, Dunlap S, Montpetit M, et al. The presence of HLA-directed antibodies after heart transplantation is associated with poor allograft outcome. Transplantation. 2005;80(8):1019–25.
10. Michaels PJ, Fishbein MC, Colvin RB. Humoral rejection of human organ transplants. Springer Semin Immunopathol. 2003;25(2):119–40.
11. Wasowska BA. Mechanisms involved in antibody- and complement-mediated allograft rejection. Immunol Res. 2010;47(1–3):25–44.
12. Loy TS, Bulatao IS, Darkow GV, Demmy TL, Reddy HK, Curtis J, et al. Immunostaining of cardiac biopsy specimens in the diagnosis of acute vascular (humoral) rejection: a control study. J Heart Lung Transplant. 1993;12(5):736–40.
13. Olsen SL, Wagoner LE, Hammond EH, Taylor DO, Yowell RL, Ensley RD, et al. Vascular rejection in heart transplantation: clinical correlation, treatment options, and future considerations. J Heart Lung Transplant. 1993;12(2):S135–42.
14. Miller LW, Wesp A, Jennison SH, Graham MA, Martin TW, McBride LR, et al. Vascular rejection in heart transplant recipients. J Heart Lung Transplant. 1993;12(2):S147–52.
15. Kobashigawa J, Crespo-Leiro MG, Ensminger SM, Reichenspurner H, Angelini A, Berry G, et al. Report from a consensus conference on antibody-mediated rejection in heart transplantation. J Heart Lung Transplant. 2011;30(3):252–69.
16. Berry GJ, Burke MM, Andersen C, Bruneval P, Fedrigo M, Fishbein MC, et al. The 2013 International Society for Heart and Lung Transplantation Working Formulation for the standardization of nomenclature in the pathologic diagnosis of antibody-mediated rejection in heart transplantation. J Heart Lung Transplant. 2013;32(12):1147–62.
17. Kfoury AG, Stehlik J, Renlund DG, Snow G, Seaman JT, Gilbert EM, et al. Impact of repetitive episodes of antibody-mediated or cellular rejection on cardiovascular mortality in cardiac transplant recipients: defining rejection patterns. J Heart Lung Transplant. 2006;25(11):1277–82.
18. Wu GW, Kobashigawa JA, Fishbein MC, Patel JK, Kittleson MM, Reed EF, et al. Asymptomatic antibody-mediated rejection after heart transplantation predicts poor outcomes. J Heart Lung Transplant. 2009;28(5):417–22.

19. Reinsmoen NL, Patel J, Mirocha J, Lai CH, Naim M, Ong G, et al.. Optimizing transplantation of sensitized heart candidates using 4 antibody detection assays to prioritize the assignment of unacceptable antigens. J Heart Lung Transplant 2016;35(2):165–172. PubMed PMID: 26683810.
20. Eckels DD, Stehlik J, Kfoury AG. The detection and role of circulating antibodies in rejection. Curr Opin Organ Transplant. 2013;18(5):589–94.
21. Toyoda M, Petrosian A, Jordan SC. Immunological characterization of anti-endothelial cell antibodies induced by cytomegalovirus infection. Transplantation. 1999;68(9):1311–8.
22. George I, Colley P, Russo MJ, Martens TP, Burke E, Oz MC, et al. Association of device surface and biomaterials with immunologic sensitization after mechanical support. J Thorac Cardiovasc Surg. 2008;135(6):1372–9.
23. Bull DA, Reid BB, Selzman CH, Mesley R, Drakos S, Clayson S, et al. The impact of bridge-to-transplant ventricular assist device support on survival after cardiac transplantation. J Thorac Cardiovasc Surg. 2010;140(1):169–73.
24. Moazami N, Itescu S, Williams MR, Argenziano M, Weinberg A, Oz MC. Platelet transfusions are associated with the development of anti-major histocompatibility complex class I antibodies in patients with left ventricular assist support. J Heart Lung Transplant. 1998;17(9): 876–80.
25. McCarthy JF, Cook DJ, Smedira NG, O'Malley KJ, Massad MG, Sano Y, et al. Vascular rejection in cardiac transplantation. Transplant Proc. 1999;31(1–2):160.
26. Greger B, Grossmann T, Gartner HV, Hopt UT, Lauchart W. Positive postoperative donor-specific crossmatch correlates with B-cell infiltration and poor graft prognosis. Transplant Proc. 1990;22(4):1900–2.
27. Ioannou A, Dalle Lucca J, Tsokos GC. Immunopathogenesis of ischemia/reperfusion-associated tissue damage. Clin Immunol. 2011;141(1):3–14.
28. Land WG. Emerging role of innate immunity in organ transplantation part II: potential of damage-associated molecular patterns to generate immunostimulatory dendritic cells. Transplant Rev (Orlando). 2012;26(2):73–87.
29. Stewart S, Winters GL, Fishbein MC, Tazelaar HD, Kobashigawa J, Abrams J, et al. Revision of the 1990 working formulation for the standardization of nomenclature in the diagnosis of heart rejection. J Heart Lung Transplant. 2005;24(11):1710–20.
30. Singhal AK, Drakos SG, Kfoury AG, Horne BD, Verma DR, Stehlik J. Prolonged allograft ischemic time is not associated with higher incidence of antibody-mediated rejection. J Heart Lung Transplant. 2010;29(10):1198–200.
31. Hammond EH, Wittwer CT, Greenwood J, Knape WA, Yowell RL, Menlove RL, et al. Relationship of OKT3 sensitization and vascular rejection in cardiac transplant patients receiving OKT3 rejection prophylaxis. Transplantation. 1990;50(5):776–82.
32. Hammond EH, Hansen JK, Spencer LS, Jensen A, Yowell RL. Immunofluorescence of endomyocardial biopsy specimens: methods and interpretation. J Heart Lung Transplant. 1993; 12(2):S113–24.
33. Keenan RJ, Lega ME, Dummer JS, Paradis IL, Dauber JH, Rabinowich H, et al. Cytomegalovirus serologic status and postoperative infection correlated with risk of developing chronic rejection after pulmonary transplantation. Transplantation. 1991;51(2):433–8.
34. Rane S, Nada R, Minz M, Sakhuja V, Joshi K. Spectrum of cytomegalovirus-induced renal pathology in renal allograft recipients. Transplant Proc. 2012;44(3):713–6.
35. Colvin-Adams M, Agnihotri A. Cardiac allograft vasculopathy: current knowledge and future direction. Clin Transpl. 2011;25(2):175–84.
36. Watkins RR, Lemonovich TL, Razonable RR. Immune response to CMV in solid organ transplant recipients: current concepts and future directions. Expert Rev Clin Immunol. 2012;8(4): 383–93.
37. Jordan SC, Quartel AW, Czer LS, Admon D, Chen G, Fishbein MC, et al. Posttransplant therapy using high-dose human immunoglobulin (intravenous gammaglobulin) to control acute humoral rejection in renal and cardiac allograft recipients and potential mechanism of action. Transplantation. 1998;66(6):800–5.

38. Bocrie O, Hussein Aly AA, Guignier F, Funes de la Vega M, Rifle G, Mousson C, et al. Distribution of donor-specific antibodies in the cortex and the medulla of renal transplants with chronic allograft nephropathy. Transpl Immunol. 2007;17(3):227–9.
39. Nath DS, Ilias Basha H, Tiriveedhi V, Alur C, Phelan D, Ewald GA, et al. Characterization of immune responses to cardiac self-antigens myosin and vimentin in human cardiac allograft recipients with antibody-mediated rejection and cardiac allograft vasculopathy. J Heart Lung Transplant. 2010;29(11):1277–85.
40. Smith JD, Brunner VM, Jigjidsuren S, Hamour IM, McCormack AM, Banner NR, et al. Lack of effect of MICA antibodies on graft survival following heart transplantation. Am J Transplant. 2009;9(8):1912–9.
41. Nace G, Evankovich J, Eid R, Tsung A. Dendritic cells and damage-associated molecular patterns: endogenous danger signals linking innate and adaptive immunity. J Innate Immun. 2012;4(1):6–15.
42. Itescu S, Schuster M, Burke E, Ankersmit J, Kocher A, Deng M, et al. Immunobiologic consequences of assist devices. Cardiol Clin. 2003;21(1):119–33 ix-x.
43. Andrade CF, Waddell TK, Keshavjee S, Liu M. Innate immunity and organ transplantation: the potential role of toll-like receptors. Am J Transplant. 2005;5(5):969–75.
44. Wyburn KR, Jose MD, Wu H, Atkins RC, Chadban SJ. The role of macrophages in allograft rejection. Transplantation. 2005;80(12):1641–7.
45. Land WG. Innate immunity-mediated allograft rejection and strategies to prevent it. Transplant Proc. 2007;39(3):667–72.
46. Lakkis FG, Sayegh MH. Memory T cells: a hurdle to immunologic tolerance. J Am Soc Nephrol. 2003;14(9):2402–10.
47. Murata K, Baldwin 3rd WM. Mechanisms of complement activation, C4d deposition, and their contribution to the pathogenesis of antibody-mediated rejection. Transplant Rev (Orlando). 2009;23(3):139–50.
48. Pietra BA. Transplantation immunology 2003: simplified approach. Pediatr Clin N Am. 2003;50(6):1233–59.
49. Wood KJ, Bushell A, Hester J. Regulatory immune cells in transplantation. Nat Rev Immunol. 2012;12(6):417–30.
50. Wood KJ, Goto R. Mechanisms of rejection: current perspectives. Transplantation. 2012; 93(1):1–10.
51. Jordan SC, Toyoda M, Vo AA. Regulation of immunity and inflammation by intravenous immunoglobulin: relevance to solid organ transplantation. Expert Rev Clin Immunol. 2011;7(3):341–8.
52. Coelho V, Saitovitch D, Kalil J, Silva HM. Rethinking the multiple roles of B cells in organ transplantation. Curr Opin Organ Transplant. 2013;18(1):13–21.
53. Baldwin 3rd WM, Halushka MK, Valujskikh A, Fairchild RL. B cells in cardiac transplants: from clinical questions to experimental models. Semin Immunol. 2012; 24(2):122–30.
54. Kwun J, Bulut P, Kim E, Dar W, Oh B, Ruhil R, et al. The role of B cells in solid organ transplantation. Semin Immunol. 2012;24(2):96–108.
55. Barnett N, Dorling A, Mamode N. B cells in renal transplantation: pathological aspects and therapeutic interventions. Nephrol Dial Transplant. 2011;26(3):767–74.
56. Nair N, Ball T, Uber PA, Mehra MR. Current and future challenges in therapy for antibody-mediated rejection. J Heart Lung Transplant. 2011;30(6):612–7.
57. Gareau A, Hirsch GM, Lee TD, Nashan B. Contribution of B cells and antibody to cardiac allograft vasculopathy. Transplantation. 2009;88(4):470–7.
58. Pratt JR, Basheer SA, Sacks SH. Local synthesis of complement component C3 regulates acute renal transplant rejection. Nat Med. 2002;8(6):582–7.
59. Pober JS, Tellides G. Participation of blood vessel cells in human adaptive immune responses. Trends Immunol. 2012;33(1):49–57.
60. Rothermel AL, Wang Y, Schechner J, Mook-Kanamori B, Aird WC, Pober JS, et al. Endothelial cells present antigens in vivo. BMC Immunol. 2004;5:5.

61. Goes N, Urmson J, Hobart M, Halloran PF. The unique role of interferon-gamma in the regulation of MHC expression on arterial endothelium. Transplantation. 1996;62(12):1889–94.
62. Kirk AD, Morrell CN, Baldwin 3rd WM. Platelets influence vascularized organ transplants from start to finish. Am J Transplant. 2009;9(1):14–22.
63. Charafeddine AH, Kim EJ, Maynard DM, Yi H, Weaver TA, Gunay-Aygun M, et al. Platelet-derived CD154: ultrastructural localization and clinical correlation in organ transplantation. Am J Transplant. 2012;12(11):3143–51.
64. Oikonomopoulou K, Ricklin D, Ward PA, Lambris JD. Interactions between coagulation and complement – their role in inflammation. Semin Immunopathol. 2012;34(1):151–65.
65. Peerschke EI, Yin W, Ghebrehiwet B. Complement activation on platelets: implications for vascular inflammation and thrombosis. Mol Immunol. 2010;47(13):2170–5.
66. Wehner J, Morrell CN, Reynolds T, Rodriguez ER, Baldwin 3rd WM. Antibody and complement in transplant vasculopathy. Circ Res. 2007;100(2):191–203.
67. Loupy A, Cazes A, Guillemain R, Amrein C, Hedjoudje A, Tible M, et al. Very late heart transplant rejection is associated with microvascular injury, complement deposition and progression to cardiac allograft vasculopathy. Am J Transplant. 2011;11(7):1478–87.
68. Taylor DO, Yowell RL, Kfoury AG, Hammond EH, Renlund DG. Allograft coronary artery disease: clinical correlations with circulating anti-HLA antibodies and the immunohistopathologic pattern of vascular rejection. J Heart Lung Transplant. 2000;19(6):518–21.
69. Tan CD, Sokos GG, Pidwell DJ, Smedira NG, Gonzalez-Stawinski GV, Taylor DO, et al. Correlation of donor-specific antibodies, complement and its regulators with graft dysfunction in cardiac antibody-mediated rejection. Am J Transplant. 2009;9(9):2075–84.
70. Billingham ME, Cary NR, Hammond ME, Kemnitz J, Marboe C, McCallister HA, et al. A working formulation for the standardization of nomenclature in the diagnosis of heart and lung rejection: Heart Rejection Study Group. The International Society for Heart Transplantation. J Heat Transf. 1990;9(6):587–93.
71. Hammond ME, Stehlik J, Snow G, Renlund DG, Seaman J, Dabbas B, et al. Utility of histologic parameters in screening for antibody-mediated rejection of the cardiac allograft: a study of 3,170 biopsies. J Heart Lung Transplant. 2005;24(12):2015–21.
72. Fedrigo M, Gambino A, Benazzi E, Poli F, Frigo AC, Tona F, et al. Role of morphologic parameters on endomyocardial biopsy to detect sub-clinical antibody-mediated rejection in heart transplantation. J Heart Lung Transplant. 2011;30(12):1381–8.
73. Fishbein GA, Fishbein MC. Morphologic and immunohistochemical findings in antibody-mediated rejection of the cardiac allograft. Hum Immunol. 2012;73(12):1213–7.
74. Chantranuwat C, Qiao JH, Kobashigawa J, Hong L, Shintaku P, Fishbein MC. Immunoperoxidase staining for C4d on paraffin-embedded tissue in cardiac allograft endomyocardial biopsies: comparison to frozen tissue immunofluorescence. Appl Immunohistochem Mol Morphol. 2004;12(2):166–71.
75. Angelini A, Andersen CB, Bartoloni G, Black F, Bishop P, Doran H, et al. A web-based pilot study of inter-pathologist reproducibility using the ISHLT 2004 working formulation for biopsy diagnosis of cardiac allograft rejection: the European experience. J Heart Lung Transplant. 2011;30(11):1214–20.
76. Labarrere CA, Nelson DR, Park JW. Pathologic markers of allograft arteriopathy: insight into the pathophysiology of cardiac allograft chronic rejection. Curr Opin Cardiol. 2001;16(2):110–7.
77. Crespo-Leiro MG, Veiga-Barreiro A, Domenech N, Paniagua MJ, Pinon P, Gonzalez-Cuesta M, et al. Humoral heart rejection (severe allograft dysfunction with no signs of cellular rejection or ischemia): incidence, management, and the value of C4d for diagnosis. Am J Transplant. 2005;5(10):2560–4.
78. Ning Q, Sun Y, Han M, Zhang L, Zhu C, Zhang W, Guo H, Li J, Yan W, Gong F, Chen Z, He W, Koscik C, Smith R, Gorczynski R, Levy G, Luo X. Role of fibrinogen-like protein 2 prothrombinase/fibroleukin in experimental and human allograft rejection. J Immunol. 2005 Jun 1;174(11):7403–11.
79. Halloran PF, de Freitas DG, Einecke G, Famulski KS, Hidalgo LG, Mengel M, et al. The molecular phenotype of kidney transplants. Am J Transplant. 2010;10(10):2215–22.

80. Einecke G, Sis B, Reeve J, Mengel M, Campbell PM, Hidalgo LG, et al. Antibody-mediated microcirculation injury is the major cause of late kidney transplant failure. Am J Transplant. 2009;9(11):2520–31.
81. Sis B, Halloran PF. Endothelial transcripts uncover a previously unknown phenotype: C4d-negative antibody-mediated rejection. Curr Opin Organ Transplant. 2010;15(1):42–8.
82. Mengel M, Sis B, Kim D, Chang J, Famulski KS, Hidalgo LG, et al. The molecular phenotype of heart transplant biopsies: relationship to histopathological and clinical variables. Am J Transplant. 2010;10(9):2105–15.
83. Freue GV, Sasaki M, Meredith A, Gunther OP, Bergman A, Takhar M, et al. Proteomic signatures in plasma during early acute renal allograft rejection. Mol Cell Proteomics. 2010;9(9): 1954–67.
84. Kfoury AG, Hammond ME, Snow GL, Stehlik J, Reid BB, Long JW, et al. Early screening for antibody-mediated rejection in heart transplant recipients. J Heart Lung Transplant. 2007;26(12):1264–9.
85. Almuti K, Haythe J, Dwyer E, Itescu S, Burke E, Green P, et al. The changing pattern of humoral rejection in cardiac transplant recipients. Transplantation. 2007;84(4):498–503.
86. Fishbein MC, Kobashigawa J. Biopsy-negative cardiac transplant rejection: etiology, diagnosis, and therapy. Curr Opin Cardiol. 2004;19(2):166–9.
87. Kfoury AG, Snow GL, Budge D, Alharethi RA, Stehlik J, Everitt MD, et al. A longitudinal study of the course of asymptomatic antibody-mediated rejection in heart transplantation. J Heart Lung Transplant. 2012;31(1):46–51.
88. Hodges AM, Lyster H, McDermott A, Rice AJ, Smith JD, Rose ML, et al. Late antibody-mediated rejection after heart transplantation following the development of de novo donor-specific human leukocyte antigen antibody. Transplantation. 2012;93(6):650–6.
89. Hammond EH, Yowell RL, Price GD, Menlove RL, Olsen SL, O'Connell JB, et al. Vascular rejection and its relationship to allograft coronary artery disease. J Heart Lung Transplant. 1992;11(3 Pt 2):S111–9.
90. Garrett Jr HE, Duvall-Seaman D, Helsley B, Groshart K. Treatment of vascular rejection with rituximab in cardiac transplantation. J Heart Lung Transplant. 2005;24(9):1337–42.
91. Gill EA, Borrego C, Bray BE, Renlund DG, Hammond EH, Gilbert EM. Left ventricular mass increases during cardiac allograft vascular rejection. J Am Coll Cardiol. 1995;25(4):922–6.
92. Kfoury AG, Hammond ME, Snow GL, Drakos SG, Stehlik J, Fisher PW, et al. Cardiovascular mortality among heart transplant recipients with asymptomatic antibody-mediated or stable mixed cellular and antibody-mediated rejection. J Heart Lung Transplant. 2009;28(8): 781–4.
93. Budge D, Khan F, Hammond M, Nilson Z, Stehlik J, Alharethi R, et al. Safety and Outcomes with Newer Treatment Strategies for Cardiac Antibody-mediated Rejection: Still in the Woods. J Heart Lung Transplant. 2010;29(2S):S42.
94. Costanzo MR, Dipchand A, Starling R, Anderson A, Chan M, Desai S, et al. The International Society of Heart and Lung Transplantation Guidelines for the care of heart transplant recipients. J Heart Lung Transplant. 2010;29(8):914–56.
95. Clatworthy MR. Targeting B cells and antibody in transplantation. Am J Transplant. 2011; 11(7):1359–67.
96. Carrier M, White M, Perrault LP, Pelletier GB, Pellerin M, Robitaille D, et al. A 10-year experience with intravenous thymoglobuline in induction of immunosuppression following heart transplantation. J Heart Lung Transplant. 1999;18(12):1218–23.
97. Goland S, Czer LS, Coleman B, De Robertis MA, Mirocha J, Zivari K, et al. Induction therapy with thymoglobulin after heart transplantation: impact of therapy duration on lymphocyte depletion and recovery, rejection, and cytomegalovirus infection rates. J Heart Lung Transplant. 2008;27(10):1115–21.
98. Yamani MH, Taylor DO, Czerr J, Haire C, Kring R, Zhou L, et al. Thymoglobulin induction and steroid avoidance in cardiac transplantation: results of a prospective, randomized, controlled study. Clin Transpl. 2008;22(1):76–81.
99. Uber PA, Mehra MR. Induction therapy in heart transplantation: is there a role? J Heart Lung Transplant. 2007;26(3):205–9.

100. Cantarovich M, Latter DA, Loertscher R. Treatment of steroid-resistant and recurrent acute cardiac transplant rejection with a short course of antibody therapy. Clin Transpl. 1997;11(4):316–21.
101. Zand MS. B-cell activity of polyclonal antithymocyte globulins. Transplantation. 2006;82(11): 1387–95.
102. Zand MS, Vo T, Huggins J, Felgar R, Liesveld J, Pellegrin T, et al. Polyclonal rabbit antithymocyte globulin triggers B-cell and plasma cell apoptosis by multiple pathways. Transplantation. 2005;79(11):1507–15.
103. Uber WE, Uber LA, VanBakel AB, Crumbley 3rd AJ, Pereira NL, Ikonomidis JS, et al. CD3 monitoring and thymoglobulin therapy in cardiac transplantation: clinical outcomes and pharmacoeconomic implications. Transplant Proc. 2004;36(10):3245–9.
104. Krasinskas AM, Kreisel D, Acker MA, Bavaria JE, Pochettino A, Kotloff RM, et al. CD3 monitoring of antithymocyte globulin therapy in thoracic organ transplantation. Transplantation. 2002;73(8):1339–41.
105. Kobashigawa JA, Miller LW, Russell SD, Ewald GA, Zucker MJ, Goldberg LR, et al. Tacrolimus with mycophenolate mofetil (MMF) or sirolimus vs. cyclosporine with MMF in cardiac transplant patients: 1-year report. Am J Transplant. 2006;6(6):1377–86.
106. Kim HS, Raskova J, Degiannis D, Raska Jr K. Effects of cyclosporine and rapamycin on immunoglobulin production by preactivated human B cells. Clin Exp Immunol. 1994;96(3): 508–12.
107. Heidt S, Roelen DL, Eijsink C, van Kooten C, Claas FH, Mulder A. Effects of immunosuppressive drugs on purified human B cells: evidence supporting the use of MMF and rapamycin. Transplantation. 2008;86(9):1292–300.
108. Keogh A, Richardson M, Ruygrok P, Spratt P, Galbraith A, O'Driscoll G, et al. Sirolimus in de novo heart transplant recipients reduces acute rejection and prevents coronary artery disease at 2 years: a randomized clinical trial. Circulation. 2004;110(17):2694–700.
109. Eisen HJ, Tuzcu EM, Dorent R, Kobashigawa J, Mancini D, Valantine-von Kaeppler HA, et al. Everolimus for the prevention of allograft rejection and vasculopathy in cardiac-transplant recipients. N Engl J Med. 2003;349(9):847–58.
110. Mancini D, Pinney S, Burkhoff D, LaManca J, Itescu S, Burke E, et al. Use of rapamycin slows progression of cardiac transplantation vasculopathy. Circulation. 2003;108(1):48–53.
111. Tzvetanov I, Spaggiari M, Oberholzer J, Setty S, Stephenson A, Thielke J, et al. Cell population in spleens during antibody-mediated rejection: pathologic and clinical findings. Transplantation. 2012;94(3):255–62.
112. Tzvetanov I, Spaggiari M, Jeon H, Roca RG, Bhati C, Oberholzer J, et al. The role of splenectomy in the setting of refractory humoral rejection after kidney transplantation. Transplant Proc. 2012;44(5):1254–8.
113. Locke JE, Zachary AA, Haas M, Melancon JK, Warren DS, Simpkins CE, et al. The utility of splenectomy as rescue treatment for severe acute antibody mediated rejection. Am J Transplant. 2007;7(4):842–6.
114. Kaplan B, Gangemi A, Thielke J, Oberholzer J, Sankary H, Benedetti E. Successful rescue of refractory, severe antibody mediated rejection with splenectomy. Transplantation. 2007;83(1): 99–100.
115. Jirasiritham S, Khunprakant R, Techawathanawanna N, Jirasiritham S, Mavichak V. Treatment of simultaneous acute antibody-mediated rejection and acute cellular rejection with alemtuzumab in kidney transplantation: a case report. Transplant Proc. 2010;42(3):987–9.
116. van den Hoogen MW, Hesselink DA, van Son WJ, Weimar W, Hilbrands LB. Treatment of steroid-resistant acute renal allograft rejection with alemtuzumab. Am J Transplant. 2013; 13(1):192–6.
117. Fassbinder W, Scheuermann EH, Stutte HJ, Bechstein PB, Fursch A, Ernst W, et al. Improved graft prognosis by treatment of steroid resistant rejections with ATG and plasmapheresis. Proc Eur Dial Transplant Assoc. 1983;20:362–7.
118. Shah A, Nadasdy T, Arend L, Brennan J, Leong N, Coppage M, et al. Treatment of C4d-positive acute humoral rejection with plasmapheresis and rabbit polyclonal antithymocyte globulin. Transplantation. 2004;77(9):1399–405.

119. Fehr T, Rusi B, Fischer A, Hopfer H, Wuthrich RP, Gaspert A. Rituximab and intravenous immunoglobulin treatment of chronic antibody-mediated kidney allograft rejection. Transplantation. 2009;87(12):1837–41.
120. Vo AA, Peng A, Toyoda M, Kahwaji J, Cao K, Lai CH, et al. Use of intravenous immune globulin and rituximab for desensitization of highly HLA-sensitized patients awaiting kidney transplantation. Transplantation. 2010;89(9):1095–102.
121. Zarkhin V, Chalasani G, Sarwal MM. The yin and yang of B cells in graft rejection and tolerance. Transplant Rev (Orlando). 2010;24(2):67–78.
122. Aranda Jr JM, Scornik JC, Normann SJ, Lottenberg R, Schofield RS, Pauly DF, et al. Anti-CD20 monoclonal antibody (rituximab) therapy for acute cardiac humoral rejection: a case report. Transplantation. 2002;73(6):907–10.
123. Garrett Jr HE, Groshart K, Duvall-Seaman D, Combs D, Suggs R. Treatment of humoral rejection with rituximab. Ann Thorac Surg. 2002;74(4):1240–2.
124. Baran DA, Lubitz S, Alvi S, Fallon JT, Kaplan S, Galin I, et al. Refractory humoral cardiac allograft rejection successfully treated with a single dose of rituximab. Transplant Proc. 2004;36(10):3164–6.
125. Kaczmarek I, Deutsch MA, Sadoni S, Brenner P, Schmauss D, Daebritz SH, et al. Successful management of antibody-mediated cardiac allograft rejection with combined immunoadsorption and anti-CD20 monoclonal antibody treatment: case report and literature review. J Heart Lung Transplant. 2007;26(5):511–5.
126. Vincenti F, Cohen SD, Appel G. Novel B cell therapeutic targets in transplantation and immune-mediated glomerular diseases. Clin J Am Soc Nephrol. 2010;5(1):142–51.
127. Ostergaard M, Baslund B, Rigby W, Rojkovich B, Jorgensen C, Dawes PT, et al. Ofatumumab, a human anti-CD20 monoclonal antibody, for treatment of rheumatoid arthritis with an inadequate response to one or more disease-modifying antirheumatic drugs: results of a randomized, double-blind, placebo-controlled, phase I/II study. Arthritis Rheum. 2010;62(8):2227–38.
128. Cang S, Mukhi N, Wang K, Liu D. Novel CD20 monoclonal antibodies for lymphoma therapy. J Hematol Oncol. 2012;5:64.
129. Tak PP, Mease PJ, Genovese MC, Kremer J, Haraoui B, Tanaka Y, et al. Safety and efficacy of ocrelizumab in patients with rheumatoid arthritis and an inadequate response to at least one tumor necrosis factor inhibitor: results of a forty-eight-week randomized, double-blind, placebo-controlled, parallel-group phase III trial. Arthritis Rheum. 2012;64(2):360–70.
130. Lulu S, Waubant E. Humoral-targeted immunotherapies in multiple sclerosis. Neurotherapeutics. 2013;10(1):34–43.
131. Dorner T, Kaufmann J, Wegener WA, Teoh N, Goldenberg DM, Burmester GR. Initial clinical trial of epratuzumab (humanized anti-CD22 antibody) for immunotherapy of systemic lupus erythematosus. Arthritis Res Ther. 2006;8(3):R74.
132. Tedder TF. CD19: a promising B cell target for rheumatoid arthritis. Nat Rev Rheumatol. 2009;5(10):572–7.
133. Lateef A, Petri M. Biologics in the treatment of systemic lupus erythematosus. Curr Opin Rheumatol. 2010;22(5):504–9.
134. Looney RJ. B cell-targeted therapies for systemic lupus erythematosus: an update on clinical trial data. Drugs. 2010;70(5):529–40.
135. Kalunian KC, Davis Jr JC, Merrill JT, Totoritis MC, Wofsy D, Group I-LS. Treatment of systemic lupus erythematosus by inhibition of T cell costimulation with anti-CD154: a randomized, double-blind, placebo-controlled trial. Arthritis Rheum. 2002;46(12):3251–8.
136. Boumpas DT, Furie R, Manzi S, Illei GG, Wallace DJ, Balow JE, et al. A short course of BG9588 (anti-CD40 ligand antibody) improves serologic activity and decreases hematuria in patients with proliferative lupus glomerulonephritis. Arthritis Rheum. 2003;48(3):719–27.
137. Kirk AD, Knechtle SJ, Sollinger HE. Preliminary results of the use of humanized anti-CD154 in human renal allotrasnplantation. Am J Transplant. 2001;1(191):suppl 1.
138. Everly JJ, Walsh RC, Alloway RR, Woodle ES. Proteasome inhibition for antibody-mediated rejection. Curr Opin Organ Transplant. 2009;14(6):662–6.
139. Eckman PM, Thorsgard M, Maurer D, Kim Y, Alloway RR, Woodle ES. Bortezomib for refractory antibody-mediated cardiac allograft rejection. Clin Transpl. 2009:475–8.

140. Trivedi HL, Terasaki PI, Feroz A, Everly MJ, Vanikar AV, Shankar V, et al. Abrogation of anti-HLA antibodies via proteasome inhibition. Transplantation. 2009;87(10):1555–61.
141. Morrow WR, Frazier EA, Mahle WT, Harville TO, Pye SE, Knecht KR, et al. Rapid reduction in donor-specific anti-human leukocyte antigen antibodies and reversal of antibody-mediated rejection with bortezomib in pediatric heart transplant patients. Transplantation. 2012;93(3):319–24.
142. Everly MJ, Terasaki PI, Hopfield J, Trivedi HL, Kaneku H. Protective immunity remains intact after antibody removal by means of proteasome inhibition. Transplantation. 2010;90(12):1493–8.
143. Grauhan O, Knosalla C, Ewert R, Hummel M, Loebe M, Weng YG, et al. Plasmapheresis and cyclophosphamide in the treatment of humoral rejection after heart transplantation. J Heart Lung Transplant. 2001;20(3):316–21.
144. Hershko AY, Naparstek Y. Removal of pathogenic autoantibodies by immunoadsorption. Ann N Y Acad Sci. 2005;1051:635–46.
145. Rummler S, Barz D. Plasma Exchange and Immunoadsorption of Patients with Thoracic Organ Transplantation. Transfus Med Hemother. 2012;39(4):234–40.
146. Jordan SC, Toyoda M, Vo AA. Intravenous immunoglobulin a natural regulator of immunity and inflammation. Transplantation. 2009;88(1):1–6.
147. Jordan SC, Toyoda M, Kahwaji J, Vo AA. Clinical aspects of intravenous immunoglobulin use in solid organ transplant recipients. Am J Transplant. 2011;11(2):196–202.
148. Nimmerjahn F, Ravetch JV. Anti-inflammatory actions of intravenous immunoglobulin. Annu Rev Immunol. 2008;26:513–33.
149. Shehata N, Palda VA, Meyer RM, Blydt-Hansen TD, Campbell P, Cardella C, et al. The use of immunoglobulin therapy for patients undergoing solid organ transplantation: an evidence-based practice guideline. Transfus Med Rev. 2010;24(Suppl 1):S7–S27.
150. Leech SH, Lopez-Cepero M, LeFor WM, DiChiara L, Weston M, Furukawa S, et al. Management of the sensitized cardiac recipient: the use of plasmapheresis and intravenous immunoglobulin. Clin Transpl. 2006;20(4):476–84.
151. Vaccaro C, Zhou J, Ober RJ, Ward ES. Engineering the Fc region of immunoglobulin G to modulate in vivo antibody levels. Nat Biotechnol. 2005;23(10):1283–8.
152. Wang H, Jiang J, Liu W, Kubelik D, Chen G, Gies D, et al. Prevention of acute vascular rejection by a functionally blocking anti-C5 monoclonal antibody combined with cyclosporine. Transplantation. 2005;79(9):1121–7.
153. Rother RP, Arp J, Jiang J, Ge W, Faas SJ, Liu W, et al. C5 blockade with conventional immunosuppression induces long-term graft survival in presensitized recipients. Am J Transplant. 2008;8(6):1129–42.
154. Gueler F, Rong S, Gwinner W, Mengel M, Brocker V, Schon S, et al. Complement 5a receptor inhibition improves renal allograft survival. J Am Soc Nephrol. 2008;19(12):2302–12.
155. Locke JE, Magro CM, Singer AL, Segev DL, Haas M, Hillel AT, et al. The use of antibody to complement protein C5 for salvage treatment of severe antibody-mediated rejection. Am J Transplant. 2009;9(1):231–5.
156. Stewart ZA, Collins TE, Schlueter AJ, Raife TI, Holanda DG, Nair R, et al. Case report: eculizumab rescue of severe accelerated antibody-mediated rejection after ABO-incompatible kidney transplant. Transplant Proc. 2012;44(10):3033–6.
157. Gonzalez-Roncero F, Suner M, Bernal G, Cabello V, Toro M, Pereira P, et al. Eculizumab treatment of acute antibody-mediated rejection in renal transplantation: case reports. Transplant Proc. 2012;44(9):2690–4.
158. Noone D, Al-Matrafi J, Tinckam K, Zipfel PF, Herzenberg AM, Thorner PS, et al. Antibody mediated rejection associated with complement factor h-related protein 3/1 deficiency successfully treated with eculizumab. Am J Transplant. 2012;12(9):2546–53.
159. De Bosscher K, Vanden Berghe W, Haegeman G. Mechanisms of anti-inflammatory action and of immunosuppression by glucocorticoids: negative interference of activated glucocorticoid receptor with transcription factors. J Neuroimmunol. 2000;109(1):16–22.
160. Almawi WY, Melemedjian OK, Rieder MJ. An alternate mechanism of glucocorticoid anti-proliferative effect: promotion of a Th2 cytokine-secreting profile. Clin Transpl. 1999; 13(5):365–74.

161. Hayashi R, Wada H, Ito K, Adcock IM. Effects of glucocorticoids on gene transcription. Eur J Pharmacol. 2004;500(1–3):51–62.
162. Zhao X, Boenisch O, Yeung M, Mfarrej B, Yang S, Turka LA, et al. Critical role of proinflammatory cytokine IL-6 in allograft rejection and tolerance. Am J Transplant. 2012;12(1):90–101.
163. Illei GG, Shirota Y, Yarboro CH, Daruwalla J, Tackey E, Takada K, et al. Tocilizumab in systemic lupus erythematosus: data on safety, preliminary efficacy, and impact on circulating plasma cells from an open-label phase I dosage-escalation study. Arthritis Rheum. 2010;62(2):542–52.
164. Hughes PD, Cohney SJ. Modifiers of complement activation for prevention of antibody-mediated injury to allografts. Curr Opin Organ Transplant. 2011;16(4):425–33.
165. Trivedi HL, Terasaki PI, Feroz A, Vanikar AV, Trivedi VB, Khemchandani SI, et al. Clonal deletion with bortezomib followed by low or no maintenance immunosuppression in renal allograft recipients. Transplantation. 2010;90(2):221–2.
166. Itescu S, Tung TC, Burke EM, Weinberg A, Moazami N, Artrip JH, et al. Preformed IgG antibodies against major histocompatibility complex class II antigens are major risk factors for high-grade cellular rejection in recipients of heart transplantation. Circulation. 1998;98(8):786–93.
167. Kobashigawa JA, Sabad A, Drinkwater D, Cogert GA, Moriguchi JD, Kawata N, et al. Pretransplant panel reactive-antibody screens. Are they truly a marker for poor outcome after cardiac transplantation? Circulation. 1996;94(9 Suppl):II294–7.
168. Nwakanma LU, Williams JA, Weiss ES, Russell SD, Baumgartner WA, Conte JV. Influence of pretransplant panel-reactive antibody on outcomes in 8,160 heart transplant recipients in recent era. Ann Thorac Surg. 2007;84(5):1556–62 discussion 62–3.
169. Vo AA, Lukovsky M, Toyoda M, Wang J, Reinsmoen NL, Lai CH, et al. Rituximab and intravenous immune globulin for desensitization during renal transplantation. N Engl J Med. 2008;359(3):242–51.
170. Kobashigawa J, Mehra M, West L, Kerman R, George J, Rose M, et al. Report from a consensus conference on the sensitized patient awaiting heart transplantation. J Heart Lung Transplant. 2009;28(3):213–25.
171. Patel J, Everly M, Chang D, Kittleson M, Reed E, Kobashigawa J. Reduction of alloantibodies via proteasome inhibition in cardiac transplantation. J Heart Lung Transplant. 2011;30(12):1320–6.
172. Kittleson MM, Kobashigawa JA. Antibody-mediated rejection. Curr Opin Organ Transplant. 2012;17(5):551–7.
173. Billingham RE, Brent L. Further attempts to transfer transplantation immunity by means of serum. Br J Exp Pathol. 1956;37(6):566–9.
174. Makela O, Mitchison NA. The role of cell number and source in adoptive immunity. Immunology. 1965;8(6):539–48.
175. Carpenter CB, d'Apice AJ, Abbas AK. The role of antibodies in the rejection and enhancement of organ allografts? 7318. Adv Immunol. 1976;22:1–65.
176. Tilney NL, Kupiec-Weglinski JW, Heidecke CD, Lear PA, Strom TB. Mechanisms of rejection and prolongation of vascularized organ allografts. Immunol Rev. 1984;77:185–216.
177. Gerlag PG, Koene RA, Hagemann JF, Wijdeveld PG. Hyperacute rejection of skin allografts in the mouse. Sensitivity of ingrowing skin grafts to the action of alloantibody and rabbit complement. Transplantation. 1975;20(4):308–13.
178. Jooste SV, Colvin RB, Soper WD, Winn HJ. The vascular bed as the primary target in the destruction of skin grafts by antiserum. I. Resistance of freshly placed xenografts of skin to antiserum. J Exp Med. 1981;154(5):1319–31.
179. Feucht HE, Felber E, Gokel MJ, Hillebrand G, Nattermann U, Brockmeyer C, et al. Vascular deposition of complement-split products in kidney allografts with cell-mediated rejection. Clin Exp Immunol. 1991;86(3):464–70.
180. Collins AB, Schneeberger EE, Pascual MA, Saidman SL, Williams WW, Tolkoff-Rubin N, et al. Complement activation in acute humoral renal allograft rejection: diagnostic significance of C4d deposits in peritubular capillaries. J Am Soc Nephrol. 1999;10(10):2208–14.

181. Minami K, Murata K, Lee CY, Fox-Talbot K, Wasowska BA, Pescovitz MD, et al. C4d deposition and clearance in cardiac transplants correlates with alloantibody levels and rejection in rats. Am J Transplant. 2006;6(5 Pt 1):923–32.
182. Qian Z, Lee CY, Murata K, Liu J, Fox-Talbot K, Wasowska BA, et al. Antibody and complement mediated injury in transplants following sensitization by allogeneic blood transfusion. Transplantation. 2006;82(7):857–64.
183. Murata K, Fox-Talbot K, Qian Z, Takahashi K, Stahl GL, Baldwin 3rd WM, et al. Synergistic deposition of C4d by complement-activating and non-activating antibodies in cardiac transplants. Am J Transplant. 2007;7(11):2605–14.
184. Wasowska BA, Qian Z, Cangello DL, Behrens E, Van Tran K, Layton J, et al. Passive transfer of alloantibodies restores acute cardiac rejection in IgKO mice. Transplantation. 2001;71(6): 727–36.
185. Rahimi S, Qian Z, Layton J, Fox-Talbot K, Baldwin 3rd WM, Wasowska BA. Non-complement- and complement-activating antibodies synergize to cause rejection of cardiac allografts. Am J Transplant. 2004;4(3):326–34.
186. Nozaki T, Amano H, Bickerstaff A, Orosz CG, Novick AC, Tanabe K, et al. Antibody-mediated rejection of cardiac allografts in CCR5-deficient recipients. J Immunol. 2007;179(8):5238–45.
187. Baldwin 3rd WM, Valujskikh A, Fairchild RL. Antibody-mediated rejection: emergence of animal models to answer clinical questions. Am J Transplant. 2010;10(5):1135–42.
188. Zhang X, Reed EF. Effect of antibodies on endothelium. Am J Transplant. 2009;9(11):2459–65.
189. Jindra PT, Jin YP, Rozengurt E, Reed EF. HLA class I antibody-mediated endothelial cell proliferation via the mTOR pathway. J Immunol. 2008;180(4):2357–66.
190. Yamakuchi M, Kirkiles-Smith NC, Ferlito M, Cameron SJ, Bao C, Fox-Talbot K, et al. Antibody to human leukocyte antigen triggers endothelial exocytosis. Proc Natl Acad Sci U S A. 2007;104(4):1301–6.
191. Jurcevic S, Ainsworth ME, Pomerance A, Smith JD, Robinson DR, Dunn MJ, et al. Antivimentin antibodies are an independent predictor of transplant-associated coronary artery disease after cardiac transplantation. Transplantation. 2001;71(7):886–92.
192. Mahesh B, Leong HS, McCormack A, Sarathchandra P, Holder A, Rose ML. Autoantibodies to vimentin cause accelerated rejection of cardiac allografts. Am J Pathol. 2007;170(4): 1415–27.
193. Uehara S, Chase CM, Cornell LD, Madsen JC, Russell PS, Colvin RB. Chronic cardiac transplant arteriopathy in mice: relationship of alloantibody, C4d deposition and neointimal fibrosis. Am J Transplant. 2007;7(1):57–65.
194. Russell PS, Chase CM, Winn HJ, Colvin RB. Coronary atherosclerosis in transplanted mouse hearts. II. Importance of humoral immunity. J Immunol. 1994;152(10):5135–41.
195. Delgado JF, Manito N, Segovia J, Almenar L, Arizon JM, Camprecios M, et al. The use of proliferation signal inhibitors in the prevention and treatment of allograft vasculopathy in heart transplantation. Transplant Rev (Orlando). 2009;23(2):69–79.
196. Jin YP, Korin Y, Zhang X, Jindra PT, Rozengurt E, Reed EF. RNA interference elucidates the role of focal adhesion kinase in HLA class I-mediated focal adhesion complex formation and proliferation in human endothelial cells. J Immunol. 2007;178(12):7911–22.
197. Hattori T, Shimokawa H, Higashi M, Hiroki J, Mukai Y, Kaibuchi K, et al. Long-term treatment with a specific Rho-kinase inhibitor suppresses cardiac allograft vasculopathy in mice. Circ Res. 2004;94(1):46–52.
198. Koch CA, Khalpey ZI, Platt JL. Accommodation: preventing injury in transplantation and disease. J Immunol. 2004;172(9):5143–8.
199. Alexandre GP, Squifflet JP, De Bruyere M, Latinne D, Reding R, Gianello P, et al. Present experiences in a series of 26 ABO-incompatible living donor renal allografts. Transplant Proc. 1987;19(6):4538–42.
200. Williams JM, Holzknecht ZE, Plummer TB, Lin SS, Brunn GJ, Platt JL. Acute vascular rejection and accommodation: divergent outcomes of the humoral response to organ transplantation. Transplantation. 2004;78(10):1471–8.

201. Soares MP, Brouard S, Smith RN, Bach FH. Heme oxygenase-1, a protective gene that prevents the rejection of transplanted organs. Immunol Rev. 2001;184:275–85.
202. Tabata T, de Perrot M, Keshavjee S, Liu M, Downey GP, Waddell TK. Accommodation after lung xenografting from hamster to rat. Transplantation. 2003;75(5):607–12.
203. Delikouras A, Hayes M, Malde P, Lechler RI, Dorling A. Nitric oxide-mediated expression of Bcl-2 and Bcl-xl and protection from tumor necrosis factor-alpha-mediated apoptosis in porcine endothelial cells after exposure to low concentrations of xenoreactive natural antibody. Transplantation. 2001;71(5):599–605.
204. Ding JW, Zhou T, Ma L, Yin D, Shen J, Ding CP, et al. Expression of complement regulatory proteins in accommodated xenografts induced by anti-alpha-Gal IgG1 in a rat-to-mouse model. Am J Transplant. 2008;8(1):32–40.
205. Jindra PT, Zhang X, Mulder A, Claas F, Veale J, Jin YP, et al. Anti-HLA antibodies can induce endothelial cell survival or proliferation depending on their concentration. Transplantation. 2006;82(1 Suppl):S33–5.
206. Colvin RB, Smith RN. Antibody-mediated organ-allograft rejection. Nat Rev Immunol. 2005; 5(10):807–17.

Chapter 23
Infections After Cardiac Transplantation

Robin K. Avery

Introduction

Recent years have seen many advances in prevention and treatment of infections in heart transplant candidates and recipients. In general, the field has adopted an increasingly proactive approach, with the advent of molecular diagnosis for early detection of viral infections, for example. In particular, strategies for prevention of cytomegalovirus (CMV) infection, either prophylaxis or pre-emptive therapy or a combination of these, have rendered CMV less likely to be symptomatic and tissue-invasive [1]. Standardization of definitions for infection in ventricular assist device (VAD) patients [2] and heart transplant recipients [3] have helped to facilitate inter-center comparisons and establish guidelines [4–6]. However, challenges remain. Multidrug-resistant bacteria [7–9] and a more virulent strain of **C. difficile** [10] have led to complicated courses for some patients over the past decade. Newer understanding of the impact of low-level or subclinical viral infections on allograft function [11, 12] has brought to our attention the importance of asymptomatic viremia in some circumstances. And longer post-transplant survival has led to increasing risk of environmental infection exposures (occupational, residential, recreational, travel-related). Future directions for research should include further studies of the impact of newer immunosuppressive agents on transplant-related infections, refinement of diagnostic techniques for assessing pathogen-specific immune function, and continuing improvements on pre-transplant screening and post-transplant infection prophylaxis and monitoring.

R.K. Avery, MD, FIDSA
Division of Infectious Disease (Transplant/Oncology), Johns Hopkins Hospital,
1830 East Monument Street #449, Baltimore, MD 21205, USA
e-mail: ravery4@jhmi.edu

H. Eisen (ed.), *Heart Failure*, DOI 10.1007/978-1-4471-4219-5_23

Pretransplant Screening, Immunizations, and VAD-Related Infections

Heart transplant candidates, like all solid organ transplant candidates, should be subjected to a rigorous pre-transplant evaluation process that includes an assessment of infections, both overt and latent, that the patient has had in the past [13]. This is accomplished by a careful medical history and thorough exam, examination of previous microbiology records if any, and full evaluation of any symptoms, physical signs, or radiographic indications of possible active infection. The purpose of this is to render transplantation safer by application of preventive measures pre-transplant, by treating active infections to the extent possible, and utilizing prophylactic measures for latent infections according to current guidelines [13].

Donor screening and prevention of donor-transmitted infections will be described below.

Patients with advanced heart failure who come to transplant evaluation may have had a variety of infections, including pneumonia, sinusitis, urinary tract infections, bloodstream infections, and skin/soft tissue infections. Particularly common are cellulitis and sometimes ulcerations of the lower extremities in the setting of peripheral edema, and infections related to (primarily central) intravenous access catheters that are placed either for long-term administration of inotropes, or short-term for inpatient treatment of acute decompensated heart failure. Infections related to other endovascular devices, including intra-aortic balloon pumps, pacemakers, or implantable defibrillators, are also common. Patients who are bridged to transplant with a ventricular assist device (VAD) are particularly subject to infections originating in the driveline site, across a spectrum that includes localized driveline site infection, pocket infection, bacteremia, candidemia, and VAD endocarditis [2, 14, 15]. In one series, half of the VAD patients bridged to transplant had post-transplant bloodstream infections, with **Staphylococcus** species being the most common organism, followed by **Candida**, **Pseudomonas**, and **Enterococcus** [15].

Treatment of active infection prior to transplantation is a central principle, but complete eradication of infection is not always possible until the transplant, particularly in patients on mechanical circulatory support for whom removal of the VAD (with transplantation) is necessary for complete resolution of infection. However, infections that do not involve mechanical circulatory support devices should be treated as fully as possible (see Table 23.1 for recommended durations of therapy of infections in the pre-transplant phase). That is to say, wherever possible, pneumonias should be treated according to standard guidelines depending on severity, organism, and whether community-acquired or healthcare-associated (Table 23.1). This treatment period should ideally result in the resolution of symptoms and radiographic findings (although in some cases, radiographic findings may persist for some time after the resolution of infection and this decision can be individualized.) Infections involving vascular access devices should be treated according to standard guidelines (Table 23.1), and repeat blood cultures at least several days after completion of the planned course of antibiotic therapy should be obtained for “proof of cure.” Urinary

Table 23.1 Duration of therapy for common pre-transplant infections [16–23]

Infection	Therapy duration	Guidelines
Pneumonia (Community-acquired)	Minimum 5 days, afebrile 48–72 h, stable	IDSA Guidelines [16]
Pneumonia (Hospital-acquired, ventilator-associated, and healthcare-associated)	8 days (if responding); unless Pseudomonas aeruginosa (14–21 days)	ATS/ IDSA Guidelines [17]
Implantable cardiac device infections		(AHA Guidelines) [18]
Pocket infection	10–14 days after device removal	
Bloodstream infection	At least 14 days after device removal	
Complicated infection	At least 4–6 weeks	AHA Guidelines [18]
Bacteremia (Catheter-related, without other implantable devices)	2–6 weeks depending on organism and clinical circumstances	(IDSA Guidelines) [19]
Infective endocarditis	4–6 weeks (depending on type, organism—although 2-week regimens have been described for certain organisms, transplant candidates should receive longer durations)	(AHA/IDSA Guidelines) [20]
Urinary tract infection		
Uncomplicated cystitis in women	3–7 days	(IDSA/ESMID Guidelines) [21]
Uncomplicated pyelonephritis in women	7–14 days (depending on antibiotic used)	(IDSA/ESMID Guidelines) [21]
Catheter-associated UTI	7 days if prompt response; 10–14 days if delayed response	IDSA Guidelines [22]
Cellulitis (non-necrotizing)	7–10 days or more (varies by organism and clinical course)	IDSA Guidelines [23]

tract infections (UTI) should be treated with removal or change of the foley catheter (if any) in addition to administration of culture-directed antimicrobial therapy. Duration of UTI therapy can range from short-course (3 day) therapy of outpatient uncomplicated UTI's in females to 6 weeks or more for prostatitis in males, but most frequently will be in the range of 7–10 days (Table 23.1) [16–23]. The patient should have a repeat urine culture off antibiotics and also a repeat urinalysis to demonstrate the resolution of pyuria. If pyuria persists, additional evaluation is warranted, which may include a urine culture specifically for fungi (**Candida glabrata** may not grow well on standard urine cultures but is increasingly seen as a pathogen in patients with multisystem illnesses.) Duration of therapy for cellulitis can be complicated by slow resolution of erythema and persistence of swelling in patients with lower extremity edema, but most often will be in the 7–14 day range. The use of oral suppression after a series of recurrent infections, such as cellulitis, is a consideration, but given the risks of complications such as **C. difficile**—associated diarrhea, such a decision should be carefully weighed and the risks and benefits discussed fully with the patient.

For patients who have an infection with a VAD in place, recent guidelines are helpful with duration of therapy and decisions about long-term suppression [2, 4]. Organisms are most frequently staphylococci, but Gram-negative bacilli such as **Pseudomonas**; other Gram-positive organisms such as enterococci; and fungal infections may occur [14, 15]. Fungemia was described in 7 VAD patients in one series (5 with candidemia, 2 with aspergillosis) for an attack rate of 0.1 infections/1000 days of device support [24]. Most patients with a VAD-related infection can safely undergo transplantation provided that their bloodstream infection is controlled at the time of transplantation, and appropriate antibiotics are administered post-transplant as well as pre-transplant to eradicate any additional remaining foci. In some cases, a bacteremia or candidemia cannot be controlled prior to transplant because of continued presence of the device. In such situations, transplantation may be undertaken, but with the known risk of persistence or recurrence of the infection and with lengthy antimicrobial therapy afterwards. It is a principle of endovascular infections in general that definitive treatment often involves removal of the device (catheter, pacemaker, ICD), but with VAD's the situation is complicated by the difficulty of removal and replacement of the device, which can only be undertaken in extreme circumstances. Therefore, control of the infection and (in some cases) continuous suppression of previous organisms until transplant may be all that can be achieved prior to transplantation. Unfortunately, as with other healthcare-associated infections, the rise of multiply-resistant bacterial pathogens has complicated therapy and sometimes led to use of newer drugs such as daptomycin [25].

As part of pre-transplant evaluation, the recipient undergoes a serologic screening panel which can help with risk stratification and with prophylaxis post-transplant (Table 23.2) [13]. This generally includes, at a minimum, serologic testing for HIV, HBV, HCV, syphilis, CMV, EBV, and VZV. Patients with a positive HCV antibody screening test should undergo HCV RNA screening and, if positive for HCV RNA, should undergo evaluation by a hepatologist. Patients with positive anti-HBc and anti-HBs but negative HBsAg are those who have had HBV in the past and have resolved it; no further therapy is necessary. Patients with positive HBsAg have active HBV infection and should be seen by a hepatologist. Patients with isolated positive anti-HBs (with negative HBsAg and negative anti-HBc) have received effective vaccination. Patients with positive anti-HBc, negative HBsAg and negative anti-HBs are either those who have resolved infection (with anti-HBs waning below the level of detectability), or those with early active infection in the "window period" (in which case the anti-HBc IgM is positive), or those with false-positive anti-HBc. Further evaluation with HBV DNA and anti-HBc IgM is desirable.

Patients with a positive non-treponemal serologic test for syphilis (e.g. RPR) should have a treponemal test performed for confirmation (e.g. FTA-ABS or MHATP). If the treponemal test is negative, the RPR is most likely a biologic false-positive and is not a contraindication to transplantation. If the treponemal test is positive, the patient should be evaluated for active syphilis and treated according to standard guidelines. Involvement of an infectious disease specialist is highly recommended. Treated syphilis is not a contraindication to transplantation. After treatment

Table 23.2 Pre-transplant testing of donor and recipient [37]

OPTN/HRSA minimum requirements for deceased donor testing (United States) for infection
U.S. FDA-licensed Anti-HIV-1 and Anti-HIV-2 serologic screening test
Hepatitis screen serological testing, including HBsAg, HBcAb, and anti-HCV
VDRL or RPR
Anti-CMV
EBV serological testing
Blood and urine cultures; urinalysis within 24 hours prior to cross-clamp http://optn.transplant.hrsa.gov/PoliciesandBylaws2/policies/pdfs/policy_2.pdf [37]
Additional donor testing (under specific circumstances)
NAT (Nucleic Acid Amplification Testing) for HCV, HBV, HIV (see text)
Recipient pre-transplant testing
Serology for HIV, HBV, HCV (anti-HCV and HCV RNA), syphilis (RPR or syphilis IgG), CMV (CMV IgG), EBV (VCA IgG) Toxoplasma IgG, as above
Serology for VZV, hepatitis A, ± HSV
Testing for latent TB infection (interferon-gamma release assay, or tuberculin skin test)
For those with possible exposures: serologies for Strongyloides, Chagas disease, schistosomiasis
Blood, urine, sputum, stool microbiologic diagnostic testing if clinically indicated
Chest Xray; CT scans and other imaging if clinically indicated

the RPR titer may take months to years to resolve, so a negative RPR is not required after treatment of syphilis before proceeding to transplantation.

Serology for VZV is performed primarily to detect the uncommon seronegative transplant candidate, and to help with management of VZV exposures post-transplant. Less than 10 % of adults are seronegative for VZV in most regions. However, VZV-seronegative individuals are at risk for severe primary varicella if exposed post-transplant, and should receive varicella vaccination pre-transplant if they are not on immunosuppression already, and if they are not expected to undergo transplantation within 4 weeks. (If they do receive varicella vaccination pre-transplant and then get a donor offer less than 4 weeks later, they may undergo transplantation but with immediate post-transplant initiation of acyclovir or ganciclovir therapy.) VZV-seronegative candidates who cannot receive varicella immunization pre-transplant (due to being on immunosuppression or being too close in time to transplant) should be counseled extensively on their risk of acquiring varicella post-transplant and should be encouraged to report any exposures immediately so that prophylactic antiviral therapy can be administered.

Serology for CMV and EBV should be performed primarily to determine risk status in conjunction with the CMV and EBV serologies of the donor (see below). The relevant serologies are CMV IgG and EBV VCA IgG. In both cases, the highest-risk status is donor-seropositive, recipient-seronegative (D+/R−) which often warrants special monitoring and in some cases for CMV, may warrant extended prophylaxis [1, 6].

HIV was once considered a contraindication to transplantation, but in recent years, successful transplantation of HIV-positive kidney and liver recipients has

been reported through a multicenter study and has become widely accepted practice [26]. Thoracic transplantation of HIV-positive candidates has been less commonly performed, but has been reported [27, 28] and is likely to increase in the future, based on the experience in abdominal transplantation, and based on the large number of individuals with HIV who have controlled viral loads and who are surviving longer with chronic diseases including heart disease. Transplantation of HIV-positive recipients requires careful monitoring of pharmacokinetics by a pharmacist with knowledge of the extensive drug interactions particularly between protease inhibitors and calcineurin inhibitors [29]. Evaluation of HIV-positive candidates should include an assessment of the patient's HIV-RNA viral load and CD4 count over time as well as any opportunistic infections in the past, and any indications of active infection that might persist or recur post-transplant [29].

The transplant candidate should undergo testing for latent TB infection with an interferon-gamma release assay (IGRA) blood test, or PPD skin testing, and should be considered for latent TB therapy with isoniazid if either of these tests is positive (see below) [13, 30].

Further recommendations on management of latent TB infection [30] as well as pre-transplant non-tuberculous mycobacterial infections [31] are given below.

The pre-transplant evaluation is also an important time to update immunizations, which are more effective when administered prior to transplant [13, 32]. The American Society for Transplantation (AST) has published guidelines for immunizations in pretransplant candidates and post-transplant recipients [32]. Because of the degree of detail of these recommendations, the reader is referred to the AST Guidelines for further information [32]. For pediatric candidates, standard immunization series should be completed prior to transplant whenever possible [32]. For adult candidates, immunizations should be administered according to the recommendations for adult immunizations with the exception that live virus vaccines (e.g. varicella vaccine, zoster vaccine) should only be administered if the patient is not on immunosuppression and transplantation is not anticipated within 4 weeks [32]. The patient should receive yearly influenza vaccine with the injected preparation rather than the live attenuated nasal vaccine [33]. The family members of the transplant candidate should also receive influenza immunization to create a "circle of protection" around the patient [33]. Pneumococcal vaccine should be administered if it has not been received within 5 years and if the patient has not already had 2 lifetime doses. The 3-dose hepatitis B vaccine series should be administered to any candidate who is seronegative for anti-HBs. Although commonly administered at 0, 1, and 6 months, an accelerated course (e.g. 0, 1, and 2 months) can be given to those in whom transplantation is anticipated to occur soon. (Although HBV vaccine can be given post-transplant, it is less effective in patients on immunosuppression.) Tetanus-diphtheria-acellular pertussis (Tdap) vaccine should be administered if not already received (although the standard time interval for repeating tetanus vaccine is 10 years, the Tdap vaccine can be given if the last tetanus vaccine was >2 years previous.) The advantage to Tdap is the additional protection against pertussis, which can cause protracted infection in immunocompromised patients.

HPV vaccine should be offered to patients aged 11–26 of both genders. HPV is a significant issue in long-term survivors of transplantation although the efficacy of pre-transplant HPV vaccine in preventing post-transplant HPV is yet unknown. Zoster vaccine should be offered to candidates age 60 and above who are not on immunosuppression and who are not anticipated to undergo transplantation within 4 weeks. It can also be offered to those aged 50–59 who meet the above criteria (it is FDA-approved but not ACIP-recommended for this age group.)

Early Post-transplant Infections

According to the paradigm initially developed by Rubin [34], there are 3 distinct time periods of post-transplant infection risk: the first month, months 2–6, and after 6 months. At any stage, the risk for infection is a combination of the "net state of immunosuppression" and the patient's particular environmental exposures [34]. In the first post-transplant month, although immunosuppressive medications are being administered at high doses, the full effects of immunosuppression have not yet taken hold on the immune system, and the vast majority of infections are not opportunistic infections, but rather are those which can occur after any major surgical procedure [34]. These include catheter-related infections, urinary tract infections, pneumonias, empyemas, sternal wound infections, and mediastinitis. Risk factors for these infections include protracted intensive care unit stay, protracted requirement for mechanical ventilation, primary graft dysfunction, technical complications of surgery, need for reoperations (such as exploration and evacuation of hematomas), renal dysfunction and need for renal replacement therapy, multiorgan dysfunction, older age, and diabetes.

Neutropenia associated with transplant medications such as ganciclovir, valganciclovir, mycophenolate mofetil, and azathioprine can also contribute to infection risk. As discussed below, multidrug-resistant organisms are increasingly seen, and occur particularly in those patients with extensive prior antibiotic exposures both pre- and post-transplant [7–9].

While most of the above infections can occur in any solid organ transplant recipient, heart recipients are particularly at risk for intrathoracic infections, including mediastinitis. Sternal wound infections may occur as after any cardiac surgery, but may be more common in transplant recipients than in nontransplanted cardiac surgery patients. A study from a large Spanish database (the RESITRA database) reported an incidence of 4.8 % for incisional surgical site infections in heart recipients, with staphylococci being the most common pathogens, but a variety of other organisms were seen including Gram-negative bacilli (Proteus, and extended-spectrum-beta-lactamase producing E. coli); and yeast (Candida albicans and C. glabrata) [35]. Patients with pre-existing VAD-related infections are at risk for mediastinitis with their previous infecting organisms unless a lengthy course (4–6 weeks) of pathogen-directed post-transplant therapy is administered.

Other commonly seen infections during the first month include candidiasis (especially oropharyngeal thrush) and herpes simplex virus (HSV) reactivation. Prophylaxis of oropharyngeal candidiasis with either nystatin oral suspension (swish and swallow) or clotrimazole troches is almost universal. Oropharyngeal and occasionally esophageal HSV infection can result from reactivation of HSV-1, while genital and perianal HSV can result from reactivation of HSV-2. Thus most patients who are not receiving ganciclovir or valganciclovir prophylaxis for CMV should be receiving acyclovir or valacyclovir prophylaxis for HSV (and VZV). Uncommonly, opportunistic infections such as cytomegalovirus or aspergillosis may be seen during the first month, in the setting of pre-transplant immunosuppression or excessive environmental exposures.

Donor-Transmitted Infections

A wide variety of organisms (bacterial, fungal, viral) have been reported to be transmitted via solid organ transplantation [36]. Some, but not all, are preventable through pre-transplant screening [13]. Like prospective transplant recipients, prospective deceased donors undergo a rigorous screening process consisting of a serologic panel, review of medical records, and detailed medical and social history (in this case from the donor's family members.) In addition, blood cultures, urine culture, and chest radiography are generally performed although the results of cultures may not be available until after the transplant has been performed. Details of standard deceased donor testing can be found in Table 23.2 and on the OPTN/HRSA website http://optn.transplant.hrsa.gov/PoliciesandBylaws2/policies/pdfs/policy_2.pdf [37].

The serologic panel performed on deceased donors is similar to that for recipients, and serves three main functions . First, certain serologies may disqualify the donor completely – in the US, in the past, this has included a positive test for HIV or a positive HBsAg indicative of active HBV infection, although in other parts of the world these criteria might not disqualify all donors. Most recently, the possible use of HIV-positive donors is being explored through the HOPE Act [38]. Second, serology results might suggest limiting the donor to a particular subgroup of recipients (e.g. an HCV-positive donor to an HCV-positive recipient, see below.) Finally, serologic screening may help to determine risk stratification and prophylaxis protocols post-transplant, as with CMV and EBV for which the highest risk group is seronegative recipients with seropositive donors (D+/R−). A positive donor serology for syphilis is not a contraindication to transplantation, but the recipient should be treated. Donor blood testing for latent TB infection, in the form of the interferon-gamma release assay (IGRA), is not yet universally available due to the requirement that the test be performed in a specialized laboratory using living cells.

Until recently, most of the elements of the serology panel were antibody serologies (IgG) indicating exposure at some time in the past. This landscape is changing, after transmissions of viral infections such as HIV and HCV were reported during the "window period" (prior to antibody seroconversion) of the donor [39, 40]. The deceased-donor time frame was traditionally not long enough to conduct assays that directly detect the presence of viral genomes, which would detect infection earlier

than antibody seroconversion and thus shorten the "window period". More recently, with development of rapid molecular testing known as NAT ("nucleic acid amplification") testing, it has become possible for the majority of organ procurement organizations (OPO's) to perform NAT testing in the deceased donor time frame [41]. A national discussion ensued regarding whether or not NAT testing should be applied to all prospective donors, or whether it should be restricted to those with CDC-defined high risk behaviors (including injection drug use, sexual promiscuity, and incarceration) [40]. Recent guidelines from the US Public Health Service have recommended NAT testing for HCV for all donors, and NAT testing for HIV in high-risk donors [41]. For further discussion on the risk of HCV and HBV in the cardiac transplant recipient, see section on "Other Viruses" below.

Other infections which would generally disqualify prospective donors include bacteremias with virulent organisms such as MRSA, VRE, or multidrug-resistant Gram-negative bacteria; active invasive fungal infection, or active tuberculosis. Occasionally, a bacterially-contaminated organ, where the infection was not previously suspected, may result in transmission of infection to the recipient [42]. However, bacterial meningitis with community-acquired organisms such as Pneumococcus is not considered a contraindication to transplantation if appropriate antibiotics are administered to the recipient post-transplant [43, 44]. Recently a study from UCLA extended this concept by reporting safe transplantation of hearts from donors with bacterial sepsis [45], although it should be noted that this referred to sepsis with community–acquired organisms and not with nosocomial, multidrug-resistant organisms. Also, caution should be exercised in prospective donors with abnormal CSF findings without positive bacterial cultures, since such fatal transmissions as West Nile virus, rabies, lymphocytic choriomeningitis virus, or even lymphoma could result [36]. If a bacterial meningitis donor is to be utilized, proof of bacterial infection with a positive culture of donor CSF is important.

The formation of the Disease Transmission Advisory Committee (DTAC) by OPTN/UNOS was a significant advance towards a more evidence-based understanding of the nature, risks, and outcomes of donor-transmitted infections [46]. Since 2005, this group has reviewed all reported possible transmissions of infection or malignancy, and have scored these as proven, probable, or possible according to uniform criteria [46]. Transplant centers and clinicians are strongly encouraged to report any suspected donor-derived infections via this mechanism, which contributes to the knowledge base of the transplant community as a whole, in addition to facilitating notifications and communications to other transplant centers who have transplanted organs from the same donor.

Cytomegalovirus

Cytomegalovirus (CMV) remains one of the most important post-transplant infections, although prophylactic and pre-emptive therapy strategies have reduced its incidence and severity [1, 5, 6]. Prior to the prophylaxis era, between 40–80 % of transplant recipients developed symptomatic CMV disease. The highest risk group

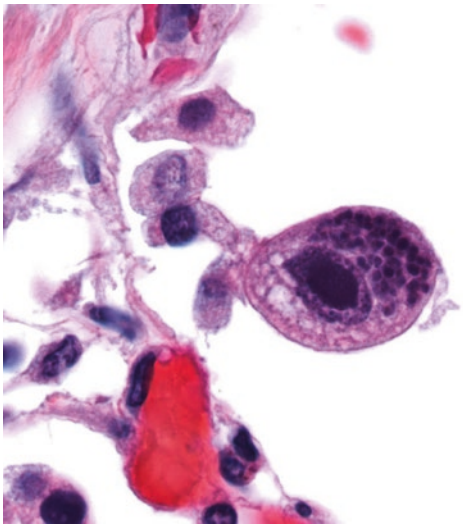


Fig. 23.1 Cytomegalovirus inclusion in type 2 pneumocyte from immunocompromised patient with CMV pneumonia. The cell contains an eosinophilic nuclear inclusion that obscures most of the cell nuclear and multiple smaller basophilic cytoplasmic inclusions. 1000× magnification (Image courtesy of Dr. Carol Farver, Pathology Department, Cleveland Clinic)

is the donor-seropositive, recipient-seronegative (CMV D+/R−) group in which the recipient has no antecedent CMV-specific immunity but acquires a CMV viral load from the donor. Those recipients who were already seropositive for CMV (R+) can develop CMV reactivation under the influence of immunosuppression, particularly after treatment for rejection, and those who are D+/R+ can either reactivate their own CMV strain from the past, or can develop superinfection with the donor's strain of CMV. Classically, symptomatic CMV appeared most frequently between 1 and 4 months post-transplant, but with prophylaxis, a first episode of CMV might occur in the second half of the first post-transplant year or even later [1] (Fig. 23.1).

Clinical manifestations of CMV infection fall into three categories: asymptomatic viremia, "CMV syndrome," and tissue-invasive CMV. All 3 categories are referred to as "CMV infection," and the latter 2 categories (CMV syndrome and tissue-invasive CMV) are referred to as "symptomatic CMV" or "CMV disease." Asymptomatic viremia is usually associated with a low blood viral load (often <10,000 copies/ml) and is usually discovered as part of a pre-emptive monitoring program. "CMV syndrome", associated with moderate elevation of the viral load (e.g. 10,000–100,000 copies/ml), is a flulike illness with fevers, chills, malaise, myalgias, and often leukopenia, thrombocytopenia, and mild elevations of the liver function tests. Tissue-invasive CMV (usually associated with high viral loads, 100,000 copies/ml and above) is the most clinically severe manifestation, and refers to the situation where CMV can be detected in tissue by histopathology and/or tissue immunostaining. The organs most commonly involved are the lung (CMV pneumonitis), liver (CMV hepatitis), GI tract (CMV esophagitis, gastritis, enteritis, colitis) and less commonly the eye (CMV retinitis) and central nervous system (CMV meningoencephalitis.) For lung and liver transplant recipients, the allograft is the most common localization for tissue-invasive CMV, but in heart recipients, CMV myocarditis is uncommon, and GI tract manifestations appear more frequently.

Tissue-invasive CMV is often associated with debilitation, multiorgan dysfunction, and a prolonged recovery phase. Higher peak viral loads in the initial CMV episode are associated with risk for recurrences, tissue-invasive disease, and development of ganciclovir resistance.

Detection of CMV was originally performed by tissue culture of peripheral blood, but this was time-consuming and labor-intensive. Shell-vial centrifugation culture reduced the turnaround time to 48 hours but was less sensitive at low viral loads. The pp65 antigenemia test provided a semi-quantitative measure of CMV load, but was labor-intensive and lost sensitivity if samples were mailed in from distant sites. Most centers now use some form of molecular diagnostic test, most commonly the quantitative CMV PCR, which expresses the viral load in copies/ml. However, inter-center comparisons have been complicated by inter-laboratory variation and a multiplicity of locally-designed assays. The recent development of a WHO standard (in IU/ml) and the advent of the first FDA-approved quantitative PCR test should help to standardize these disparate results [47].

Given the severity of CMV in the early years of transplantation, considerable effort has been devoted to developing systems of prevention. Two main strategies, termed "prophylaxis" and "pre-emptive therapy", have been shown to reduce CMV incidence and severity.

"Prophylaxis" refers to administration of an antiviral agent to an entire group. In cardiac transplantation, this approach was pioneered by Merigan et al. in 1992, with a randomized trial of a 4-week intravenous ganciclovir regimen compared with placebo [48]. This regimen significantly reduced the incidence of symptomatic CMV from 46 % to 9 % in the recipient-seropositive (R+) subgroup, but did not significantly reduce symptomatic CMV in the high-risk D+/R− subgroup [48]. Today, most centers use prophylaxis with valganciclovir, which is an oral analogue of IV ganciclovir but which has greater bioavailability than the older formulation of oral ganciclovir. The PV16000 study compared 100 days of prophylaxis with valganciclovir to oral ganciclovir in kidney, heart, pancreas, and liver transplant recipients, and found that oral valganciclovir prophylaxis was associated with less breakthrough viremia while on prophylaxis and less ganciclovir resistance, but the incidence of viremia and symptomatic CMV disease by the end of 1 year were comparable between the two groups [49]. In D+/R− kidney [50] and in all lung recipients [51], extended courses of prophylaxis have recently been reported in randomized trials to be beneficial with regards to reduction in CMV events (6 months and 12 months respectively) but whether this is the case for D+/R− heart recipients remains to be demonstrated. The addition of CMV hyperimmune globulin (CMVIg) to prophylaxis regimens for D+/R− recipients, a once-popular strategy [52], is now less frequently used due to the high cost of this therapy and the perceived efficacy of valganciclovir. However, recent studies using large databases suggest that the use of CMVIg as well as use of antiviral prophylaxis may improve long-term outcomes in cardiac transplantation [53, 54].

The other main strategy for CMV prevention is "pre-emptive therapy," which restricts anti-CMV antiviral usage only to those who develop evidence of CMV infection on a sensitive early detection test (usually either quantitative CMV PCR or

pp65 antigenemia.) This requires surveillance monitoring of all patients at risk. Advocates of pre-emptive therapy cite reductions in cost, toxicity, and possibly antiviral resistance associated with use of less antiviral drug [55]. They also point out that "late CMV" can occur after discontinuation of prophylaxis, and can be highly symptomatic [56]. However, the overall efficacy of prophylaxis has been shown in many studies over time [57]. With pre-emptive therapy, logistics can be daunting, and missing even one sample can lead to development of high viral loads and overt CMV disease prior to detection. Prophylaxis may also provide other benefits, such as prevention of other herpesviruses such as Epstein-Barr virus [58] and human herpesvirus-6 (HHV-6). Most centers now use valganciclovir prophylaxis, at least for D+/R− recipients (for at least 3 months), but may choose either prophylaxis or pre-emptive therapy for lower-risk (R+) recipients. Some centers have chosen to use a combined strategy of prophylaxis and pre-emptive therapy in order to detect "late CMV" occurring after prophylaxis while still at a low level of viral load, although this strategy has yet to be subjected to a randomized trial. It should be noted that valganciclovir causes both neutropenia and thrombocytopenia, and the CBC with differential should be carefully monitored (at least every 1–2 weeks, preferably weekly) while on extended courses of valganciclovir. CMV D−/R− recipients do not require anti-CMV prophylaxis, but generally receive prophylaxis for herpes simplex virus (HSV) and varicella-zoster virus (VZV) in the form of acyclovir or valacyclovir, for at least the first 1–3 months post-transplant.

The effects of CMV on the function of the allograft, particularly on cardiac allograft vasculopathy, have been the subject of intense research interest [12, 59, 60]. Early studies suggested that development of symptomatic CMV, or being in the high-risk D+/R− subgroup, were associated with greater risk for allograft dysfunction and development of CAV [61]. However, not all studies have uniformly shown this [62, 63]. Valantine et al. examined late outcomes of the groups from the original 1992 heart transplant IV ganciclovir prophylaxis study [48], who had been randomized to ganciclovir or no ganciclovir prophylaxis [64]. She found that ganciclovir prophylaxis (especially in patients who did not receive calcium channel blockers) was associated with significantly less risk for CAV [64]. There is also a suggestion that longer-term, low-level CMV viremia may be more deleterious to the allograft than short-term, high-level viremia [65, 66]. The impact of subclinical CMV was reported by Tu et al., in a study showing that CMV-specific CD4 cell activity was associated with better control of CMV viremia and a decreased risk for allograft vasculopathy and rejection [67]. In another study from the same group, aggressive prophylaxis (for the high-risk D+/R− group) was associated with better CMV outcomes than less aggressive prophylaxis (for the lower-risk R+ group), showing that the expected findings were reversed by the intensity of prophylaxis [11]. A nonrandomized but intriguing study by Potena et al. recently reported that prophylaxis was associated with less symptomatic CMV disease and smaller changes in maximal intimal thickness than pre-emptive therapy [68]. However this study compared two different eras of CMV prevention at one center, and so these findings await larger and preferably randomized studies for confirmation.

Different immunosuppressive agents can have differential effects on CMV risk. It has long been known that administration of antilymphocyte therapy for rejection markedly raises risk for symptomatic CMV in the weeks following such treatment [69], and that that increased risk can be counterbalanced by administration of antiviral prophylaxis with ganciclovir derivatives during and after this anti-rejection treatment [70]. In addition, the mTOR inhibitor everolimus was associated with significantly lower risk for CMV in a large randomized trial comparing regimens containing two doses of everolimus with a non-everolimus regimen [71], as well as a lower risk for CAV in the everolimus groups [71]. Future studies of novel immunosuppressive agents should ideally include an assessment of the impact of these agents on current rates of CMV infection and disease.

Epstein-Barr Virus (EBV) and Post-transplant Lymphoproliferative Disorder (PTLD)

Epstein-Barr virus is a lymphotropic and oncogenic virus which remains latent in lymphocytes over the lifetime of an infected individual, and can reactivate under the influence of immunosuppression [72]. Transplant immunosuppression reduces EBV-specific immune function, allowing replication of EBV in infected lymphocytes to proceed unchecked, resulting first in a polyclonal lymphoproliferative syndrome, and progressing in some cases to a full-blown monoclonal B-cell lymphoma. Over 90 % of adults have had EBV at some time in the past, reflected in a positive EBV VCA IgG serology at the time of transplant. Consequently, almost all adult donors are also EBV-seropositive. The uncommon EBV D+/R− group is at high risk for primary EBV acquired from the donor, and for transformation to PTLD/lymphoma [72]. Pediatric transplant recipients are more likely than adults to be EBV D+/R− (since they may not yet have had time to acquire EBV infection), and as such, are at high risk for PTLD [73]. In addition, EBV R+ recipients may develop symptomatic EBV/PTLD particularly after intensification of immunosuppression for rejection, such as treatment with antilymphocyte therapy [74]. EBV infection may take the form of asymptomatic viremia, an undifferentiated febrile illness, a mononucleosis-like syndrome, or a monoclonal lymphoma (PTLD) that can affect any organ including the allograft, but is particularly common in the lung, GI tract, central nervous system, and liver. Peripheral lymphadenopathy may not be present. For GI tract lesions, sudden gastrointestinal hemorrhage or perforation may be the presenting symptom. Although overt lymphoma from PTLD is usually associated with high blood viral loads of EBV, there are exceptions where PTLD occurs with low or even undetectable blood viral load [72]. Such cases may be EBV-negative PTLD, or may be EBV-positive when detected in tissue by in situ hybridization (EBER).

Treatment of PTLD involves reduction of immunosuppression, to the extent possible. For heart recipients, this option is limited by the risk of rejection, in contrast

to kidney recipients who can go back on dialysis if they lose the allograft. Reduction of immunosuppression generally works best in the setting of EBV viremia before frank lymphoma has developed, but is still worth doing even after biopsy-proven lymphoma has been diagnosed. If reduction of immunosuppression does not reverse the process, treatment of full-blown PTLD generally consists of rituximab-based regimens (rituximab alone, or in combination with chemotherapy regimens such as R-CHOP.) For localized disease, surgery or radiation therapy can be an option. Prior to the rituximab era, the prognosis of PTLD was poor, but has been improved by the addition of rituximab therapy [72].

Prevention of PTLD involves careful use of immunosuppression in high-risk patients, and monitoring of EBV D+/R− patients with quantitative EBV PCR over time [73, 75]. As with pre-emptive therapy for CMV, this approach offers the opportunity to intervene early with reduction of immunosuppression when the EBV PCR turns positive, in hopes of avoiding progression to high viral loads and PTLD [73, 75]. The utility of antiviral therapy in preventing PTLD has been debated, but a body of indirect evidence suggests a potential role for ganciclovir derivatives in this regard [58, 73, 76].

Other Viral Infections

Other viruses in the herpesvirus family share the characteristic of lifelong latency with CMV and EBV. Herpes simplex virus (HSV) is common in the general population, particularly HSV-1 (the oropharyngeal strain of HSV). Reactivation occurs early post-transplant in the form of oral ulcers and occasionally esophagitis, if prophylaxis is not administered. Patients who are seropositive for HSV-2 can experience reactivation in the genital/perianal area. Rarely, HSV can cause other more serious infections such as hepatitis, pneumonitis, and meningoencephalitis. These are uncommonly seen now due to the widespread use of antiviral prophylaxis (ganciclovir derivatives as well as acyclovir and valacyclovir prevent HSV and VZV).

Varicella-zoster virus (VZV) reactivation is common as well, and >90 % of adults are VZV-seropositive. Most zoster reactivations are in the form of zoster (shingles) extending over one to two or occasionally several dermatomes. In severely immunosuppressed patients, disseminated zoster can occur, including both cutaneous and visceral dissemination (involving lungs, liver, central nervous system, and sometimes other organs.) In occasional cases, “rashless” zoster can occur, either with cutaneous symptoms in the absence of a rash, or purely visceral involvement. Diagnosis of either HSV or VZV in the central nervous system rests upon the CSF PCR for those viruses.

In addition to HSV, VZV, CMV, and EBV, the herpesvirus family also includes human herpesviruses 6, 7, and 8. HHV-6 and 7 are the agents of roseola in infants, and seropositivity is almost universal in adults. Reactivation of HHV-6 is common post-transplant and may occur earlier than CMV [77]. It may take the form of asymptomatic viremia, a febrile illness, pancytopenia, or tissue localization in lung,

liver, or the central nervous system (meningoencephalitis). HHV-7 produces a similar array of infections though it is less commonly detected post-transplant than HHV-6. HHV-8 is the agent of Kaposi's sarcoma and may also reactivate post-transplant, although this appears to be uncommon in the US and more frequently seen in certain transplant centers in the Middle East and Europe [78].

Community respiratory viruses are important pathogens post-transplant, as hypoxemia and severe and protracted respiratory illness can result, sometimes requiring mechanical ventilation [79, 80]. Given that RSV infection can be particularly severe in pediatric cardiac patients and transplant recipients, nearly half of pediatric transplant centers in a survey in the U.S. utilize RSV prophylaxis with palivizumab, mostly below age 24 months [81]. In addition, in lung transplant recipients, profound allograft dysfunction can result 3–6 months after resolution of a respiratory viral infection [82]. Multiplex viral panels for diagnosis of respiratory viral infections are available to be performed on either nasopharyngeal viral swabs or bronchoalveolar lavage specimens [83]. These panels often consist of PCR's for influenza, parainfluenza virus (1, 2, 3), adenovirus, respiratory syncytial virus (RSV), human metapneumovirus (h-MP), and sometimes other viruses. Early diagnosis of influenza and institution of therapy within 48 hours can reduce the risk of ICU admission and severe complications [79]. Antiviral resistance in influenza may vary from year to year, and each year's updated recommendations from the Centers for Disease Control and Prevention (CDC) should be consulted [84]. Patients with symptomatic RSV, parainfluenza, or hMP infection may be candidates for inhaled or oral ribavirin therapy to prevent worsening lower-tract disease (and allograft dysfunction in lung transplant recipients) [85, 86]. Adenovirus deserves special mention because it was the most common viral genome detected in a pediatric heart transplant study of myocardial biopsies by Shirali et al., in which detection of myocardial viral genomes was associated with allograft dysfunction and adverse events [87]. In this study it was far more commonly detected in myocardial biopsies than was CMV [87]. Adenovirus infection, however, is likely less common in adults.

Parvovirus B19 may reactivate in immunocompromised patients and most frequently presents with severe anemia in the absence of blood loss [88]. The classic presentation with a slapped-cheek rash is usually not seen. Diagnosis is by blood parvovirus PCR and/or a bone marrow biopsy showing characteristic changes. Treatment is with intravenous immunoglobulin as there are currently no available antivirals with parvovirus-specific activity [88].

The gastrointestinal viruses (including norovirus and rotavirus) are very common in the general population, and are acquired through fecal-oral spread or foodborne illness. Although generally short and self-limited infections in healthy people, these viruses can cause protracted syndromes of chronic diarrhea in transplant recipients [89] and should be specifically sought in patients with unexplained diarrhea in whom C. difficile, bacterial enteric pathogens, and stool examination for ova and parasites has been negative.

Hepatitis B (HBV) and hepatitis C (HCV) may have a variety of effects on the heart transplant recipient, depending on the circumstances. Donors positive for hepatitis B surface antigen (HBsAg) are not generally used in the US although a

literature from Taiwan demonstrates safe transplantation from such donors with intensive prophylaxis in an endemic region [90]. On the other hand, the "core-positive" donor (HBsAg negative, anti-HBc positive) conveys a much lower risk of HBV transmission (1 in 30 or 1 in 60) which may be further reduced by effective pre-transplant immunization of the recipient and by prophylaxis of HBV-seronegative recipients [91, 92].

Hepatitis C is transmitted highly efficiently from seropositive donors to seropositive recipients (up to 75 % of the time in different studies), and carried a risk of increased cardiac allograft vasculopathy in one study [93] whereas another study showed poorer overall outcomes [94]. Although hepatitis C positive donors are sometimes targeted for HCV+ recipients and/or elderly recipients, the latter study by Gasink et al. demonstrated less successful outcomes with these groups as well [94]. HCV-positive donors should be used with great caution and only with stringent informed consent, preferably in life-threatening situations in which it would be difficult for another donor to be found.

Bacterial Infections Including MRSA, VRE, and Multidrug-Resistant Gram-Negative Bacteria

In the current era, some strains of both Gram-positive and Gram-negative organisms have increasingly developed resistance to standard antibiotics. Methicillin-resistant Staphylococcus aureus (MRSA) has become common in the general community as well as in healthcare-associated infections [7, 25]. Vancomycin-resistant **Enterococcus** (VRE) has also become a common colonizer of the GI tract particularly in patients with protracted hospitalizations and extensive antibiotic use [9]. More recently, Gram-negative bacilli such as **E. coli** and **Klebsiella pneumoniae** that produce extended-spectrum beta-lactamases (ESBL) have become increasingly common, and these strains are resistant to all beta-lactam-related antibiotics except for carbapenems (imipenem, meropenem, ertapenem) [8]. Resistance to quinolones is also on the rise, due to widespread use of quinolones for respiratory and urinary tract infections in the general population. Susceptibility to quinolones can no longer be assumed, as with a patient with fever and pyuria. Most concerning is the rise of carbapenem-resistant organisms such as KPC, which may be resistant to all antibiotics except for amikacin, colistin, and tigecycline [8]. The first two of these agents are nephrotoxic, and tigecycline is not highly active for bacteremic infections. Development of more effective and less toxic antibiotics for these multiresistant Gram-negative organisms would be a welcome development. Awareness of past colonization or infection with these any antimicrobial-resistant organisms in the recipient can inform decisions about empiric therapy for febrile illnesses post-transplant while awaiting culture results. Whether infection or colonization with such organisms should disqualify recipients from transplantation is debated. If past MRSA or VRE or ESBL-Gram negative infection has been treated and is no longer active, most clinicians would not consider these to be contraindications to transplantation, but past infection with more highly-resistant organisms such as KPC may be, given the difficulty of complete

eradication of these types of organisms and the limitations of available antibiotic therapy. Studies are currently underway to provide more evidence-based risk assessment in this regard.

Bacterial Infections: Clostridium difficile

C. difficile infection, though known for decades, rose to prominence in 2005 with the advent of a new and more virulent strain which produced an upsurge in infections and an increase in morbidity and mortality [10]. It may be hospital-acquired, or may be triggered by antibiotic usage which alters the balance of normal organisms in the intestine, allowing **C. difficile** to multiply. The organism produces a toxin which causes inflammation and pseudomembranes of the colonic mucosa, and presents clinically as severe diarrhea which can be accompanied by fever, leukocytosis, and abdominal pain. When C. difficile occurs in the setting of ileus, with increasing abdominal distention and pain rather than diarrhea, the complication of colonic dilatation and perforation is a significant risk. Fulminant infection may require colectomy for control. Infection in transplant recipients is common, partly due to their frequent and lengthy hospitalizations and partly as a result of extensive antibiotic use both pre- and post-transplant in this population [10, 95]. Detection of C. difficile by PCR is more sensitive than the previous enzyme immunoassays for C. difficile toxin. Oral metronidazole remains the initial treatment of choice except in severe infection, in which oral vancomycin is generally used. Oral vancomycin may be substituted if oral metronidazole has not produced improvement. When ileus is present, intravenous metronidazole is used, sometimes in combination with rectal vancomycin enemas or instillation of enteral vancomycin via nasogastric tube. The new drug fidaxomicin appears to be associated with decreased risk of C. difficile recurrences [96], but is expensive. Its use in transplant recipients is currently under study.

Recurrences of C. difficile-associated diarrhea may occur in transplant recipients due to the persistence of **C. difficile** spores that are unaffected by anti-**C. difficile** antibiotic therapy and that subsequently germinate and cause recrudescence of the infection, as well as frequent use of antibiotics in this population. Another area of controversy is how long to wait after a **C. difficile** episode in a recipient on the waiting list, before reactivating their candidacy for transplantation. Further studies of optimal therapy, duration, and prophylaxis of **C. difficile** would be helpful in the transplant population.

Bacterial Infections: Nocardia, Legionella, Listeria, Salmonella, Tuberculosis, Nontuberculous Mycobacteria

Some bacterial infections are seen principally in immunocompromised patients (e.g. nocardiosis) and some are more severe in their manifestations in immunocompromised patients (e.g. salmonellosis, mycobacterial infection.) Nocardiosis, like

fungal infections, likely relates to environmental exposures in the setting of immunosuppression [97]. Most common presentations include pulmonary nodules and nodular infiltrates, with occasional CNS involvement (including space-occupying brain abscesses) and skin and soft-tissue infections. Trimethoprim-sulfamethoxazole prophylaxis (administered for Pneumocystis prevention) provides some but not complete protection.

Legionella pneumonia occurs in the community particularly in older individuals or those with chronic lung disease, but can be particularly severe, multilobar, and rapidly progressive in immunocompromised individuals [98, 99]. It is associated with water sources including water leaks in patient homes, and also hospital water supplies in some centers. Hallmarks of legionellosis include rapid radiographic progression and presence of polymorphonuclear leukocytes but absence of conventional organisms on Gram staining of sputum. It is likely an under-recognized infection in transplant recipients [98, 99]. Culture or PCR for **Legionella** can be performed as part of an immunocompromised bronchoalveolar lavage panel, and inclusion of a macrolide (e.g. azithromycin) as part of empiric therapy for pneumonia provides Legionella coverage. The urine antigen test detects only **Legionella pneumophila** type 1, but other species (e. g L**. micdadei**, **L. longbeachae**) may cause pneumonia in immunocompromised hosts, so the urine antigen test should not be considered to rule out **Legionella** [100]. Along with **Legionella**, other "atypical" organisms such as **Mycoplasma pneumoniae** and **Chlamydophila** (formerly **Chlamydia**) **pneumoniae** should be considered in the differential diagnosis of severe pneumonia. PCR testing for these organisms is also available, and this group responds to azithromycin, doxycycline, or respiratory quinolones such as moxifloxacin and levofloxacin.

Listeria monocytogenes causes meningitis, bacteremia, and occasionally other infections in infants, the elderly, pregnant women, and immunocompromised patients [101, 102]. Myocarditis in cardiac transplant recipients has been occasionally reported [103]. It is a foodborne illness associated with unpasteurized dairy foods and soft cheeses, deli meats, frankfurters including turkey franks, and other foods as well. A large outbreak in 2012 was traced to contaminated cantaloupe. Other foodborne pathogens may have protracted or unusually severe presentations in transplant recipients, including **Salmonella**, which is more likely to cause bacteremia and metastatic seeding in this group. Eggs and poultry should always be cooked thoroughly, and utensils and cutting boards thoroughly cleaned.

Tuberculosis is a major problem for transplant programs in endemic areas [104]. In addition to classic pulmonary TB presentations, extrapulmonary, military, and atypical presentations are common in transplant recipients [104–106]. Most post-transplant TB occurs by reactivation of latent TB infection in the recipient, but approximately 4 % is donor-derived [105]. In the past, detection of TB infection relied on the PPD skin test, but anergy in chronically ill or immunocompromised individuals has led to false negative tests in some transplant candidates and recipients. In the last several years, interferon-gamma release assay (IGRA) testing has become available, which detects the patient's lymphocyte reactivity to TB antigens [30]. The advantages of this test are that it differentiates between Mycobacterium

tuberculosis infection (positive) and BCG vaccination (negative) and that it is performed as a single step rather than requiring reassessment in 48 hours as with the skin test. However, the IGRA assay may still be falsely negative in immunocompromised individuals as it depends on cellular immune function. In addition, it must be transported promptly to the laboratory and processed immediately, or an "indeterminate" result may be received.

Development of active TB post-transplant is associated with high rates of extrapulmonary and disseminated infection, morbidity, and mortality. Use of rifampin, one of the most effective anti-TB drugs, in a combination regimen, is associated with decreased levels of calcineurin inhibitors and consequently a risk of rejection. Even with increased doses of cyclosporine or tacrolimus, it may be very difficult to achieve adequate levels. It is far safer to prevent active TB by detecting and treating latent TB infection, preferably starting in the pre-transplant phase if possible, and completing a 9-month course of isoniazid post-transplant. Liver function tests should be monitored during these courses of latent TB infection therapy, but isoniazid hepatotoxicity appears to be less common in transplant candidates and recipients than previously thought [107–109]. Administration of pyridoxine (vitamin B6) 50 mg/day while on isoniazid serves to prevent the development of neuropathy as a side effect of isoniazid.

As yet, the deceased donor time frame does not usually allow for testing of the donor for latent TB infection, so transplant clinicians should be alert for risk factors in the history or clinical presentation of the patient (e.g. homelessness, alcoholism, incarceration, residence or country of origin in endemic areas, compatible radiographic abnormalities such as apical scarring or calcified hilar nodes, or multiple "culture-negative" pulmonary infections.)

Nontuberculous mycobacterial infection is often related to environmental exposures (soil, gardening, lake or pond water, hot tubs or jacuzzis) [31, 110]. Most often this presents with chronic pulmonary nodules and nodular infiltrates with or without cavitation. Bronchoalveolar lavage is often necessary to make this diagnosis and distinguish this from nocardiosis, tuberculosis, fungal infection, and other entities. If expectorated sputum is used for diagnosis, two samples showing the same organism should be obtained for confirmation according to current guidelines. A single sputum culture is not necessarily an indication for therapy. Chest CT scanning is helpful in delineating the nature and extent of parenchymal disease, which may or may not be assessable by plain chest radiography.

The most common nontuberculous mycobacterial (NTM) infection seen in this population is that caused by the Mycobacterium avium complex (MAC, also known as MAI.) Although most commonly seen in a pulmonary presentation as above, disseminated infection in severely immunocompromised patients can present with fever, pancytopenia, diarrhea, and elevated liver function tests. Other NTM infections include M. kansasii (which can produce a tuberculosis-like presentation) and the rapid-grower mycobacteria, including M. fortuitum, M. chelonae, and M. abscessus [31, 110]. These may be highly antimicrobial-resistant, especially M. abscessus. These organisms may cause sternal wound infections and soft tissue infections as well as pulmonary infections. Treatment of any of these NTM infections

usually involves lengthy combination therapy (usually at least 12 months with at least 3 drugs) and is associated with GI intolerance and other adverse effects of the antimicrobial regimen, so decisions regarding therapy should be made after a thorough diagnostic process and careful consideration.

Fungal Infections: Candidiasis

Candida spp. are members of the normal flora of the oropharynx, intestinal tract, and skin. Not surprisingly, under the influence of steroids and other immunosuppression with the addition of antibacterial antibiotics, **Candida** spp. can overgrow and cause mucosal and other infections [111]. Oropharyngeal candidiasis, and less commonly esophageal candidiasis, can occur in the early period post-transplant, and at later times particularly when immunosuppression is intensified. Administration of oral nystatin suspension or clotrimazole troches for the first month and during subsequent time periods of increased risk is usually effective for prevention. Candidal colonization of the urinary tract can also occur, particularly in the setting of prolonged bladder catheterization. Treatment involves removal or change of the bladder catheter, and in some cases, antifungal (usually fluconazole) therapy.

Although many Candida spp. including most C. albicans, C. tropicalis, C. parapsilosis are fluconazole-sensitive, occasionally fluconazole resistance can occur in these species. In addition, it should be noted that certain Candida spp., including **C. krusei** and many **C. glabrata**, are fluconazole-resistant. Echinocandins such as micafungin, caspofungin, or anidulafungin are frequently used for infections with these organisms, but are not ideal for the urinary tract as they achieve low concentrations there. Standard amphotericin B is quite nephrotoxic in the transplant population, and generally when amphotericin is needed, it is administered in the form of a less nephrotoxic lipid preparation (liposomal amphotericin or amphotericin B lipid complex), but these preparations may still cause adverse renal effects, electrolyte depletion, and infusion-related reactions.

Epidemiology of invasive fungal infections has recently been described using large multicenter databases. In a prospective registry of 17 U. S. hospitals, 515 proven or probable invasive fungal infections were identified in solid organ transplant recipients, of which 59 % were due to **Candida** spp. Almost half of these infections in heart recipients occurred during the first 100 post-transplant days [112]. Predictors of mortality included poor organ function, neutropenia, and steroids [112]. **Candida** spp. were the second most common cause of invasive fungal infections (after **Aspergillus** spp) in a large Italian series of thoracic transplant recipients [113]. However, a single-center study from Stanford found that the incidence and attributable mortality of invasive candidiasis in thoracic transplant recipients was decreasing over a 24-year period [114]. Invasive candidal infections include candidemias, which are mostly catheter-related bloodstream infections but occasionally can stem from a urinary tract or other source. Deep candidal infection of the surgical site (sternal wound and mediastinum) may occur [115], particularly

in patients bridged to transplant on a VAD who had pre-transplant candidal infection or candidemia. Administration of appropriate antifungal therapy for 6 weeks post-transplant should treat or prevent this complication. Candidal pericarditis in relation to retained epicardial leads has been described [116].

Candidal empyemas are more common in lung or heart-lung transplant recipients, but can also occur in heart-alone transplant recipients particularly with prolonged chest tube drainage and reoperations. Mycotic rupture of the ascending aorta has been described in a heart/lung transplant recipient [117]. Patients who receive combined heart/abdominal organ, particularly heart-liver or heart-pancreas transplants, may have candidal infection at the abdominal site.

Fungal Infections: Aspergillosis and Other Mold Infections

Aspergillosis was traditionally one of the most feared post-transplant infections, due to its high mortality in the pre-azole era. Remarkable improvements in prognosis have accompanied the use of voriconazole and of combination therapy (voriconazole plus echinocandin) [118] but some patients, particularly those with disseminated or CNS infection, may still have poor outcomes [119].

Acquisition of colonization by Aspergillus spp. is generally a result of environmental exposures, particularly the outdoors (gardening, farming, landscaping) or construction activity involving either residential or hospital construction [119]. Nosocomial outbreaks have been linked to hospital construction in the past, and new construction plans involving wards where immunocompromised patients are housed should be carefully designed, with measures in place to limit spread of dust and aerosolized spores. Smoking marijuana also increases exposure to Aspergillus spores [120]. All transplant candidates and recipients should be counseled to avoid marijuana smoking. Another risk factor for aspergillosis and other mold infections is neutropenia, which can result from medications such as valganciclovir, ganciclovir, mycophenolate mofetil, and azathioprine. In the above-mentioned large prospective study from 17 U.S. transplant centers, aspergillosis was the second most common cause of invasive fungal infection (IFI) in solid organ transplant recipients overall, comprising one-quarter of proven or probable IFI's, and the most common in lung recipients [112]. In the Italian study of thoracic (mainly heart) transplant recipients mentioned above, aspergillosis accounted for two-thirds of IFI's [113].

Clinical presentations of aspergillosis in the transplant population are most frequently pulmonary or sinopulmonary, with nodular and often cavitary pulmonary nodules with or without a halo sign and associated infiltrates [119]. Occasionally **Aspergillus** can colonize a pre-existing cavity in the lung. Disseminated aspergillosis can present in any organ, including the brain and meninges, spinal cord, abdominal organs, and skin-soft tissue. Late-onset aspergillosis has been described and now may occur in as many as half of patients with post-transplant aspergillosis [121]. The late-onset disease carries a poorer prognosis and was associated in one study with the use of sirolimus plus tacrolimus for refractory rejection or cardiac allograft vasculopathy [121].

Aspergillosis is much more common in lung and heart-lung recipients than in heart-alone recipients, due to the exposure of the lung allograft to the external environment, and the high rate of pretransplant colonization with Aspergillus particularly in patients with cystic fibrosis. Lung and heart-lung recipients may develop distinctive syndromes of airway aspergillosis, especially in the presence of stents and/or stenosis [122]. Therefore, most lung transplant programs administer antimold prophylaxis (voriconazole, itraconazole, and/or inhaled amphotericin preparations) whereas most heart transplant programs do not.

Recent years have seen the rise of non-**Aspergillus** mold infections, which may be more likely to involve the CNS and may have a poorer prognosis in the azole era than aspergillosis itself [123, 124]. Some concerns have been raised that the widespread use of voriconazole for prophylaxis in lung and bone marrow transplant patients might lead to selection for zygomycetes, including **Mucor** and **Rhizopus**, with attendant high mortality. The azole antifungal posaconazole has a broad spectrum that includes zygomycetes as well as **Aspergillus**, but absorption requires ingestion of food containing fat with each dose, and therefore therapeutic levels may be difficult to maintain. The newer extended-release formulation achieves better levels.

Fungal Infections: Cryptococcosis

Cryptococcosis is a common fungal infection in the immunocompromised host [125]. Cryptococcal infection presents most frequently in the form of cryptococcal meningitis, although a nodular pulmonary presentation is not uncommon. Other localizations include mass-like lesions in the brain (cryptococcomas), cellulitis, and peritoneal cryptococcosis (particularly in liver transplant candidates.) A large multicenter registry has explored a variety of characteristics and risk factors for cryptococcosis in solid organ transplant recipients. Although most cryptococcal infections are caused by **C. neoformans**, a more recently identified species, **C. gattii**, has been increasingly recognized, particularly in the Northwest US [126].

Treatment of cryptococcosis in the solid organ transplant population is generally with liposomal amphotericin preparations as induction therapy, particularly if the infection involves the central nervous system, dissemination, or fungemia [127]. Many patients are then transitioned to fluconazole maintenance regimens when stabilization of disease has been achieved. In selected individuals with clinically mild disease or infection limited to the lungs, initial therapy with high-dose fluconazole may be attempted [127]. In a multicenter cohort, the duration of maintenance therapy was a median of 6 months, with a relapse rate of 1.3 % [127]. CSF cryptococcal antigen titers should be followed with serial lumbar punctures in patients with cryptococcal meningitis. However, for others with nonmeningeal cryptococcosis, the blood cryptococcal antigen titer is less reliable as an indicator of the activity of disease. An immune reconstitution inflammatory syndrome (IRIS) occurs shortly after the start of therapy in about 5 % of patients [128],

owing to the fact that treatment of severe fungal infections in transplant recipients usually also includes reduction of immunosuppression. Hallmarks of an IRIS include a flare of signs or symptoms at previously noted sites of infection, but with negative cultures or declining measures of organism presence (such as the cryptococcal antigen on CSF.)

Fungal Infections: Endemic Mycoses

Of the geographically endemic mycoses, the two that are most likely to be seen post-transplant are histoplasmosis and coccidioidomycosis [129–133]. Disseminated blastomycosis has been described after heart transplantation [134], but appears to be less common. Histoplasmosis is endemic in the Midwestern US and many individuals residing in that area have been exposed early in life, particularly if they have had contact with farms, chickens or other birds. Hallmarks of latent histoplasmosis include calcified granulomata, including within the spleen. In most patients with past histoplasmosis that has not yet reactivated, the urine antigen and blood antibody levels are negative. However, the urine **Histoplasma** antigen test is very useful in patients with febrile or other compatible illnesses post-transplant, in whom histoplasmosis is a diagnostic consideration [130].

There is as yet no specific recommendation for prophylaxis for histoplasmosis for heart transplant recipients who show radiographic evidence of past histoplasmosis, although heightened clinical awareness and vigorous pursuit of the diagnosis in patients who develop febrile illnesses is important. Both blood fungal isolator cultures and (if a pulmonary presentation) BAL fungal cultures should be sent. **Histoplasma** cultures may take up to 4 weeks to grow, so if not detected by urine antigen or on transbronchial biopsy or on initial fungal stains of the BAL sample, it may be necessary to institute empiric therapy (with liposomal amphotericin or an azole) prior to diagnostic confirmation. Disseminated histoplasmosis may present with unexplained fever and pancytopenia, with or without diarrhea, elevated liver function tests, or pulmonary or CNS involvement, and should be suspected in any such presentations, since diagnosis is often delayed.

Coccidioidomycosis is endemic in the Southwest US, especially Arizona, New Mexico, southern California and parts of Texas. This organism is found in the desert and has been associated with reactivation of latent pulmonary, CNS, or disseminated infection after the onset of immunosuppression. When infection involves the CNS, it is particularly difficult to eradicate, and therefore prevention is paramount. For individuals who have a past history of coccidioidomycosis, lifelong post-transplant prophylaxis is indicated [131]. In a series of 100 transplant recipients with prior coccidioidomycosis, all of the 6 % who did not receive antifungal prophylaxis all reactivated coccidioidomycosis; and only 5 of the 94 who did receive prophylaxis reactivated this infection [131]. For those who have had active coccidioidomycosis prior to transplant, full treatment and resolution of prior infection, where possible, is desirable.

Fungal Infections: Pneumocystis

Pneumocystis jiroveci (formerly **P. carinii**) was formerly considered to be a parasite, but has been found to be more related to the fungi. **Pneumocystis** causes a diffuse pneumonia (PCP) characterized by bilateral interstitial infiltrates, severe hypoxemia, elevated LDH, pulmonary dysfunction, and sometimes the formation of blebs and spontaneous pneumothoraces [135]. The recovery phase from this infection is extremely protracted, and persistent pulmonary disability is common. Prior to the use of universal trimethoprim-sulfa prophylaxis in organ transplantation, the incidence of PCP was high. PCP prophylaxis should be administered to any non-sulfa-allergic heart transplant recipients, preferably for at least the first year (or longer in situations of enhanced immunosuppression.) For sulfa-allergic patients, alternatives include dapsone, aerosolized pentamidine, or atovaquone. Before administration of dapsone, the patient should be screened for G6PD deficiency. If a non-sulfa-based prophylaxis is used, the side benefits of sulfa are lost (including some prevention of **Nocardia**, **Listeria**, **Toxoplasma**, and some respiratory and urinary bacterial pathogens.) Late PCP after discontinuation of prophylaxis sometimes occurs, especially in the setting of augmented immunosuppression. For lung and heart-lung recipients, PCP prophylaxis should be administered lifelong, as those patients have a continued risk for PCP that does not diminish after the first year [136].

Parasitic Infections: Toxoplasmosis, Strongyloidiasis, Chagas' Disease, Schistosomiasis

Since the early days of transplantation, it has been recognized that toxoplasmosis is a particular problem in heart recipients, due to the propensity of **Toxoplasma** to encyst in myocytes including cardiac myocytes [137]. The highest risk for development of active toxoplasmosis is in the Toxoplasma D+/R− patient where the parasite load is acquired via the donor heart [137]. Pyrimethamine prophylaxis was used with success at Papworth Hospital, who had described primary toxoplasmosis in 4 of the first 7 **Toxoplasma** D+/R− heart recipients in their program [138]. Clinical manifestations of toxoplasmosis include most frequently single or multiple brain abscesses, and occasionally pulmonary nodules and infiltrates, meningitis, and other localizations of infection. In many cases, administration of sulfa-based prophylaxis for PCP is also sufficient to prevent toxoplasmosis [139, 140], but the sulfa-allergic patient who is **Toxoplasma** D+/R− is at particular risk and should receive alternative **Toxoplasma** prophylaxis e.g. with pyrimethamine for at least the first post-transplant year. Patients should also be counseled to avoid eating undercooked or raw meat, and to avoid contact with cat litter boxes as these are also ways of acquiring toxoplasmosis after transplant.

Strongyloides stercoralis is a parasite of worldwide endemicity in tropical and subtropical regions, including the southeastern US. Unusual among intestinal

parasites, it possesses an auto-infection cycle that can perpetuate the lifecycle of the parasite in the intestine even years to decades after leaving an endemic area. Under the influence of immunosuppression, hyperinfection and dissemination can occur, leading to high mortality [141–143]. Clinical presentation of disseminated strongyloidiasis may involve Gram-negative bacteremias or meningitis, as the migrating **Strongyloides** larvae carry intestinal bacteria with them as they migrate widely through the lungs and the CNS. Given the severity of this illness, pretransplant screening is indicated for any individual who has resided in an endemic area. Screening can be accomplished with a **Strongyloides** IgG serologic test and treatment, if that test is positive, with a relatively simple regimen of oral ivermectin (e.g. 0.2 mg/kg/dose, for 2 doses given 1 week apart). This intervention, performed pretransplant, can effectively prevent one of the most devastating of post-transplant infections.

Chagas disease (**Trypanosoma cruzi**) is a major problem in endemic areas of Central and South America, and in some nonendemic areas where a substantial number of individuals' country of origin is endemic [144, 145]. Chagas disease can be donor-transmitted by transplantation [146] or may reactivate in the seropositive recipient [147]. Chagas cardiomyopathy may be the underlying disease leading to the need for heart transplantation [148, 149]. In patients at risk for reactivation of Chagas disease, current recommendations include minimization of immunosuppression, and parasitemia PCR monitoring with some centers administering preemptive therapy with antiparasitic agents such as benznidazole in PCR-positive individuals [149–151].

Other parasitic infections may occur in association with specific geographic regions or activities. Schistosomiasis due to **S. mansoni**, **S. japonicum**, **S. haematobium** and other species occurs in multiple tropical countries. For patients who originate from or who have resided in endemic areas, screening with **Schistosoma** serology, and treatment with praziquantel for those with positive serology, is recommended.

Antimicrobial Drug Interactions and Adverse Effects

Many medications interact with the calcineurin inhibitors (tacrolimus and cyclosporine) and with the mTOR inhibitors (sirolimus and everolimus) [152]. The AST ID Guidelines provides a comprehensive list [152]. Among antibiotics, the most common drug classes to elevate these levels include macrolides and azole antifungals. Among macrolides, this effect is most pronounced with clarithromycin and erythromycin, and is minimal to negligible with azithromycin; thus azithromycin is the macrolide of choice in the transplant population. In the unusual circumstance where clarithromycin or erythromycin must be given, close monitoring and readjustment of calcineurin inhibitor or mTOR inhibitor levels and doses is necessary, both at the initiation and right after discontinuation of therapy.

Azole antifungals are very frequently used for either prophylaxis or therapy in transplant recipients. The azole antifungals also raise levels of the transplant

immunosuppressive medications above; in some cases, co-administration is officially contraindicated (as in the case of sirolimus plus voriconazole.) However, in most cases, the levels of calcineurin inhibitors or mTOR inhibitors can be managed by dose-decreasing and close monitoring of levels, but in some cases this may prove too difficult and alternate therapies might be pursued. Monitoring of levels, as with the macrolides, is particularly important just after the start of azole therapy and right after discontinuation (when the level will fall and rejection is a risk if an adjustment in dosage is not made promptly.)

As previously mentioned, there is a profound interaction between HIV protease inhibitors and calcineurin inhibitors [153], resulting in an up to 50-fold reduction in the dose of tacrolimus; being administered much less frequently than the usual dosing, for example only one dose every 1–2 weeks in some patients. HIV-positive transplant recipients should have their medication list monitored by an experienced pharmacist in ongoing fashion and particularly during each new hospital admission, at which times the medical regimen is most likely to be changed.

Antimicrobials that decrease levels of calcineurin inhibitors and mTOR inhibitors are less numerous. The most common antimicrobial agent causing this type of interaction is rifampin, which results in extremely low levels of calcineurin inhibitors, even when doses are increased and levels carefully monitored. Rifampin is better avoided in this population, except in cases of active TB (and even then, rifampin-sparing regimens have sometimes been advocated), and in cases of refractory MRSA infection in which its administration as adjunct therapy may be lifesaving. However, alternative immunosuppression may have to be temporarily substituted.

Transplant recipients and primary physicians and local (non-transplant) cardiologists must be educated on reporting every new proposed prescription or non-prescription medication to the cardiac transplant team for review. Cases and anecdotes abound, such as a heart transplant recipient who went to an urgent care center for bronchitis and was prescribed clarithromycin, resulting in his hospital admission with acute renal failure due to a high cyclosporine level. This is particularly important as transplant recipients are surviving longer, returning to sometimes distant home communities, and as their care is increasingly delegated to local clinicians, particularly in the late post-transplant phase.

Immunizations and Strategies for Safer Living

A major goal of transplantation is for the recipient to have a long life with a well-functioning allograft, and to be able to return to the activities that he or she wishes to pursue. In some ways, the more successful the transplant, the greater number of potential infectious risks the long-term transplant survivor may encounter, either on the job (if they choose to return to work) or in the home or recreational environment [154]. Although the total immunosuppression burden is likely to be less after the first year post-transplant, the patient still remains at increased risk from a variety of infections. In addition, transplant recipients may (with or without informing their

coordinators) gradually resume activities that they were previously advised were risky, as they get farther out from the experience of transplantation and feel healthier and safer. The reader is referred to the American Society of Transplantation (AST) ID Guidelines section on "Strategies for Safe Living" for full detailed recommendations on food, water, outdoor, pet, occupational, and other exposures [154]. While the recommendations from different centers may differ in minor respects, the principles of such advice given to transplant recipients over many years are shared ones, and are based on knowledge of transmission modalities, case reports and case series, and pooling of clinical experience from multiple clinicians. It is recommended to include this advice in initial pre- and post-transplant teaching, but also to review and refresh the recipients' knowledge and assess their understanding at some point after the first post-transplant year.

Immunizations in the post-transplant patient are also important. Detailed recommendations for immunizations both pre- and post-transplant, and for patients contemplating international travel, can also be found in the AST ID Guidelines [32]. It is particularly important for patients contemplating travel to visit a Travel Clinic that has experience with transplant recipients, at least 2–3 months prior to the planned trip, as additional immunizations, destination-specific advice, prophylaxis for malaria and traveler's diarrhea, as well as additional infection prevention measures can be accomplished in an individualized fashion.

In general, only non-live vaccines are administered post-transplant. Routine post-transplant immunizations should include the yearly seasonal injected (non-live) influenza vaccine [32, 33]. The live attenuated nasal influenza vaccine should not be administered to transplant recipients. Because the protection afforded by the influenza vaccine may be less than 100 % in immunocompromised patients, all family members in close contact with the patient, as well as all health care workers, should be vaccinated to create a "cocoon" or circle of protection around the patient [33]. Influenza vaccination is safe for transplant recipients, and has not been found to cause rejection or allograft dysfunction in any larger studies, despite case reports and small case series to the contrary [33, 155]. In fact, a large database study of kidney transplant recipients with Medicare insurance found that receiving influenza vaccination was associated with better allograft function than not receiving influenza vaccination [156]. Influenza itself carries a high risk of morbidity and mortality in the transplant patient [79]. It is influenza itself, not the flu shot that should be feared.

Pneumococcal vaccine (the 23-valent pneumococcal polysaccharide vaccine) should be repeated up to a lifetime 2 doses, if not received within the last 5 years [32]. Recently a new recommendation for administration of the conjugated PCV-13 vaccine to immunocompromised patients was announced by the Advisory Committee on Immunization Practices (ACIP), followed 8 or more weeks later by the 23-valent pneumococcal vaccine (if not received within the last 5 years, and up to 2 lifetime doses) [157]. However, studies of the previous PCV-7 conjugated vaccine failed to demonstrate any advantage in immunogenicity or durability of protection over standard pneumococcal vaccine in a group of renal transplant recipients [158], and the prime-boost strategy of PCV-7 followed by 23-valent pneumococcal vaccine in liver transplant recipients did not result in enhanced immunogenicity [159].

Tetanus-diphtheria-acellular pertussis (Tdap) vaccine should be administered if a tetanus booster has not been received within 10 years, or to any individual involved in health care or in care of infants (such as a grandparent who is also a transplant recipient) with the recognition that pertussis can cause severe respiratory infection in adults are well as children. Generally the Tdap vaccine will have been administered in the pre-transplant period, but if missed at that time, can be administered post-transplant as well. Hepatitis A and B vaccines can be administered to complete a series post-transplant, but are likely to be less immunogenic than when given in the pre-transplant setting.

Live vaccines including varicella vaccine, measles-mumps-rubella (MMR), zoster vaccine, live attenuated nasal influenza vaccine, yellow fever vaccine, oral typhoid vaccine, oral polio vaccine, and smallpox vaccine are contraindicated in the transplant recipient [32], although small series and case reports have documented safe administration of MMR and varicella vaccine in some pediatric recipients [160, 161]. Oral polio vaccine is no longer used in the US. Smallpox vaccine is administered only to selected members of the military, and not to the general public. A letter of exemption may be provided for transplant recipients who are "required" to receive MMR vaccine (for school or employment) or yellow fever vaccine (for travel to specific countries that have that requirement.)

Infants and children in the household of a transplant recipient may receive any vaccines currently licensed in the US and recommended in age-specific immunization guidelines. There is a common misconception, even among some pediatricians, that live vaccines must be withheld from the child if there is a transplant recipient in the household. This would only be true for oral polio vaccine, which is no longer used in the US. MMR vaccine has not been shown to be transmitted in households; rotavirus vaccine also has not posed transmission problems, and the wild-type rotavirus would pose more of a threat to the transplant recipient. It is best for the transplant recipient to employ excellent hand hygiene and to avoid changing diapers. With the varicella vaccine, which is live-attenuated, there is a very small chance of transmission to a seronegative transplant recipient in the home, but <10 % of adults are varicella-seronegative, and the child would pose much more of a risk if they acquired natural varicella, so it is still recommended that the child receive varicella vaccine. If the vaccinated child develops a rash, and the transplant recipient in the household is seronegative for VZV, some clinicians would administer antiviral therapy (acyclovir) for 3 weeks.

Conclusion

Heart transplantation continues to carry risks of infection, although the current emphasis on prophylaxis, early detection, and rapid therapy has diminished these risks. There are special considerations for the transplant candidate bridged to transplantation on a VAD, but VAD-related infections can frequently be effectively suppressed until transplantation and eradicated thereafter. The pre-transplant evaluation

offers an excellent opportunity to update immunizations, educate the patient on infection prevention, and ensure the resolution of any previous infections. Post-transplant prevention and management strategies for CMV, EBV/PTLD, and other organisms are outlined above. Effects of infections on the allograft, particularly viral infections, constitute an area of active research. The rise of multiresistant bacteria and **C. difficile** infection has provided an ongoing challenge, and effective prevention programs for these organisms rely mainly on hospital infection control. Any newer immunosuppressive medications should be thoroughly studied as to their effects on infection incidence and type. Finally, review of immunizations, drug interactions, and strategies for safe living can help minimize complications of transplantation and maximize the patient's post-transplant health.

References

1. Razonable RR, Humar A. Cytomegalovirus in solid organ transplantation. Am J Transplant. 2013;13:93–106.
2. Hannan MM, Husain S, Mattner F, Danziger-Isakov L, Drew RJ, Corey GR, et al. Working formulation for the standardization of definitions of infections in patients using ventricular assist devices. J Heart Lung Transplant. 2011;30(4):375–84.
3. Husain S, Mooney ML, Danziger-Isakov L, Mattner F, Singh N, Avery R, et al. A 2010 working formulation for the standardization of definitions of infections in cardiothoracic transplant recipients. J Heart Lung Transplant. 2011;30(4):361–74.
4. Mooney ML Hannan MM, Husain S, Kirklin JK. ISHLT monograph series volume 5: diagnosis and management of infectious diseases in cardiothoracic transplantation and mechanical circulatory support. Int Soc Heart Lung Transplant. 2011;5.
5. Snydman DR, Limaye AP, Potena L, Zamora MR. Update and review: state-of-the-art management of cytomegalovirus infection and disease following thoracic organ transplantation. Transplant Proc. 2011;43(3 Suppl):S1–S17.
6. Kotton CN, Kumar D, Caliendo AM, Asberg A, Chou S, Danziger-Isakov L, Humar A, Transplantation Society International CMV Consensus Group. Updated international consensus guidelines on the management of cytomegalovirus in solid-organ transplantation. Transplantation. 2013;96:333–60.
7. Garzoni C. Multiply resistant gram-positive bacteria methicillin-resistant, vancomycin-intermediate and vancomycin-resistant Staphylococcus aureus (MRSA, VISA, VRSA) in solid organ transplant recipients. Am J Transplant. 2009;9(Suppl 4):S41–9.
8. van Duin D, van Delden C. Multidrug resistant gram-negative bacteria infections in solid organ transplantation. Am J Transplant. 2013;13:31–41.
9. Patel G, Snydman DR. Vancomycin-resistant enterococcus infection in solid organ transplantation. Am J Transplant. 2013;13:59–67.
10. Dubberke ER, Burdette SD. Clostridium difficile infections in solid organ transplantation. Am J Transplant. 2013;13:42–9.
11. Potena L, Holweg CT, Vana ML, Bashyam L, Rajamani J, McCormick AL, et al. Frequent occult infection with Cytomegalovirus in cardiac transplant recipients despite antiviral prophylaxis. J Clin Microbiol. 2007;45(6):1804–10.
12. Potena L, Valantine HA. Cytomegalovirus-associated allograft rejection in heart transplant patients. Curr Opin Infect Dis. 2007;20(4):425–31.
13. Fischer SA, Lu K. Screening of donor and recipient in solid organ transplantation. Am J Transplant. 2013;13:9–21.

14. Gordon SM, Schmitt SK, Jacobs M, Smedira NM, Goormastic M, Banbury MK, et al. Nosocomial bloodstream infections in patients with implantable left ventricular assist devices. Ann Thorac Surg. 2001;72(3):725–30.
15. McCarthy PM, Schmitt SK, Vargo RL, Gordon S, Keys TF, Hobbs RE. Implantable LVAD infections: implications for permanent use of the device. Ann Thorac Surg. 1996;61(1):359–65 ; discussion 372–3.
16. Mandell LA, Wunderink RG, Anzueto A, Bartlett JG, Campbell GD, Dean NC, et al. Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. Clin Infect Dis. 2007;44(Suppl 2):S27–72.
17. American Thoracic Society; Infectious Diseases Society of America. Guidelines for the management of adults with hospital-acquired, ventilator-associated, and healthcare-associated pneumonia. Am J Respir Crit Care Med. 2005;171(4):388–416.
18. Baddour LM, Epstein AE, Erickson CC, Knight BP, Levison ME, Lockhart PB, et al. Update on cardiovascular implantable electronic device infections and their management: a scientific statement from the American Heart Association. Circulation. 2010;121(3):458–77.
19. Mermel LA, Allon M, Bouza E, Craven DE, Flynn P, O'Grady NP, et al. Clinical practice guidelines for the diagnosis and management of intravascular catheter-related infection: 2009 Update by the Infectious Diseases Society of America. Clin Infect Dis. 2009;49(1):1–45.
20. Baddour LM, Wilson WR, Bayer AS, Fowler Jr VG, Bolger AF, Levison ME, et al. Infective endocarditis: diagnosis, antimicrobial therapy, and management of complications: a statement for healthcare professionals from the Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease, Council on Cardiovascular Disease in the Young, and the Councils on Clinical Cardiology, Stroke, and Cardiovascular Surgery and Anesthesia, American Heart Association: endorsed by the Infectious Diseases Society of America. Circulation. 2005;111(23):e394.
21. Gupta K, Hooton TM, Naber KG, Wullt B, Colgan R, Miller LG, et al. International clinical practice guidelines for the treatment of acute uncomplicated cystitis and pyelonephritis in women: A 2010 update by the Infectious Diseases Society of America and the European Society for Microbiology and Infectious Diseases. Clin Infect Dis. 2011;52(5):e103–20.
22. Hooton TM, Bradley SF, Cardenas DD, Colgan R, Geerlings SE, Rice JC, et al. Diagnosis, prevention, and treatment of catheter-associated urinary tract infection in adults: 2009 International Clinical Practice Guidelines from the Infectious Diseases Society of America. Clin Infect Dis. 2010;50(5):625–63.
23. Stevens DL, Bisno AL, Chambers HF, Everett ED, Dellinger P, Goldstein EJ, et al. Practice guidelines for the diagnosis and management of skin and soft-tissue infections. Clin Infect Dis. 2005;41(10):1373–406.
24. Bagdasarian NG, Malani AN, Pagani FD, Malani PN. Fungemia associated with left ventricular assist device support. J Card Surg. 2009;24(6):763–5.
25. Beiras-Fernandez A, Kur F, Kiefer S, Sodian R, Schmoeckel M, Weis M, et al. Multidrug-resistant gram-positive infections in patients with ventricular assist devices: the role of daptomycin. Transplant Proc. 2009;41(6):2589–91.
26. Stock PG, Barin B, Murphy B, Hanto D, Diego JM, Light J, et al. Outcomes of kidney transplantation in HIV-infected recipients. N Engl J Med. 2010;363(21):2004–14.
27. Calabrese LH, Albrecht M, Young J, McCarthy P, Haug M, Jarcho J, et al. Successful cardiac transplantation in an HIV-1-infected patient with advanced disease. N Engl J Med. 2003;348(23):2323–8.
28. Bertani A, Grossi P, Vitulo P, D'Ancona G, Arcadipane A, Nanni Costa A, et al. Successful lung transplantation in an HIV- and HBV-positive patient with cystic fibrosis. Am J Transplant. 2009;9(9):2190–6.
29. Blumberg EA, Rogers CC. HIV in solid organ transplantation. Am J Transplant. 2013;13:169–78.
30. Kim SY, Jung GS, Kim SK, Chang J, Kim MS, Kim YS, et al. Comparison of the tuberculin skin test and interferon-gamma release assay for the diagnosis of latent tuberculosis infection before kidney transplantation. Infection. 2013;41(1):103–10.

31. Keating MR, Daly JS. Nontuberculous mycobacterial infections in solid organ transplantation. Am J Transplant. 2013;13:77–82.
32. Danziger-Isakov L, Kumar D. Vaccination in solid organ transplantation. Am J Transplant. 2013;311:317.
33. Kumar D, Blumberg EA, Danziger-Isakov L, Kotton CN, Halasa NB, Ison MG, et al. Influenza vaccination in the organ transplant recipient: review and summary recommendations. Am J Transplant. 2011;11(10):2020–30.
34. Fishman JA, Rubin RH. Infection in organ-transplant recipients. N Engl J Med. 1998;338(24):1741–51.
35. Ramos A, Asensio A, Munez E, Torre-Cisneros J, Blanes M, Carratala J, et al. Incisional surgical infection in heart transplantation. Transpl Infect Dis. 2008;10(4):298–302.
36. Ison MG, Grossi P. Donor-derived infections in solid organ transplantation. Am J Transplant. 2013;13:22–30.
37. Organ Procurement and Transplantation Network (OPTN) Policies. http://optn.transplant.hrsa.gov/PoliciesandBylaws2/policies/pdfs/policy_2.pdf
38. https://www.whitehouse.gov/the-press-office/2013/11/21/statement-president-hiv-organ-policy-equity-hope-act
39. Ison MG, Llata E, Conover CS, Friedewald JJ, Gerber SI, Grigoryan A, et al. Transmission of human immunodeficiency virus and hepatitis C virus from an organ donor to four transplant recipients. Am J Transplant. 2011;11(6):1218–25.
40. Humar A, Morris M, Blumberg E, Freeman R, Preiksaitis J, Kiberd B, et al. Nucleic acid testing (NAT) of organ donors: is the 'best' test the right test? A consensus conference report. Am J Transplant. 2010;10(4):889–99.
41. Seem DL, Lee I, Umscheid CA, Kuehnert MJ. PHS guideline for reducing human immunodeficiency virus, hepatitis B virus, and hepatitis C virus transmission through organ transplantation. Public Health Rep. 2013;128:247–343.
42. Burket JS, Chenoweth CE, Meyer TL, Barg NL. Donor-to-recipient transmission of bacteria as an unusual cause of mediastinitis in a heart transplant recipient. Infect Control Hosp Epidemiol. 1999;20(2):132–3.
43. Little DM, Farrell JG, Cunningham PM, Hickey DP. Donor sepsis is not a contraindication to cadaveric organ donation. QJM. 1997;90(10):641–2.
44. Lopez-Navidad A, Domingo P, Caballero F, Gonzalez C, Santiago C. Successful transplantation of organs retrieved from donors with bacterial meningitis. Transplantation. 1997;64(2):365–8.
45. Kubak BM, Gregson AL, Pegues DA, Leibowitz MR, Carlson M, Marelli D, et al. Use of hearts transplanted from donors with severe sepsis and infectious deaths. J Heart Lung Transplant. 2009;28(3):260–5.
46. Ison MG, Hager J, Blumberg E, Burdick J, Carney K, Cutler J, et al. Donor-derived disease transmission events in the United States: data reviewed by the OPTN/UNOS Disease Transmission Advisory Committee. Am J Transplant. 2009;9(8):1929–35.
47. Caliendo AM. Editorial commentary: the long road toward standardization of viral load testing for cytomegalovirus. Clin Infect Dis. 2013;56(3):374–5.
48. Merigan TC, Renlund DG, Keay S, Bristow MR, Starnes V, O'Connell JB, et al. A controlled trial of ganciclovir to prevent cytomegalovirus disease after heart transplantation. N Engl J Med. 1992;326(18):1182–6.
49. Paya C, Humar A, Dominguez E, Washburn K, Blumberg E, Alexander B, et al. Efficacy and safety of valganciclovir vs. oral ganciclovir for prevention of cytomegalovirus disease in solid organ transplant recipients. Am J Transplant. 2004;4(4):611–20.
50. Humar A, Limaye AP, Blumberg EA, Hauser IA, Vincenti F, Jardine AG, et al. Extended valganciclovir prophylaxis in D+/R- kidney transplant recipients is associated with long-term reduction in cytomegalovirus disease: two-year results of the IMPACT study. Transplantation. 2010;90(12):1427–31.
51. Palmer SM, Limaye AP, Banks M, Gallup D, Chapman J, Lawrence EC, et al. Extended valganciclovir prophylaxis to prevent cytomegalovirus after lung transplantation: a randomized, controlled trial. Ann Intern Med. 2010;152(12):761–9.

52. Valantine HA, Luikart H, Doyle R, Theodore J, Hunt S, Oyer P, et al. Impact of cytomegalovirus hyperimmune globulin on outcome after cardiothoracic transplantation: a comparative study of combined prophylaxis with CMV hyperimmune globulin plus ganciclovir versus ganciclovir alone. Transplantation. 2001;72(10):1647–52.
53. Snydman DR, Kistler KD, Ulsh P, Bergman GE, Vensak J, Morris J. The impact of CMV prevention on long-term recipient and graft survival in heart transplant recipients: analysis of the Scientific Registry of Transplant Recipients (SRTR) database. Clin Transplant. 2011;25(4):E455–62.
54. Snydman DR, Kistler KD, Ulsh P, Morris J. Cytomegalovirus prevention and long-term recipient and graft survival in pediatric heart transplant recipients. Transplantation. 2010;90(12):1432–8.
55. Singh N. Preemptive therapy versus universal prophylaxis with ganciclovir for cytomegalovirus in solid organ transplant recipients. Clin Infect Dis. 2001;32(5):742–51.
56. Singh N. Late-onset cytomegalovirus disease as a significant complication in solid organ transplant recipients receiving antiviral prophylaxis: a call to heed the mounting evidence. Clin Infect Dis. 2005;40(5):704–8.
57. Snydman DR. Cytomegalovirus prevention strategies: the case for prophylaxis. Am J Transplant. 2009;9(5):1254.
58. Keay S, Oldach D, Wiland A, Klassen D, Schweitzer E, Abruzzo LV, et al. Posttransplantation lymphoproliferative disorder associated with OKT3 and decreased antiviral prophylaxis in pancreas transplant recipients. Clin Infect Dis. 1998;26(3):596–600.
59. Fateh-Moghadam S, Bocksch W, Wessely R, Jager G, Hetzer R, Gawaz M. Cytomegalovirus infection status predicts progression of heart-transplant vasculopathy. Transplantation. 2003;76(10):1470–4.
60. Koskinen PK, Kallio EA, Tikkanen JM, Sihvola RK, Hayry PJ, Lemstrom KB. Cytomegalovirus infection and cardiac allograft vasculopathy. Transpl Infect Dis. 1999;1(2):115–26.
61. Grattan MT, Moreno-Cabral CE, Starnes VA, Oyer PE, Stinson EB, Shumway NE. Cytomegalovirus infection is associated with cardiac allograft rejection and atherosclerosis. JAMA. 1989;261(24):3561–6.
62. Luckraz H, Charman SC, Wreghitt T, Wallwork J, Parameshwar J, Large SR. Does cytomegalovirus status influence acute and chronic rejection in heart transplantation during the ganciclovir prophylaxis era? J Heart Lung Transplant. 2003;22(9):1023–7.
63. Mahle WT, Fourshee MT, Naftel DM, Alejos JC, Caldwell RL, Uzark K, et al. Does cytomegalovirus serology impact outcome after pediatric heart transplantation? J Heart Lung Transplant. 2009;28(12):1299–305.
64. Valantine HA, Gao SZ, Menon SG, Renlund DG, Hunt SA, Oyer P, et al. Impact of prophylactic immediate posttransplant ganciclovir on development of transplant atherosclerosis: a post hoc analysis of a randomized, placebo-controlled study. Circulation. 1999;100(1):61–6.
65. Everett JP, Hershberger RE, Norman DJ, Chou S, Ratkovec RM, Cobanoglu A, et al. Prolonged cytomegalovirus infection with viremia is associated with development of cardiac allograft vasculopathy. J Heart Lung Transplant. 1992;11(3 Pt 2):S133–7.
66. Arkonac B, Mauck KA, Chou S, Hosenpud JD. Low multiplicity cytomegalovirus infection of human aortic smooth muscle cells increases levels of major histocompatibility complex class I antigens and induces a proinflammatory cytokine milieu in the absence of cytopathology. J Heart Lung Transplant. 1997;16(10):1035–45.
67. Tu W, Potena L, Stepick-Biek P, Liu L, Dionis KY, Luikart H, et al. T-cell immunity to subclinical cytomegalovirus infection reduces cardiac allograft disease. Circulation. 2006;114(15):1608–15.
68. Potena L, Grigioni F, Magnani G, Lazzarotto T, Musuraca AC, Ortolani P, et al. Prophylaxis versus preemptive anti-cytomegalovirus approach for prevention of allograft vasculopathy in heart transplant recipients. J Heart Lung Transplant. 2009;28(5):461–7.
69. Hibberd PL, Tolkoff-Rubin NE, Cosimi AB, Schooley RT, Isaacson D, Doran M, et al. Symptomatic cytomegalovirus disease in the cytomegalovirus antibody seropositive renal transplant recipient treated with OKT3. Transplantation. 1992;53(1):68–72.

70. Hibberd PL, Tolkoff-Rubin NE, Conti D, Stuart F, Thistlethwaite JR, Neylan JF, et al. Preemptive ganciclovir therapy to prevent cytomegalovirus disease in cytomegalovirus antibody-positive renal transplant recipients. A randomized controlled trial. Ann Intern Med. 1995;123(1):18–26.
71. Eisen HJ, Tuzcu EM, Dorent R, Kobashigawa J, Mancini D, Valantine-von Kaeppler HA, et al. Everolimus for the prevention of allograft rejection and vasculopathy in cardiac-transplant recipients. N Engl J Med. 2003;349(9):847–58.
72. Allen UD, Preiksaitis JK. Epstein-Barr virus and posttransplant lymphoproliferative disease in solid organ transplantation. Am J Transplant. 2013;13:107–20.
73. McDiarmid SV, Jordan S, Kim GS, Toyoda M, Goss JA, Vargas JH, et al. Prevention and preemptive therapy of postransplant lymphoproliferative disease in pediatric liver recipients. Transplantation. 1998;66(12):1604–11.
74. Swinnen LJ, Costanzo-Nordin MR, Fisher SG, O'Sullivan EJ, Johnson MR, Heroux AL, et al. Increased incidence of lymphoproliferative disorder after immunosuppression with the monoclonal antibody OKT3 in cardiac-transplant recipients. N Engl J Med. 1990;323(25):1723–8.
75. Green M, Cacciarelli TV, Mazariegos GV, Sigurdsson L, Qu L, Rowe DT, et al. Serial measurement of Epstein-Barr viral load in peripheral blood in pediatric liver transplant recipients during treatment for posttransplant lymphoproliferative disease. Transplantation. 1998;66(12):1641–4.
76. Funch DP, Walker AM, Schneider G, Ziyadeh NJ, Pescovitz MD. Ganciclovir and acyclovir reduce the risk of post-transplant lymphoproliferative disorder in renal transplant recipients. Am J Transplant. 2005;5(12):2894–900.
77. Ljungman P, Singh N. Human herpesvirus-6 infection in solid organ and stem cell transplant recipients. J Clin Virol. 2006;37(Suppl 1):S87–91.
78. Hosseini-Moghaddam SM, Soleimanirahbar A, Mazzulli T, Rotstein C, Husain S. Post renal transplantation Kaposi's sarcoma: a review of its epidemiology, pathogenesis, diagnosis, clinical aspects, and therapy. Transpl Infect Dis. 2012;14(4):338–45.
79. Kumar D, Michaels MG, Morris MI, Green M, Avery RK, Liu C, et al. Outcomes from pandemic influenza A H1N1 infection in recipients of solid-organ transplants: a multicentre cohort study. Lancet Infect Dis. 2010;10(8):521–6.
80. Krinzman S, Basgoz N, Kradin R, Shepard JA, Flieder DB, Wright CD, et al. Respiratory syncytial virus-associated infections in adult recipients of solid organ transplants. J Heart Lung Transplant. 1998;17(2):202–10.
81. Michaels MG, Fonseca-Aten M, Green M, Charsha-May D, Friedman B, Seikaly M, et al. Respiratory syncytial virus prophylaxis: a survey of pediatric solid organ transplant centers. Pediatr Transplant. 2009;13(4):451–6.
82. Kumar D, Erdman D, Keshavjee S, Peret T, Tellier R, Hadjiliadis D, et al. Clinical impact of community-acquired respiratory viruses on bronchiolitis obliterans after lung transplant. Am J Transplant. 2005;5(8):2031–6.
83. Caliendo AM. Multiplex PCR and emerging technologies for the detection of respiratory pathogens. Clin Infect Dis. 2011;52(Suppl 4):S326–30.
84. Fiore AE, Fry A, Shay D, Gubareva L, Bresee JS, Uyeki TM. Antiviral agents for the treatment and chemoprophylaxis of influenza. Recommendations of the Advisory Committee on Immunization Practices (ACIP). Morb Mortal Wkly Rep Recomm Rep. 2011;60(1):1–28.
85. Pelaez A, Lyon GM, Force SD, Ramirez AM, Neujahr DC, Foster M, et al. Efficacy of oral ribavirin in lung transplant patients with respiratory syncytial virus lower respiratory tract infection. J Heart Lung Transplant. 2009;28(1):67–71.
86. Shah JN, Chemaly RF. Management of RSV infections in adult recipients of hematopoietic stem cell transplantation. Blood. 2011;117(10):2755–63.
87. Shirali GS, Ni J, Chinnock RE, Johnston JK, Rosenthal GL, Bowles NE, et al. Association of viral genome with graft loss in children after cardiac transplantation. N Engl J Med. 2001;344(20):1498–503.

88. Eid AJ, Posfay-Barbe KM. Parvovirus B19 in solid organ transplant recipients. Am J Transplant. 2009;9(Suppl 4):S147–50.
89. Kaltsas A, Sepkowitz K. Community acquired respiratory and gastrointestinal viral infections: challenges in the immunocompromised host. Curr Opin Infect Dis. 2012;25(4):423–30.
90. Ko WJ, Chou NK, Hsu RB, Chen YS, Wang SS, Chu SH, et al. Hepatitis B virus infection in heart transplant recipients in a hepatitis B endemic area. J Heart Lung Transplant. 2001;20(8):865–75.
91. Huprikar S, Danziger-Isakov L, Ahn J, Naugler S, Blumberg E, Avery RK, et al. Solid organ transplantation from hepatitis B virus – positive donors: consensus guidelines for recipient management. Am J Transplant. 2015;15:1162–72.
92. Pinney SP, Cheema FH, Hammond K, Chen JM, Edwards NM, Mancini D. Acceptable recipient outcomes with the use of hearts from donors with hepatitis-B core antibodies. J Heart Lung Transplant. 2005;24(1):34–7.
93. Haji SA, Starling RC, Avery RK, Mawhorter S, Tuzcu EM, Schoenhagen P, et al. Donor hepatitis-C seropositivity is an independent risk factor for the development of accelerated coronary vasculopathy and predicts outcome after cardiac transplantation. J Heart Lung Transplant. 2004;23(3):277–83.
94. Gasink LB, Blumberg EA, Localio AR, Desai SS, Israni AK, Lautenbach E. Hepatitis C virus seropositivity in organ donors and survival in heart transplant recipients. JAMA. 2006;296(15):1843–50.
95. Dubberke ER, Sadhu J, Gatti R, Reske KA, DiPersio JF, Devine SM, et al. Severity of Clostridium difficile-associated disease (CDAD) in allogeneic stem cell transplant recipients: evaluation of a CDAD severity grading system. Infect Control Hosp Epidemiol. 2007;28(2):208–11.
96. Crook DW, Walker AS, Kean Y, Weiss K, Cornely OA, Miller MA, et al. Fidaxomicin versus vancomycin for Clostridium difficile infection: meta-analysis of pivotal randomized controlled trials. Clin Infect Dis. 2012;55(Suppl 2):S93–103.
97. Peleg AY, Husain S, Qureshi ZA, Silveira FP, Sarumi M, Shutt KA, et al. Risk factors, clinical characteristics, and outcome of Nocardia infection in organ transplant recipients: a matched case-control study. Clin Infect Dis. 2007;44(10):1307–14.
98. Chow JW, Yu VL. Legionella: a major opportunistic pathogen in transplant recipients. Semin Respir Infect. 1998;13(2):132–9.
99. Singh N, Stout JE, Yu VL. Prevention of Legionnaires' disease in transplant recipients: recommendations for a standardized approach. Transpl Infect Dis. 2004;6(2):58–62.
100. Muder RR, Stout JE, Yu VL. Nosocomial Legionella micdadei infection in transplant patients: fortune favors the prepared mind. Am J Med. 2000;108(4):346–8.
101. Wiesmayr S, Tabarelli W, Stelzmueller I, Nachbaur D, Boesmueller C, Wykypiel H, et al. Listeria meningitis in transplant recipients. Wien Klin Wochenschr. 2005;117(5–6):229–33.
102. Goulet V, Hebert M, Hedberg C, Laurent E, Vaillant V, De Valk H, et al. Incidence of listeriosis and related mortality among groups at risk of acquiring listeriosis. Clin Infect Dis. 2012;54(5):652–60.
103. Stamm AM, Smith SH, Kirklin JK, McGiffin DC. Listerial myocarditis in cardiac transplantation. Rev Infect Dis. 1990;12(5):820–3.
104. Chou NK, Liu LT, Ko WJ, Hsu RB, Chen YS, Yu HY, et al. Various clinical presentations of tuberculosis in heart transplant recipients. Transplant Proc. 2004;36(8):2396–8.
105. Singh N, Paterson DL. Mycobacterium tuberculosis infection in solid-organ transplant recipients: impact and implications for management. Clin Infect Dis. 1998;27(5):1266–77.
106. Munoz P, Palomo J, Munoz R, Rodriguez-Creixems M, Pelaez T, Bouza E. Tuberculosis in heart transplant recipients. Clin Infect Dis. 1995;21(2):398–402.
107. Antony SJ, Ynares C, Dummer JS. Isoniazid hepatotoxicity in renal transplant recipients. Clin Transplant. 1997;11(1):34–7.
108. Naqvi R, Akhtar S, Noor H, Saeed T, Bhatti S, Sheikh R, et al. Efficacy of isoniazid prophylaxis in renal allograft recipients. Transplant Proc. 2006;38(7):2057–8.

109. Vikrant S, Agarwal SK, Gupta S, Bhowmik D, Tiwari SC, Dash SC, et al. Prospective randomized control trial of isoniazid chemoprophylaxis during renal replacement therapy. Transpl Infect Dis. 2005;7(3–4):99–108.
110. Longworth SA, Vinnard C, Lee I, Sims KD, Barton TD, Blumberg EA. Risk factors for nontuberculous mycobacterial infections in solid organ transplant recipients: a case-control study. Transpl Infect Dis. 2014;16:76–83.
111. Silveira FP, Kusne S. Candida infections in solid organ transplantation. Am J Transplant. 2013;13:220–7.
112. Neofytos D, Fishman JA, Horn D, Anaissie E, Chang CH, Olyaei A, et al. Epidemiology and outcome of invasive fungal infections in solid organ transplant recipients. Transpl Infect Dis. 2010;12(3):220–9.
113. Grossi P, Farina C, Fiocchi R, Dalla GD. Prevalence and outcome of invasive fungal infections in 1,963 thoracic organ transplant recipients: a multicenter retrospective study. Italian Study Group of Fungal Infections in Thoracic Organ Transplant Recipients. Transplantation. 2000;70(1):112–6.
114. Schaenman JM, Rosso F, Austin JM, Baron EJ, Gamberg P, Miller J, et al. Trends in invasive disease due to Candida species following heart and lung transplantation. Transpl Infect Dis. 2009;11(2):112–21.
115. Garlicki M, Czub P, Filczak K, Wojdyga R, Puchniewicz M, Labus K, et al. A case of Candida albicans mediastinitis after heart transplantation successfully treated with caspofungin. Ann Transplant. 2006;11(1):47–8.
116. Puius YA, Scully B. Treatment of Candida albicans pericarditis in a heart transplant patient. Transpl Infect Dis. 2007;9(3):229–32.
117. Albes J, Haverich A, Freihorst J, von der Hardt H, Manthey-Stiers F. Management of mycotic rupture of the ascending aorta after heart-lung transplantation. Ann Thorac Surg. 1990;50(6):982–3.
118. Singh N, Limaye AP, Forrest G, Safdar N, Munoz P, Pursell K, et al. Combination of voriconazole and caspofungin as primary therapy for invasive aspergillosis in solid organ transplant recipients: a prospective, multicenter, observational study. Transplantation. 2006;81(3):320–6.
119. Singh N, Husain S. Aspergillosis in solid organ transplantation. Am J Transplant. 2013;13:228–41.
120. Hamadeh R, Ardehali A, Locksley RM, York MK. Fatal aspergillosis associated with smoking contaminated marijuana, in a marrow transplant recipient. Chest. 1988;94(2):432–3.
121. Singh N, Limaye AP, Forrest G, Safdar N, Munoz P, Pursell K, et al. Late-onset invasive aspergillosis in organ transplant recipients in the current era. Med Mycol. 2006;44(5):445–9.
122. Singh N, Husain S. Aspergillus infections after lung transplantation: clinical differences in type of transplant and implications for management. J Heart Lung Transplant. 2003;22(3):258–66.
123. Husain S, Alexander BD, Munoz P, Avery RK, Houston S, Pruett T, et al. Opportunistic mycelial fungal infections in organ transplant recipients: emerging importance of non-Aspergillus mycelial fungi. Clin Infect Dis. 2003;37(2):221–9.
124. Huprikar S, Shoham S. Emerging fungal infections in solid organ transplantation. Am J Transplant. 2013;13:262–71.
125. Baddley JW, Forrest GN. Cryptococcosis in solid organ transplantation. Am J Transplant. 2013;13:242–9.
126. Marr KA. Cryptococcus gattii as an important fungal pathogen of western North America. Expert Rev Anti Infect Ther. 2012;10(6):637–43.
127. Singh N, Lortholary O, Alexander BD, Gupta KL, John GT, Pursell KJ, et al. Antifungal management practices and evolution of infection in organ transplant recipients with Cryptococcus neoformans infection. Transplantation. 2005;80(8):1033–9.
128. Singh N, Lortholary O, Alexander BD, Gupta KL, John GT, Pursell K, et al. An immune reconstitution syndrome-like illness associated with Cryptococcus neoformans infection in organ transplant recipients. Clin Infect Dis. 2005;40(12):1756–61.

129. Holt CD, Winston DJ, Kubak B, Imagawa DK, Martin P, Goldstein L, et al. Coccidioidomycosis in liver transplant patients. Clin Infect Dis. 1997;24(2):216–21.
130. Cuellar-Rodriguez J, Avery RK, Lard M, Budev M, Gordon SM, Shrestha NK, et al. Histoplasmosis in solid organ transplant recipients: 10 years of experience at a large transplant center in an endemic area. Clin Infect Dis. 2009;49(5):710–6.
131. Keckich DW, Blair JE, Vikram HR, Seville MT, Kusne S. Reactivation of coccidioidomycosis despite antifungal prophylaxis in solid organ transplant recipients. Transplantation. 2011;92(1):88–93.
132. Miller R, Assi M. Endemic fungal infections in solid organ transplantation. Am J Transplant. 2013;13:250–61.
133. Freifeld AG, Wheat LJ, Kaul DR. Histoplasmosis in solid organ transplant recipients: early diagnosis and treatment. Curr Opin Organ Transplant. 2009;14(6):601–5.
134. Serody JS, Mill MR, Detterbeck FC, Harris DT, Cohen MS. Blastomycosis in transplant recipients: report of a case and review. Clin Infect Dis. 1993;16(1):54–8.
135. Martin SI, Fishman JA. Pneumocystis pneumonia in solid organ transplantation. Am J Transplant. 2013;13:272–9.
136. Gordon SM, LaRosa SP, Kalmadi S, Arroliga AC, Avery RK, Truesdell-LaRosa L, et al. Should prophylaxis for Pneumocystis carinii pneumonia in solid organ transplant recipients ever be discontinued? Clin Infect Dis. 1999;28(2):240–6.
137. Wreghitt TG, Hakim M, Gray JJ, Balfour AH, Stovin PG, Stewart S, et al. Toxoplasmosis in heart and heart and lung transplant recipients. J Clin Pathol. 1989;42(2):194–9.
138. Wreghitt TG, Gray JJ, Pavel P, Balfour A, Fabbri A, Sharples LD, et al. Efficacy of pyrimethamine for the prevention of donor-acquired Toxoplasma gondii infection in heart and heart-lung transplant patients. Transpl Int. 1992;5(4):197–200.
139. Gourishankar S, Doucette K, Fenton J, Purych D, Kowalewska-Grochowska K, Preiksaitis J. The use of donor and recipient screening for toxoplasma in the era of universal trimethoprim sulfamethoxazole prophylaxis. Transplantation. 2008;85(7):980–5.
140. Baran DA, Alwarshetty MM, Alvi S, Arroyo LH, Lubitz S, Pinney S, et al. Is toxoplasmosis prophylaxis necessary in cardiac transplantation? Long-term follow-up at two transplant centers. J Heart Lung Transplant. 2006;25(11):1380–2.
141. Roxby AC, Gottlieb GS, Limaye AP. Strongyloidiasis in transplant patients. Clin Infect Dis. 2009;49(9):1411–23.
142. Schaeffer MW, Buell JF, Gupta M, Conway GD, Akhter SA, Wagoner LE. Strongyloides hyperinfection syndrome after heart transplantation: case report and review of the literature. J Heart Lung Transplant. 2004;23(7):905–11.
143. El Masry HZ, O'Donnell J. Fatal stongyloides hyperinfection in heart transplantation. J Heart Lung Transplant. 2005;24(11):1980–3.
144. Pinazo MJ, Miranda B, Rodriguez-Villar C, Altclas J, Brunet Serra M, Garcia-Otero EC, et al. Recommendations for management of Chagas disease in organ and hematopoietic tissue transplantation programs in nonendemic areas. Transplant Rev (Orlando). 2011;25(3):91–101.
145. Casadei D. Chagas' disease and solid organ transplantation. Transplant Proc. 2010;42(9):3354–9.
146. Kun H, Moore A, Mascola L, Steurer F, Lawrence G, Kubak B, et al. Transmission of Trypanosoma cruzi by heart transplantation. Clin Infect Dis. 2009;48(11):1534–40.
147. Altclas JD, Barcan L, Nagel C, Lattes R, Riarte A. Organ transplantation and Chagas disease. JAMA. 2008;299(10):1134 .author reply 1134-5
148. Fiorelli AI, Santos RH, Oliveira Jr JL, Lourenco-Filho DD, Dias RR, Oliveira AS, et al. Heart transplantation in 107 cases of Chagas' disease. Transplant Proc. 2011;43(1):220–4.
149. Chin-Hong PV, Schwartz BS, Bern C, et al. Screening and treatment of Chagas disease in organ transplant recipients in the United States: recommendations from the Chagas in Transplant Working Group. Am J Transplant. 2011;11:672–80.
150. Duffy T, Bisio M, Altcheh J, Burgos JM, Diez M, Levin MJ, et al. Accurate real-time PCR strategy for monitoring bloodstream parasitic loads in chagas disease patients. PLoS Negl Trop Dis. 2009;3(4):e419.

151. Diez M, Favaloro L, Bertolotti A, Burgos JM, Vigliano C, Lastra MP, et al. Usefulness of PCR strategies for early diagnosis of Chagas' disease reactivation and treatment follow-up in heart transplantation. Am J Transplant. 2007;7(6):1633–40.
152. Trofe-Clark J, Lemonovich TL. Interactions between anti-infective agents and immunosuppressants in solid organ transplantation. Am J Transplant. 2013;318-26.
153. Jain AK, Venkataramanan R, Shapiro R, Scantlebury VP, Potdar S, Bonham CA, et al. The interaction between antiretroviral agents and tacrolimus in liver and kidney transplant patients. Liver Transpl. 2002;8(9):841–5.
154. Avery RK, Michaels MG. Strategies for safe living following solid organ transplantation. Am J Transplant. 2013;13:304–10.
155. Avery RK. Influenza vaccines in the setting of solid-organ transplantation: are they safe? Curr Opin Infect Dis. 2012;25(4):464–8.
156. Hurst FP, Lee JJ, Jindal RM, Agodoa LY, Abbott KC. Outcomes associated with influenza vaccination in the first year after kidney transplantation. Clin J Am Soc Nephrol. 2011;6(5):1192–7.
157. Centers for Disease Control and Prevention (CDC). Use of 13-valent pneumococcal conjugate vaccine and 23-valent pneumococcal polysaccharide vaccine for adults with immunocompromising conditions: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Morb Mortal Wkly Rep. 2013;61(40):816–9.
158. Kumar D, Welsh B, Siegal D, Chen MH, Humar A. Immunogenicity of pneumococcal vaccine in renal transplant recipients–three year follow-up of a randomized trial. Am J Transplant. 2007;7(3):633–8.
159. Kumar D, Chen MH, Wong G, Cobos I, Welsh B, Siegal D, et al. A randomized, double-blind, placebo-controlled trial to evaluate the prime-boost strategy for pneumococcal vaccination in adult liver transplant recipients. Clin Infect Dis. 2008;47(7):885–92.
160. Weinberg A, Horslen SP, Kaufman SS, Jesser R, Devoll-Zabrocki A, Fleckten BL, et al. Safety and immunogenicity of varicella-zoster virus vaccine in pediatric liver and intestine transplant recipients. Am J Transplant. 2006;6(3):565–8.
161. Khan S, Erlichman J, Rand EB. Live virus immunization after orthotopic liver transplantation. Pediatr Transplant. 2006;10(1):78–82.

Chapter 24
Post-transplant Complications: Hypertension, Renal Dysfunction, Diabetes Mellitus, Malignancy, Arrhythmias, Osteoporosis, Sexual Dysfunction

Jose Nativi Nicolau and Josef Stehlik

Introduction

Apart from morbidity related to the allograft, post-transplant complications are often related to the long-term use of immunosuppressive therapy. In addition, post-transplant morbidity may also be related to the medical conditions that lead to the need for heart transplantation in the first place. In this chapter, we review the incidence of key post-transplant complications, risk factors that make their clinical presentation more likely, as well as approaches to prevent and treat these complications.

Hypertension

Epidemiology

Systemic hypertension is a frequent comorbidity in heart transplant recipients. Close to half of adult heart recipients have a diagnosis of hypertension at the time of transplant [1]. In addition, a number of factors lead to further elevation of systemic blood pressure after heart transplant. In the first weeks to months after heart transplantation, there is a gradual increase in the systolic blood pressure of 12–15 mmHg and in the diastolic blood pressure of 15–18 mmHg [2]. This rise is not accompanied by the typical nighttime decrease in blood pressure that is observed in essential hypertension, and usually requires treatment with multiple anti-hypertensives [2]. Cyclosporine-based immunosuppression, male gender, age older than 20 years and previous history of cardiovascular disease are common characteristics in

J.N. Nicolau, MD • J. Stehlik, MD, MPH (✉)
Division of Cardiovascular Medicine, University of Utah School of Medicine,
50 North Medical Drive 4A100 SOM, Salt Lake City, UT 84132, USA
e-mail: jose.nativi-nicolau@hsc.utah.edu; josef.stehlik@hsc.utah.edu

H. Eisen (ed.), *Heart Failure*, DOI 10.1007/978-1-4471-4219-5_24

Table 24.1 Causes of post-transplant hypertension

1. Calcineurin inhibitors
Increased calcium permeability into mesangial cells
Increased free calcium in smooth muscle cells
Reduced glomerular ultrafiltration and renal failure
Increased sympathetic activity
Increased vasoconstrictive neurohormones (endothelin)
2. Steroids
Sodium and water retention
3. Extracellular volume expansion
Surgical denervation interrupts response of renin-angiotensin system, inhibiting diuresis and natriuresis

hypertensive heart transplant recipients; while donor characteristics have not been linked to post-transplant hypertension [3]. With early immunosuppressive regimens including steroids and azathioprine, hypertension developed in approximately 20 % of the patients [4]. With the introduction of cyclosporine the rate of treated hypertension increased to 73 % in the first year and 92.6 % 5 years after transplantation [1]. Presence of hypertension after transplant has not been associated with worse survival, however, possibly due to close monitoring of these patients and early introduction of antihypertensive therapies [1, 5].

Pathophysiology

The pathophysiology of systemic hypertension after heart transplantation has been originally attributed mainly to calcineurin inhibitors (CNI). It has been later shown that patients on CNI-free immunosuppression also tend to develop hypertension, and several additional mechanisms have been proposed (Table 24.1).

Calcineurin Inhibitors

A number of mechanisms associated with CNI have been linked to development of hypertension after transplant. Cyclosporine is known to enhance calcium permeability into mesangial cells in the glomerulus and also augments the angiotensin II-induced increases in free calcium in the smooth muscle cell [6, 7]. In animal models, cyclosporine use resulted in a reduced mesangial cell area and glomerular ultrafiltration [8]. These mechanisms likely result in increased renal vascular resistance, proteinuria, renal insufficiency and systemic hypertension observed in patients treated with cyclosporine [9]. In addition, in heart transplant recipients treated with cyclosporine, the systemic sympathetic activity increases approximately threefold compared to transplant recipients treated without cyclosporine and

compared to patients with essential hypertension [10]. Moreover, neurohormones like endothelin are elevated in transplant patients treated with cyclosporine and the potent vasoconstrictive properties of endothelin could have a significant role in systemic vasoconstriction and hypertension [11–13].

Tacrolimus is structurally different than cyclosporine and has been associated with decreased incidence of hypertension [14–16]. Taylor et al. compared the effects of tacrolimus and cyclosporine on systemic blood pressure in a multicenter randomized trial. At 12 months after heart transplantation, the incidence of hypertension was significantly lower (48 %) in the tacrolimus group compared to the cyclosporine group (71 %) [16].

Steroids

Steroids cause sodium and water retention and have been linked to elevation of blood pressure. Whether steroid-free immunosuppression could decrease the incidence of hypertension has been tested. However, two studies showed no significant differences in hypertension between steroid and steroid-free regimens [17, 18]. Moreover, higher number of patients on steroid-free maintenance developed acute rejection and required re-introduction of steroid therapy.

Extracellular Fluid Volume Expansion

Increase in plasma volume is common in heart transplant recipients. Braith et al. demonstrated that heart transplant recipients develop extracellular volume expansion of 14 % and a significant increase in atrial natriuretic peptide compared to healthy controls, or even other solid organ transplant recipients [19]. Interestingly, this volume expansion is accompanied by normal plasma angiotensinogen, aldosterone and angiotensin converting enzyme activity [19, 20]. This abnormal volume expansion has been attributed to the interruption of the interplay between the renin-angiotensin- aldosterone system and the atrial mechanoreceptors. In the transplanted heart, the natriuretic response of these receptors to the negative feedback of the renin-angiotensin-aldosterone system is lost [21–24]. Animal models confirmed that it is the surgical denervation of the afferent fibers from the atrial and ventricular mechanoreceptors that causes the decrease in the expected diuresis and natriuresis from volume expansion [25, 26].

Treatment

Calcium Channel Blockers

Based on the increased calcium permeability seen with cyclosporine, calcium channel blockers have been tested in post-transplant hypertension. The nondihydropyridine calcium channel blocker diltiazem was compared in a randomized controlled

trial to lisinopril, as monotherapy. Neither of these drugs achieved adequate blood pressure control, with only 38 and 46 % satisfactory response, respectively [27]. In some studies, diltiazem has been associated with decreased glomerular filtration rate and increased creatinine levels in heart transplant recipients [28, 29]. Leenen et al. tested the dihydropyridine amlodipine in a double blind placebo controlled trial. Amlodipine was started at 2.5 mg and uptitrated to 10 mg over several weeks after heart transplantation. The average daily dose was 6.8 mg at 12 months. Compared to the placebo group, amlodipine decreased the systolic blood pressure by 15–20 mmHg and diastolic blood pressure by 7–10 mmHg at 12 months after heart transplantation [30].

Angiotensin Converting Enzyme Inhibitors

In the above mentioned trial of diltiazem vs lisinopril as monotherapy in heart transplant recipients, only 48 % of the patients treated with lisinopril achieved adequate blood pressure control with a mean daily dose of 18 mg [27]. A small prospective study in hypertensive heart transplant recipients treated with the combination of enalapril (mean dose 11 mg/daily) and furosemide (mean dose 62 mg/daily) successfully controlled systolic and diastolic blood pressure without affecting renal function [31]. Similar results were reported with the combination of enalapril (mean dose 20 mg/daily) plus furosemide (mean dose 40 mg/daily) alone, or with verapamil (mean dose 168 mg/daily) [32]. A prospective study of 15 heart transplant recipients treated with fosinopril demonstrated a significant reduction in systolic and diastolic blood pressure (basal 160 ± 11 mmHg/98 ± 8 mmHg) compared to 12 months after therapy (137 ± 12 mmHg/84 ± 9 mmHg) [33].

In relation to the volume expansion after transplant, Braith et al. demonstrated with a cross-over design that the suppression of the renin-angiotensin-aldosterone system with high dose captopril (225 mg/day) produced a normovolemic state in heart transplant recipients but it is unclear if this outcome is related to a normotensive state [34].

Low-Salt Diet

Blood pressure in heart transplant recipients is sensitive to salt intake. This was reported by Singer et al. who demonstrated that heart transplant recipients who received 5 days of low sodium intake (10 mmol/d) had lower blood pressure compared to those who received a high sodium intake (350 mmol/d), 137/94 ± 8/4 vs. 148/97 ± 5/3, respectively [35].

The International Society for Heart and Lung Transplantation Guidelines for the care of heart transplant recipients (ISHLT guidelines) recommend the same blood pressure goals for patients with hypertension after heart transplant as for patients with essential hypertension. Lifestyle modifications (low salt diet, weight loss and

exercise) and control of risk factors (diabetes, hyperlipidemia) are encouraged. Calcium channel blockers, especially non-dyhidropyridines, are considered first line of therapy, followed by angiotensin converting enzyme inhibitors or angiotensin receptor blockers [36].

Renal Dysfunction

Epidemiology

Renal dysfunction is a leading post-transplant morbidity in solid organ transplantation. Among patients who received heart transplant in the U.S. between 1990 and 2000, 20 % had advanced renal dysfunction (glomerular filtration rate <29 ml/min/1.73 m^2 or were receiving renal replacement therapy) by 10 years after transplant [37]. Typically, a steeper decrease in glomerular filtration rate (GFR) is seen in the first year after transplant, with a more gradual but continued decline in renal function thereafter. The etiology of renal dysfunction after heart transplant is multifactorial. The key factors that can negatively influence renal function after transplant are reviewed below.

Pathophysiology

Calcineurin Inhibitors (CNIs)

CNIs, which are used almost universally after heart transplant, have nephrotoxic properties and represent one of the leading factors for decline of renal function after transplant. Initiation of CNI therapy results in vasoconstriction of the afferent glomerular arteriole and decrease in GFR. While this acute 'hemodynamic' effect is often reversible, continued use of CNIs also results in chronic nephrotoxicity, which is not easily reversible. Some of these chronic effects have been attributed to CNI mediated activation of the renin-angiotensin-aldosterone axis and increase in endothelin levels [38, 39]. Histologically, CNI nephrotoxicity presents as interstitial fibrosis, tubular atrophy, arteriolar hyalinosis and glomerulosclerosis [40].

The acute effects of CNIs appear to be more pronounced with intravenous administration of cyclosporine and tacrolimus, and are related to the serum concentration of these drugs. Therefore, if intravenous administration of CNIs is necessary, it is recommended that these are administered as an infusion, either over 6 h in a twice daily dose, or as continuous infusion, until parenteral administration is possible. As bioavailability of parenteral CNI formulations is only 20–35 %, it is important to adjust the intravenous dose accordingly to avoid excessive serum CNI levels and the resulting nephrotoxicity. Long-term nephrotoxic effects of CNIs have also been correlated with CNI serum levels [41].

Different approaches to reduction of the nephrotoxic effects of CNIs have been proposed. A number of clinical studies tested the utility of calcium channel blockers, angiotensin converting enzyme inhibitors and angiotensin receptor blockers in mitigating CNI nephrotoxicity [30, 42–44]. While the results have not been consistent, it appears prudent to preferentially use these classes of drugs in heart transplant recipients who also have hypertension [45].

Reduction of target CNI levels (or CNI minimization) is another approach to reduce nephrotoxicity and consists of reducing the target serum levels of CNI in patients considered to be at particularly high risk of renal dysfunction. The introduction of mycophenolate mofetil, which antirejection effect is more potent compared to the previously used cell cycle inhibitor azathioprine, has been especially important in enabling reduction of CNI levels without substantially increasing the risk of rejection [46, 47]. While CNI minimization has been shown to preserve renal function when implemented early, it is less clear how effective this approach is if implemented later after transplant in patients with established renal dysfunction [48, 49]. Finally, CNI-free regimens have been tested to determine the efficacy of this approach in preventing or reversing renal injury after heart transplant. Substitution of cyclosporine or tacrolimus by a target of rapamycin (mTOR) inhibitor, sirolimus or everolimus, in patients who developed renal dysfunction after transplant, has been tested. A number of mostly single center studies have shown that discontinuation of CNI and use of an mTOR inhibitor in combination with a cell cycle inhibitor in patients typically several years after heart transplant resulted in improvement of renal function, and this strategy appeared to be safe [50–53]. A recent multicenter study randomized 116 patients at a mean time of 3.9 years after transplant to continuation of CNI based regimen vs conversion of CNI to sirolimus. One year after randomization, the patients assigned to sirolimus had significantly higher creatinine clearance (delta of +4.4 mL/min/1.73 m^2), however they also had a numerically higher incidence of acute rejection, and a full one third of the patients had to discontinue sirolimus due to significant side effects [54]. The use of a CNI-free regimen in de novo heart transplantation has been tested in the multicenter randomized STN-Heart trial. This approach has resulted in an unacceptably high rate of acute rejection in the sirolimus/mycophenolate mofetil arm and this trial was stopped prematurely. In summary, most heart transplant recipients remain on CNIs in the current era. In addition to the approaches described above, best outcome as far as renal function will be achieved through careful long-term monitoring of CNI serum levels, avoidance of excessive CNI serum concentrations during times of unstable drug metabolism, and attention to additional nephrotoxic factors.

Hypertension

The effects of hypertension after heart transplant are described in detail earlier in this chapter. Hypertension before heart transplant is a risk factor for renal dysfunction after transplant. Heart transplant recipients without history of hypertension are likely to develop hypertension after transplant. CNIs, mTOR inhibitors,

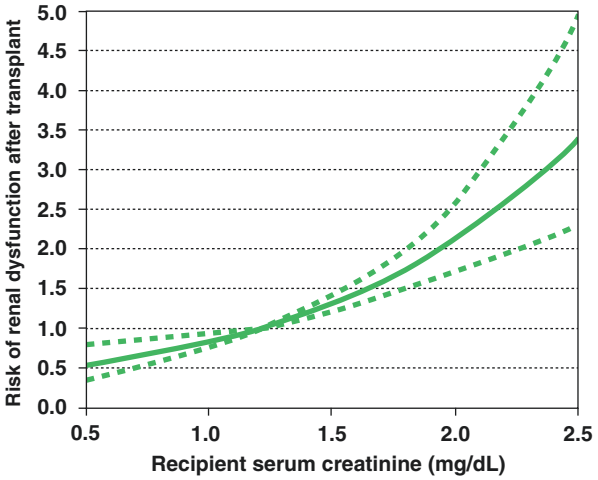


Fig. 24.1 Relative risk of severe renal dysfunction within 5 years after transplant as a function of recipient's serum creatinine level at the time of transplant. Patients without severe renal dysfunction at the time of transplant, transplanted 2001–6/2006 (Reprinted with permission from the *International Society for Heart and Lung Transplantation* [1] © 2012)

mycophenolate mofetil and corticosteroids can all cause or contribute to the development of hypertension. At 1 year after transplant, 72 % of adult heart transplant recipients are treated for hypertension, and this number increases to >90 % at 5 years after transplant [1]. Strict blood pressure control should be pursued in heart transplant recipients who also have hypertension and renal dysfunction [55]. ACE-I and ARBs should be considered as first line therapy. Calcium channel blockers may also have specific advantages in this patient population [45].

Pre-existing Renal Dysfunction

Abnormal renal function before transplant represents a risk factor for developing severe renal dysfunction after transplant (Fig. 24.1). Twenty-four hour urine collection for determination of creatinine clearance should be obtained in patients being evaluated for heart transplantation. In patients with abnormal renal function, etiology of the renal dysfunction should be determined. While patients with cardiorenal syndrome have a good chance for improvement and stabilization of renal function after transplant, renal dysfunction of other causes is likely to further progress after transplant and represent a challenge in clinical management of the heart transplant recipient. Therefore, irreversible renal dysfunction with estimated GFR <40 ml/min should be considered a relative contraindication for heart transplantation [56]. Combined heart and kidney transplantation can be considered in carefully selected candidates who have advanced heart and kidney disease in the absence of additional comorbidities likely to compromise post-transplant survival.

Table 24.2 Risk factors for renal dysfunction after heart transplant

1. Recipient comorbidities
Renal dysfunction
Hypertension
Diabetes mellitus
History of infection requiring IV antibiotic therapy at the time of transplant
Acute graft rejection
2. Recipient age
3. CNI therapy:
Cyclosporine
Tacrolimus
4. Combined use of CNIs and mTOR inhibitors[a]

CNI calcineurin inhibitor, *mTOR* target of rapamycin
[a]May be avoided if CNI exposure is reduced

Diabetes Mellitus

Recipients with history of diabetes mellitus are more likely to develop renal dysfunction after heart transplant. Strict control of normoglycemia and ACE-I or ARB therapy in patients with diabetes mellitus and proteinuria may decrease the risk of progressive renal dysfunction in this patient cohort.

Recipient Age

Older patients are more likely to develop renal dysfunction after transplant, independently of their baseline renal function at the time of transplant or additional relevant comorbidities [1].

BK Virus Infection

Polyoma BK virus infection in heart transplant recipients is relatively rare [57]. This diagnosis should however be ruled out in patients with unexplained worsening of renal function. Reduction of immunosuppression is likely to result in clearance of the BK virus and improvement in renal function.

Other Risk Factors

Additional predictors of renal dysfunction after heart transplant are listed in Table 24.2.

Renal dysfunction is a potent risk factor for short and long-term mortality after heart transplant [1]. Control of progression of renal disease should be addressed by aggressively pursuing all modifiable risk factors. When etiology of renal disease, or of an unexpected progression of renal dysfunction, is not certain, renal biopsy

should be considered [58]. The incidence of severe renal failure after transplant has been gradually decreasing. This has been attributed to reduction of the target serum CNI levels (partly enabled by the introduction of mycophenolate mofetil), as well as to implementation of renal protective strategies described above. Despite that, some heart transplant recipients will develop end-stage kidney disease. These patients will be candidates for renal replacement therapy. This should include kidney transplantation in eligible heart transplant recipients.

Diabetes Mellitus

Epidemiology

Approximately 25 % of heart transplant recipients carry a diagnosis of diabetes mellitus at the time of transplant and this proportion increases to 40 % by 5 years after heart transplant [1]. The increased prevalence of diabetes mellitus after transplant is a well described side effect of immunosuppressive therapies.

Risk factors for development of post-transplant diabetes mellitus include pre-transplant hyperglycemia, family history of diabetes, need for insulin use postoperatively, older age, non-white race, body mass index >25, tobacco use, steroid and tacrolimus use at discharge and higher number of rejections after transplant [59–62]. No direct relationship has been found with pre-transplant oral glucose tolerance test or with the presence of HLA Class II phenotypes associated with Type 1 diabetes mellitus [63].

Pre and post-transplant diabetes mellitus have different implications for survival. While pre-transplant diabetes has been shown to have a negative impact on post-transplant survival, [1, 64–66] it has been suggested that this risk mainly applies to patients with more advanced forms of the disease that has resulted in end-organ complications such as nephropathy, retinopathy or neuropathy before transplantation. On the other hand, post-transplant diabetes mellitus has not been associated with decreased survival at two [67] or five [65] years after transplantation. Post-transplant diabetes has similarly not been shown to result in higher risk of cardiac allograft vasculopathy [61, 68] or higher risk of infections compared to heart transplant recipients without diabetes mellitus [67]. Whether this is due to a different pathophysiology of this disorder, or due to a better control of glycemia in carefully monitored transplant recipients, is not known.

Pathophysiology

The development of post-transplant diabetes mellitus has been associated with the use of corticosteroids and calcineurin inhibitors (Table 24.3). Steroid-induced diabetes is well described and is caused by abnormal glucose metabolism due to increased insulin resistance [69]. CNI can also cause post-transplant diabetes mellitus by decreasing

Table 24.3 Causes and mechanism of post-transplant diabetes mellitus

1. Corticosteroids
Insulin resistance
2. Calcineurin inhibitors
Decreased insulin secretion
Increased insulin resistance
Toxic effects on pancreatic islet cells

insulin secretion, increasing insulin resistance and by a direct toxic effect on the pancreatic beta cell [70]. While both cyclosporine and tacrolimus may cause diabetes mellitus, the onset of hyperglycemia is typically more abrupt in patients on tacrolimus therapy. Whether the risk of post-transplant diabetes is higher with tacrolimus compared to cyclosporine is not well established. An analysis of the United Network of Organ Sharing (UNOS) database demonstrated that patients on tacrolimus therapy had an 85 % higher relative risk of developing post-transplant diabetes [61] compared to cyclosporine treated patients, but this trend was not observed in several other studies [71, 72]. In a multicenter randomized trial of cyclosporine and tacrolimus, similar rates of treated diabetes in heart transplant recipients were observed—12 % and 14 % at 12 months, respectively [16].

Treatment

Attempts to decrease the incidence of post-transplant diabetes have focused on adjustments in immunosuppression regimens. Lizak et al. explored the effects of early (within 12 months) vs late (after 12 months) steroid withdrawal in heart transplant recipients. Unexpectedly, at 5 years after transplant, the group of patients who had an early steroid withdrawal had a higher rate of diabetes compared to the patients who had a late withdrawal (80 vs 51 %, $p = 0.018$) [73].

The ISHLT guidelines recommend routine screening for early detection of post-transplant diabetes. Heart transplant recipients with diabetes should be encouraged to make life style changes including weight control, low carbohydrate-lipid diet and regular exercise. The goals of medical therapy with oral hypoglycemic drugs and insulin are similar to goals in patients without history of transplant [36].

Malignancy

Epidemiology

Past 5 years after transplant, malignancy is responsible for approximately 20 % of deaths in adult heart transplant recipients; and, more heart transplant recipients will die from malignancy than from cardiac allograft vasculopathy [1]. In a transplant recipient, we can encounter malignancy as a result of three clinical scenarios: de novo,

donor derived, and as a recurrence of previously treated recipient cancer. In general, the pathogenesis of cancer is influenced by genetics, immune mechanisms and environmental factors. In transplant recipients, it is the long-term exposure to immunosuppressive medications that is believed to weaken the native barriers to cancer development and progression, and result in higher risk of malignancy.

Pathophysiology

De Novo Malignancy

In a healthy individual, T lymphocytes, natural killer cells and various cytokines are believed to participate in cancer immune surveillance—protection of the host from newly forming tumors [74]. Immunosuppressive medications impair the ability of the host immune system to eliminate tumor cells. More recent investigations have shown, however, that direct effects of immunosuppressive medications (e.g. CNIs and azathioprine) at the site of tumor development may also play a role, raising mutagenesis in cells and speeding up tumor growth [75]. This explains why certain malignancies, e.g. skin cancers, or cancers associated with viral infections, are frequent in transplant recipients. Interestingly, the effect of mTOR inhibitors on cancer risk may be favorable. The effects of rapamycin on TGF-β and angiogenesis are opposite to CNIs— rapamycin suppresses TGF- β and decreases angiogenesis [76]. As an extension of these experimental findings, several clinical investigations have suggested that use of mTOR inhibitors may be associated with lower incidence of skin malignancy after organ transplant [77, 78].

Skin cancer is the most frequent type of malignancy after heart transplant. Analysis of a multicenter U.S. registry has demonstrated that at 10 years after transplant, 11 % of patients have developed squamous cell skin cancer, 8 % have developed basal cell carcinoma and 1 % of patients have developed melanoma [79]. The risk factors for skin cancer development included lighter skin, older age, pre-transplant history of skin cancer and residence in latitude with higher UV-light exposure. Patients receiving higher doses of cyclosporine, azathioprine and mycophenolate were also shown to have higher incidence of skin cancer. Compared to age- and gender-matched general population, the incidence of the different types of skin cancer was elevated up to 30-fold, and the diagnosis of skin cancer was associated with higher mortality [79].

The incidence of **non-skin malignancies** after heart transplantation is also increased compared to a general population. An analysis of the Canadian Organ Replacement Register, Canadian Mortality Database and Canadian Cancer Registry has shown that the 15-year cumulative incidence of all cancers excluding squamous basal cell skin carcinoma among 1,703 heart transplant recipients was 17 %. A total of 160 cancers developed in these patients, compared to an expected 59. Among specific cancers, the incidence was statistically higher for lymphoma, lung cancer, oral cancer and multiple myeloma, and numerically higher for a number of additional malignancies, including cancer of kidney, prostate, pancreas and others [80].

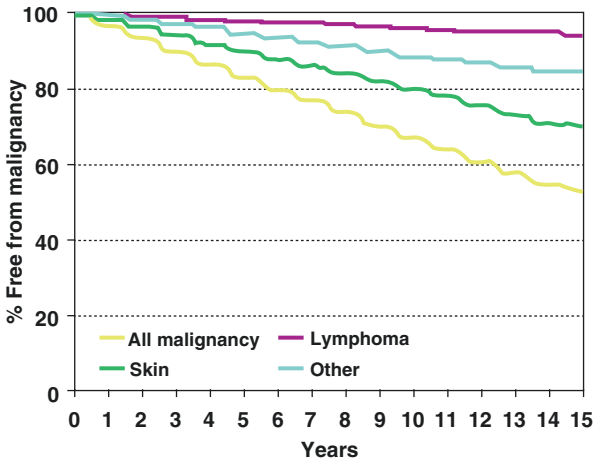


Fig. 24.2 Incidence of cancer after heart transplant. Adult patients transplanted 4/1994–6/2011 (Reprinted with permission from the *International Society for Heart and Lung Transplantation* [1] © 2012)

A study that included large number of transplant recipients in Australia demonstrated higher risk of 12 types of cancer in heart transplant recipients compared to the matched general population [81]. Increased incidence of non-skin cancer in solid organ recipients has also been confirmed by a number of other reports (Fig. 24.2) [1, 82–84].

Apart from skin cancer, hematological malignancies after solid organ transplant show the highest increase in incidence compared to the general population. **Post-transplant lymphoproliferative disorder (PTLD)** represents the bulk of the hematological malignancies. Its incidence in children is approximately 1.5 % and 6 %, and in adults 0.3 % and 0.7 %, 1- and 5-years after heart transplant, respectively [85]. Epstein Barr Virus (EBV) plays a key role in PTLD pathogenesis. EBV is a herpesvirus with a seroprevalence of approximately 50 % in children by the age of 5 years and of over 90 % in adults [86]. The lack of an effective T-cell response in immunosuppressed recipients compromises the ability of the organism to control EBV replication and leads to uncontrolled polyclonal or monoclonal replication of EBV-infected lymphocytes—PTLD. The risk of PTLD development is especially high after a primary EBV infection. Therefore, pediatric heart transplant recipients are at a higher risk of developing PTLD than adults, and most cancers diagnosed after heart transplant in children are PTLD [87]. In the pediatric heart transplant population, children between 1 and 10 years are at the highest risk, with 25 % of patients in this age group who were seronegative at the time of transplant developing PTLD [88]. In addition to young age and EBV seronegativity, use of certain immunosuppressive agents has been associated with increased risk of PTLD – OKT3, antilymphocyte globulin, and most recently belatacept [89, 90].

EBV positive forms of PTLD often occur early after transplant. EBV-negative forms of PTLD do not appear to be linked to EBV infection, can occur in both pediatric and adult heart transplant recipients, and typically presents later (years) after transplant [91].

Table 24.4 Diagnostic workup of suspected post-transplant lymphoproliferative disorder

1. **Routine testing**
Complete blood count, differential, platelet count
Serum electrolytes, calcium, blood urea nitrogen, creatinine
Liver function tests
Uric acid
Lactate dehydrogenase
Quantitative immunoglobulins
EBV serologies (anti-EBNA, VCA and EA)
EBV viral load from peripheral blood
Stool for occult bleeding
Chest radiograph
CT scan of neck/chest/abdomen/pelvis
Core needle or excisional biopsy of lesion(s)
Flow cytometry of lymphocytes
EBER, CD20 histochemistry studies of pathologic samples
2. **Testing indicated in selected patients**
Gastrointestinal endoscopy
Bone scan
Bone marrow biopsy
Brain computed tomography / magnetic resonance imaging
Lumbar puncture

Reproduced with permission from Green and Michaels [92], Table 3, © 2013, John Wiley and Sons
EBER EBV-encoded RNA, *EBNA* Epstein–Barr nuclear antigens, *EA* early antigen, *VCA* viral capsid antigen

The PTLD presentation may be somewhat non-specific. This diagnosis should be considered in patients with high EBV viral load in blood and pharyngitis, enlarged tonsils, lymphadenopathy, hepatomegaly or splenomegaly. Gastrointestinal symptoms including indigestion, diarrhea and abdominal pain may be present as lymphocyte proliferation often takes place in the abundant gut lymphoid tissue. Neurological symptoms can be seen when central nervous system is involved, which is considered a marker of worse outcome. Focal presentation in the form of EBV-associated lymphoma can also be seen, and the lymphoma may infiltrate any organ. The full diagnostic workup of a suspected PTLD is outlined in Table 24.4 [92].

Treatment of PTLD includes aggressive reduction of immunosuppression, aimed at restoring of the recipient's ability to generate cytotoxic lymphocytes and control the proliferation of the EBV infected lymphocytes. Reduction of immunosuppression alone can lead to PTLD remission in up to 40 % of patients with EBV positive PTLD [93]. Additional pharmacotherapy includes the use of antivirals acyclovir and ganciclovir, anti-CD-20 antibody rituximab, or cyclophosamide and prednisone chemotherapy. The efficacy of intravenous immunoglobulin and interferon is less well established. The utility of a proteasome inhibitor bortezomib is also being tested. Surgical debulking may be needed in selected cases, and radiation has been used, especially when CNS involvement is present [92].

Chronic chemoprophylaxis with acyclovir in recipients who are EBV seronegative at the time of transplant, especially if the donor is EBV seropositive, has been practiced by some heart transplant programs. The intent is to reduce the likelihood of PTLD development in this high risk cohort of patients, but data evaluating the efficacy of this approach are limited. Surveillance monitoring of EBV load and preemptive reduction in immunosuppressive therapy is an alternate approach used especially in pediatric programs. This strategy has been shown to decrease PTLD incidence in pediatric kidney and liver transplant [55, 94].

One-year survival after PTLD diagnosis has been reported at 55–75 %, with 5-year survival 40–60 % [7, 12–14]. Survival in children is in general better compared to adults and survival in EBV positive PTLD is better compared to EBV negative forms of the disease. Outcomes after PTLD have been improving recently, likely a result of earlier diagnosis allowed by EBV surveillance, use of preemptive reduction in immunosuppressive therapy and introduction of therapy with rituximab [92].

Prevention of malignancy after transplant starts with heart transplant candidate evaluation. All candidates should undergo age appropriate cancer screening, including colonoscopy, mammogram and PAP cervical smear. Skin exam should also be done and a Dermatology consultation obtained should any suspicious skin lesions be identified. If precancerous lesions are identified during cancer screening, treatment should be initiated without delay. After transplant, cancer screening should be continued. Patients should be instructed to protect their skin from UV radiation by appropriate clothing, head cover and skin sun-block. Dermatology skin cancer screening should be done every 6–12 months. Annual physical examination for adenopathy or abnormal masses should be done, and age appropriate colon, breast and cervical cancer screening should be continued. Chest radiography is in general performed annually, as is serum prostate-specific antigen (PSA) level, although data regarding its utility is limited. Surveillance monitoring of EBV load or chemoprophylaxis with antivirals should be done in patients who are at high risk for PTLD. All patients should be encouraged to report any unusual findings or symptoms. Minimization of immunosuppression is recommended when safe and feasible in heart transplant candidates at risk of, or with history of, malignancy [45].

Donor Derived Malignancy

While donor derived malignancy is relatively rare, the consequences of such an event can be devastating [95, 96]. A detailed personal medical history obtained from donor family at the time of organ procurement should specifically inquire about any history of tumor diagnosis or treatment. A careful physical exam of the donor should focus on ruling out malignancy that could be detected by physical exam, such as skin cancer. Results of imaging studies obtained during donor evaluation should also be reviewed to rule out possible diagnosis of cancer. This should especially apply to older donors, and donors whose cause of death is an intracranial bleed or whose cause of death may not be fully explained.

In donors with history of a tumor, the risk of donor related malignancy transmission needs to be assessed and balanced with a benefit of using the particular organ for transplantation. In 2011, the Disease Transmission Advisory Committee (DTAC) of the Organ Procurement and Transplantation Network/United Network for Organ Sharing (OPTN/UNOS) published a report that assigned various tumors with specific levels of risk for transmission to the recipient (Table 24.5) [97]. Benign tumors in which malignancy is excluded represents no significant risk to the recipient and their presence should not alter organ allocation decisions. A minimal risk category designates tumors with a risk of transmission of <0.1 %. Donors with tumors in this category should be strongly considered for heart transplantation. Use of organs from donors with tumors with low risk of transmission (0.1–1 %) should be evaluated on a case by case basis, and the risk of transmission weighed against the benefit of transplantation in the particular recipient. Transplantation of heart allografts from donors with more than low risk (>1 %) of malignancy transmission should only be considered in exceptional circumstances.

Personal History of Malignancy

Heart transplant candidacy decisions in patients with history of malignancy can be challenging. In general, a cancer-free period likely to assure a sufficiently low risk of cancer recurrence should be achieved before listing for transplantation. Cardiac transplant may be considered when tumor recurrence is low based on tumor type, response to therapy and negative metastatic work-up [56]. This approach has resulted in favorable outcomes in transplant recipients with history of malignancy [98, 99], however shorter cancer-free survival before thoracic transplant has been associated with higher recurrence rate of malignancy, and with higher post-transplant mortality in those transplanted <12 months after cancer treatment [100].

The number of patients with advanced heart failure and history of malignancy has been on the rise, as novel oncotherapy regimens have significantly improved survival, at times at the expense of increased cardiotoxic risk [101]. Frequently used chemotherapeutic agents associated with cardiotoxicity include anthracyclines, cyclophosphamide, 5-fluorouracil, and more recently trastuzumab and tyrosine kinase inhibitors [102–105]. A review of a contemporary cohort of 232 patients with chemotherapy induced cardiomyopathy transplanted between 2000 and 2008 has demonstrated similar survival compared to patients without history of malignancy. The group of patients with chemotherapy induced cardiomyopathy did have however a higher rate of infection after transplant (22 vs. 14 %, p = 0.004) [106]. It would therefore appear reasonable to reduce immunosuppression levels when feasible in this group of patients. Finally, durable left ventricular assist devices have become a useful tool in bridging patients with severe forms of heart failure and history of recent malignancy to transplant eligibility.

In summary, cancer represents a major post-transplant morbidity and remains a leading cause of mortality after transplant. However, advances in cancer surveillance and treatment, and in immunosuppressive approaches after heart transplant have resulted in reduced incidence of malignancy after heart transplant in the most recent era [1].

Table 24.5 Risk categories for donor derived tumor transmission

Risk category (% risk of transmission)	Tumor type
No significant risk	Benign tumors in which malignancy is excluded
Minimal risk (<0.1 %)	Basal cell carcinoma, skin
	Squamous cell carcinoma, skin without metastases
	Carcinoma in situ, skin (non-melanoma)
	In situ cervical carcinoma
	In situ vocal cord carcinoma
	Superficial (noninvasive) papillary carcinoma of bladder (T0N0M0 by TNM stage)
	Solitary papillary thyroid carcinoma, ≤0.5 cm
	Minimally invasive follicular carcinoma, thyroid, ≤1.0 cm
	Resected solitary renal cell carcinoma, ≤1.0 cm, well differentiated
Low risk (0.1–1 %)	Resected solitary renal cell carcinoma, >1.0 cm ≤2.5 cm, well differentiated
	Low grade CNS tumor (WHO grade I or II)
	Primary CNS mature teratoma
	Solitary papillary thyroid carcinoma, 0.5–2.0 cm
	Minimally invasive follicular carcinoma, thyroid, 1.0–2.0 cm
	History of treated non-CNS malignancy (≥5 years prior) with >99 % probability of cure
Intermediate risk (1–10 %)	Breast carcinoma in situ (stage 0)
	Colon carcinoma in situ (stage 0)
	Resected solitary renal cell carcinoma T1b (4–7 cm) well differentiated stage I
	History of treated non-CNS malignancy (≥5 years prior) with probability of cure between 90 and 99 %
High risk (>10 %)	Malignant melanoma
	Breast carcinoma >stage 0
	Colon carcinoma >stage 0
	Choriocarcinoma
	Any CNS tumor with ventriculoperitoneal or ventriculoatrial shunt, surgery, irradiation or extra-CNS metastasis
	CNS Tumor WHO grade III or IV
	Leukemia or lymphoma
	History of melanoma, leukemia or lymphoma, small cell lung/ neuroendocrine carcinoma
	Any other history of treated non-CNS malignancy with either (a) insufficient follow-up to predict behavior, (b) considered incurable or (c) with probability of cure <90 %
	Metastatic carcinoma
	Sarcoma
	Lung cancer (stages I–IV)
	Renal cell carcinoma >7 cm or stage II–IV
	Small cell/neuroendocrine carcinoma, any site of origin
	Active cancer not listed elsewhere

Adapted with permission from Nalesnik et al. [97], Table 2, © 2011, with permission from John Wiley and Sons

Arrhythmias

In most instances, arrhythmias after transplant originate in the donor heart. When the biatrial anastomosis technique is used, the recipient's right and left atrial tissue is anastomosed to the donor heart, and both the recipient and the donor sinus nodes will be in place after transplant. A surface EKG will show two sets of p-waves, however atrial depolarization driven by the recipient's sinus activity will be interrupted at the suture line, and only the donor sinus activity will be conducted to the ventricles. During bicaval anastomosis, only left atrial donor tissue will remain in place, while donor right atrium is excised.

Cryopreservation of the donor allograft at the time of organ procurement results in ischemic myocardial injury, which severity depends on the length of ischemic time, age of the donor, presence of myocardial hypertrophy and other factors. Ischemic injury as well as surgical trauma may result in sinus node dysfunction; this is seen in up to 50 % of patients when electrophysiologic studies are performed, and this dysfunction is typically temporary [107, 108]. The resulting rhythm is marked sinus bradycardia or slow junctional escape rhythm. In a freshly transplanted heart with restrictive filling, bradycardia may result in reduced cardiac output and restoration of higher heart rate is necessary. This can be achieved with isoproterenol infusion or temporary atrial pacing. Theophylline has also been used, but whether this therapy results in a faster return of sinus activity has not been well established [109]. When marked sinus bradycardia persists for more than 2 or 3 weeks, permanent atrial pacemaker is the treatment of choice.

Of note, atropine will be void of its parasympatholytic effects on the denervated transplanted heart. Similarly, in the absence of sinus node dysfunction, the baseline heart rate after heart transplant will be elevated (typically 90–110 beats/min), as the resting heart rate of the denervated transplanted heart is no longer modulated by the vagal tone. Whether this chronically elevated resting heart rate has any negative consequences is not known. Studies in patients with heart failure that showed beneficial effects of ivabradine, an I_f—channel inhibitor with strong negative chronotropic properties, have generated recent interest in this topic, and some studies suggested that patients with higher heart rate after transplant may have a higher risk of mortality. Whether this relationship is causal needs further study [110–113].

The most frequent group arrhythmias after heart transplant are supraventricular arrhythmias. Most will be donor derived, however some may result from development of electrical conductivity between the recipient and the donor atrial tissue late after transplant, and this can become clinically apparent when recipient-derived atrial arrhythmias are conducted to the donor atrial tissue [114, 115]. Atrial flutter is the most common atrial arrhythmia, followed by atrial fibrillation and supraventricular reentry arrhythmias resulting from accessory or dual atrioventricular nodal pathways [115]. Atrial fibrillation occurring in the peritransplant period usually results from perioperative irritation of the pericardium. Expeditious electrical cardioversion will usually convert the patient to sinus rhythm, and extended antiarrhythmic or anticoagulation therapy will typically not be needed. Atrial fibrillation

later after transplant can be seen in the setting of acute rejection or cardiac allograft vasculopathy, and these diagnoses should be considered in these circumstances. Otherwise, treatment of supraventricular arrhythmias in heart transplant recipients is similar to treatment of patients with native heart. A notable exception is the use of adenosine. The transplanted heart is hypersensitive to the effects of adenosine, and its intravenous bolus administration can result in atrioventricular block lasting for dozens of seconds and up to several minutes [116]. Radiofrequency ablation of arrhythmias can be used after heart transplantation; knowledge of the anatomy and the physiology of the transplanted heart and the possible role of donor atrial tissue should be taken into consideration during this therapy [117].

Malignant ventricular arrhythmias in a normally functioning heart allograft are rare. When ventricular systolic dysfunction develops due to cardiac allograft vasculopathy or due to myocardial injury of other etiology, the risk of ventricular arrhythmias is increased, but accurate data regarding the risk of arrhythmic sudden cardiac death in this clinical scenario are lacking. ICDs have been used in these patients for primary prevention of sudden cardiac death, and for secondary prevention in patients with documented ventricular tachycardia or with unexplained syncope [118].

Osteoporosis

Osteoporosis is a metabolic bone disease characterized by low bone mass and microarchitectural deterioration of bony tissue leading to enhanced bone fragility and a consequent increase in fracture risk [119]. Clinically, bone mass is evaluated by measurements of Bone Mineral Density (BMD) using Dual X-ray Absorptiometry (DXA). BMD is expressed as absolute BMD (g/cm^2) and is usually designated by the number of standard deviations (SD) from the normal mean (T score). The World Health Organization developed criteria for the clinical diagnosis of osteoporosis based on the T score. A normal value for BMD ranges within 1 SD of the young adult reference mean. Osteopenia is a value for BMD more than 1 SD below the young adult mean but less than 2.5 SD below this value. Osteoporosis is defined as a value for BMD 2.5 or more below the young adult mean [119].

Epidemiology

Bone density decreases in almost all patients after heart transplantation [120]. The decline occurs faster during the first 6 months after heart transplantation, after which it slows down, even if moderate maintenance doses of corticosteroids are used [121, 122]. Higher bone loss is observed in the lumbar spine and in patients with more exposure to corticosteroids, lower serum vitamin D metabolites, higher

Table 24.6 Causes and mechanisms of post-transplant bone loss

1. Decreased bone mass before transplantation
2. Corticosteroids
Decreased osteogenesis (main mechanism)
Increased bone resorption
3. Calcineurin inhibitors
Increased bone resorption

levels of resorption markers, and in men with lower testosterone levels [122]. Vertebral fractures are common (35–44 %) and often occur during the first 6 months after heart transplantation [123–125]. Pre-transplant evaluation of bone density or measurement of biochemical indexes of mineral metabolism (1,25-dihydroxyvitamin D or intact PTH) have not been associated with increased risk of fracture after heart transplantation [125].

Pathophysiology

The reasons for bone loss after heart transplantation are multifactorial (Table 24.6). A decreased bone mass before transplantation combined with a fast bone loss triggered by immunosuppressive agents are the main contributors. Patients with chronic heart failure are known to have decrease BMD, most likely from decreased physical activity and also from the utilization of loop diuretics causing a secondary increase in the PTH [126].

Corticosteroids

The main effect of corticosteroids on bone metabolism is through decreasing of the number and function of osteoblasts and a consequent significant reduction in bone formation. There is also an increase in bone resorption through stimulation of osteoclastogenesis [127]. In heart transplant recipients, glucocorticoid-induced osteopenia is observed as early as 2 months after transplant [128].

Calcineurin Inhibitors

Animal studies have demonstrated a fast and severe bone loss with cyclosporine, and the severity depends on the dose and duration of therapy. Cyclosporine causes bone resorption and also stimulates bone formation [129–131]. This effect on bone formation could potentially counteract the suppressive effects of glucocorticosteroids on the osteoblasts [132]. Tacrolimus stimulates bone resorption thorough mechanisms similar to cyclosporine [133].

Treatment

The treatment of post-transplant osteoporosis includes exercise, calcium and vitamin D supplementation, calcitonin and bisphosphonates.

Exercise

Animal studies have demonstrated that mechanical loading with exercise produces small bone deformations. These deformations stimulate paracrine and autocrine factors that increases bone formation [134, 135]. Insulin-like growth factor (IGF-1) is expressed in mechanically stimulated vertebrae [136] and is associated with markers of bone synthesis and collagen production [137]. In a small randomized control trial in heart transplant recipients, 6 months of low back and resistance exercises restored BMD of the whole body, femur neck and lumbar vertebra to within pre-transplant levels [138].

Elemental Calcium + Vitamin D

Calcium is needed for bone formation and vitamin D increases its intestinal absorption. The combination therapy of calcium with vitamin D decreases fractures in women with osteoporosis. In heart transplant recipients, bone density decreases despite calcium supplementation, [128], however the combination of calcium and vitamin D has been shown to decrease the rate of bone loss during corticosteroid therapy [139].

Active Metabolites of Vitamin D

Calcidiol, also known as 25-hydroxyvitamin D, is a prohormone that is converted in the kidneys to calcitriol, the active form of vitamin D. The combination of calcium with alphacalcidiol reduces, but does not fully prevent, the early accelerated bones loss seen after heart transplantation [140]. Smabrook et al. have also shown that the combination of calcitriol with calcium prevents post-transplant bone loss [141, 142].

Calcitonin

Calcitonin is a hormone produced in the thyroid that reduces serum calcium levels and inhibits the resorptive activity of osteoclasts. As monotherapy, it decreases bone density loss [128]. Braith et al. compared calcitonin vs calcitonin + resistance exercise after heart transplantation. Calcitonin as monotherapy decreased bone loss in the total body and femoral neck but not in the lumbar area. Calcitonin and exercise successfully decreased bone loss in the total body, femoral neck and also in the lumbar spine [143].

Biphosphonates

The effect of bisphosphonates on bone metabolism is in inhibition in osteoclast-mediated bone-resorption. Alendronate and risedronate are approved by the FDA for the treatment of glucocorticosteroid-induced osteoporosis. While some data suggested better efficacy of alendronate compared to calcitriol in the prevention of bone loss after heart transplantation, others have shown comparable effects on BMD [144]. As far as treatment side effects, the rates of gastrointestinal adverse events were similar between the groups, while patients receiving calcitriol developed more hypercalcemia (8 vs 1 %) and hypercalciuria (27 vs 7 %) [145].

The ISHLT guidelines recommend screening for osteoporosis before and 12 months after heart transplantation. Weight-bearing and muscle strengthening regular exercise should be encouraged. Calcium (1,000–1,500 mg/day) and vitamin D (400–1000 IU/day) should be initiated before and continued after heart transplantation. Adult patients should be treated with bisphosphonates for the first 12 months after transplant, at which point these can be discontinued if there is no evidence of osteopenia or osteoporosis on DXA scan. Yearly DXA scans are recommended thereafter, with re-initiation of bisphosphonates if evidence of bone loss is detected. Active metabolites of vitamin D (calcidiol, alfacalcidiol and calcitriol) should not be first line of therapy; if they are used, serum and urinary calcium should be monitored. Calcitonin is not recommended for bone loss after heart transplantation [36].

Sexual Dysfunction

The first reports of sexual dysfunction in heart transplant recipients were by Christian Barnard in 1978 [146]. Sexual function is an important part of quality of life. Heart transplant improves the overall quality of life, [147] but satisfaction in sexual life is known to be negatively affected, compared to other elements such as physical capacity, family and social relationships, which typically improve [148]. While previous reports suggested improvement in the sexual activity after heart transplantation, [149] more objective assessment such as the International Index of Erectile Dysfunction and the Female Sexual Function Index have shown that 78 % of men and 50 % of women suffered from sexual dysfunction at 6 months after heart transplantation, with symptoms including impotence, ejaculation problems, changes in libido and avoidance of sexual opportunities [150–153].

Pathophysiology

The causes of sexual dysfunction after heart transplantation are not well described, but could be related to immunosuppression and decreased physical health. Chronic glucocorticosteroid therapy reduces serum testosterone levels [154]. Cyclosporine

alters libido and mycophenolate is associated with impotence. Target of rapamycin inhibitors are known to inhibit spermatogonia [155]. Measures of mental health and depression were similar in recipients with and without sexual dysfunction suggesting that psychological causes are less related to post-transplant sexual dysfunction [150].

Treatment

Erectile dysfunction in heart transplant recipients is underdiagnosed and undertreated. Successful interventions with phosphodiesterase inhibitors, intracavernosal injections, vacuum constriction device, testosterone supplementation and penile prosthesis have been used without significant complications in this patient population [156].

References

1. Stehlik J, Edwards LB, Kucheryavaya AY, Benden C, Christie JD, Dipchand AI, Dobbels F, Kirk R, Rahmel AO, MI H. The registry of the international society for heart and lung transplantation: 29th official adult heart transplant report-2012. J Heart Lung Transplant. 2012;31:1052–64.
2. Leenen FH, Holliwell DL, Cardella CJ. Blood pressure and left ventricular anatomy and function after heart transplantation. Am Heart J. 1991;122:1087–94.
3. Ozdogan E, Banner N, Fitzgerald M, Musumeci F, Khaghani A, et al. Factors influencing the development of hypertension after heart transplantation. J Thermophys Heat Transf. 1990;9:548–53.
4. Thompson ME, Shapiro AP, Johnsen AM, Itzkoff JM, Hardesty RL, et al. The contrasting effects of cyclosporin-A and azathioprine on arterial blood pressure and renal function following cardiac transplantation. Int J Cardiol. 1986;11:219–29.
5. Murali S, Uretsky BF, Reddy PS, Griffith BP, Hardesty RL, et al. Hemodynamic abnormalities following cardiac transplantation: relationship to hypertension and survival. Am Heart J. 1989;118:334–41.
6. Pfeilschifter J, Ruegg UT. Cyclosporin A augments angiotensin II-stimulated rise in intracellular free calcium in vascular smooth muscle cells. Biochem J. 1987;248:883–7.
7. Meyer-Lehnert H, Schrier RW. Cyclosporine A enhances vasopressin-induced Ca2+ mobilization and contraction in mesangial cells. Kidney Int. 1988;34:89–97.
8. Rodriguez-Puyol D, Lamas S, Olivera A, Lopez-Farre A, Ortega G, et al. Actions of cyclosporin A on cultured rat mesangial cells. Kidney Int. 1989;35:632–7.
9. Myers BD, Sibley R, Newton L, Tomlanovich SJ, Boshkos C, et al. The long-term course of cyclosporine-associated chronic nephropathy. Kidney Int. 1988;33:590–600.
10. Scherrer U, Vissing SF, Morgan BJ, Rollins JA, Tindall RS, et al. Cyclosporine-induced sympathetic activation and hypertension after heart transplantation. N Engl J Med. 1990;323:693–9.
11. Edwards BS, Hunt SA, Fowler MB, Valantine HA, Anderson LM, et al. Effect of cyclosporine on plasma endothelin levels in humans after cardiac transplantation. Am J Cardiol. 1991;67:782–4.
12. Grieff M, Loertscher R, Shohaib SA, Stewart DJ. Cyclosporine-induced elevation in circulating endothelin-1 in patients with solid-organ transplants. Transplantation. 1993;56:880–4.

13. Dorent R, Cacoub P, Carayon A, Nataf P, Golmard JL, et al. Endothelin levels after orthotopic heart transplantation. Transplant Proc. 1994;26:250.
14. Pham SM, Kormos RL, Hattler BG, Kawai A, Tsamandas AC, et al. A prospective trial of tacrolimus (FK 506) in clinical heart transplantation: intermediate-term results. J Thorac Cardiovasc Surg. 1996;111:764–72.
15. Rinaldi M, Pellegrini C, Martinelli L, Goggi C, Gavazzi A, et al. FK506 effectiveness in reducing acute rejection after heart transplantation: a prospective randomized study. J Heart Lung Transplant. 1997;16:1001–10.
16. Taylor DO, Barr ML, Radovancevic B, Renlund DG, Mentzer Jr RM, et al. A randomized, multicenter comparison of tacrolimus and cyclosporine immunosuppressive regimens in cardiac transplantation: decreased hyperlipidemia and hypertension with tacrolimus. J Heart Lung Transplant. 1999;18:336–45.
17. Keogh A, Macdonald P, Harvison A, Richens D, Mundy J, et al. Initial steroid-free versus steroid-based maintenance therapy and steroid withdrawal after heart transplantation: two views of the steroid question. J Heart Lung Transplant. 1992;11:421–7.
18. Pritzker MR, Lake KD, Reutzel TJ, Hoffman FM, Jorgensen CR, et al. Steroid-free maintenance immunotherapy: Minneapolis Heart Institute experience. J Heart Lung Transplant. 1992;11:415–20.
19. Braith RW, Mills Jr RM, Wilcox CS, Convertino VA, Davis GL, et al. Fluid homeostasis after heart transplantation: the role of cardiac denervation. J Heart Lung Transplant. 1996;15:872–80.
20. Bellet M, Cabrol C, Sassano P, Leger P, Corvol P, et al. Systemic hypertension after cardiac transplantation: effect of cyclosporine on the renin-angiotensin-aldosterone system. Am J Cardiol. 1985;56:927–31.
21. Henry JP, Gauer OH, Reeves JL. Evidence of the atrial location of receptors influencing urine flow. Circ Res. 1956;4:85–90.
22. Johnson JA, Moore WW, Segar WE. Small changes in left atrial pressure and plasma antidiuretic hormone titers in dogs. Am J Phys. 1969;217:210–4.
23. Karim F, Kidd C, Malpus CM, Penna PE. The effects of stimulation of the left atrial receptors on sympathetic efferent nerve activity. J Physiol. 1972;227:243–60.
24. Lee ME, Thrasher TN, Ramsay DJ. Mechanism of inhibition of renin secretion by increased left atrial pressure. Am J Phys. 1985;248:R641–4.
25. Gilmore JP, Daggett WM. Response of the chronic cardiac denervated dog to acute volume expansion. Am J Phys. 1966;210:509–12.
26. Willman VL, Merjavy JP, Pennell R, Hanlon CR. Response of the autotransplanted heart to blood volume expansion. Ann Surg. 1967;166:513–7.
27. Brozena SC, Johnson MR, Ventura H, Hobbs R, Miller L, et al. Effectiveness and safety of diltiazem or lisinopril in treatment of hypertension after heart transplantation. Results of a prospective, randomized multicenter trail. J Am Coll Cardiol. 1996;27:1707–12.
28. Legault L, Ogilvie RI, Cardella CJ, Leenen FH. Calcium antagonists in heart transplant recipients: effects on cardiac and renal function and cyclosporine pharmacokinetics. Can J Cardiol. 1993;9:398–404.
29. Schroeder JS, Gao SZ, Alderman EL, Hunt SA, Johnstone I, et al. A preliminary study of diltiazem in the prevention of coronary artery disease in heart-transplant recipients. N Engl J Med. 1993;328:164–70.
30. Leenen FH, Coletta E, Davies RA. Prevention of renal dysfunction and hypertension by amlodipine after heart transplant. Am J Cardiol. 2007;100:531–5.
31. Elliott WJ, Murphy MB, Karp R. Long-term preservation of renal function in hypertensive heart transplant recipients treated with enalapril and a diuretic. J Heart Lung Transplant. 1991;10:373–9.
32. Angermann CE, Spes CH, Willems S, Dominiak P, Kemkes BM, et al. Regression of left ventricular hypertrophy in hypertensive heart transplant recipients treated with enalapril, furosemide, and verapamil. Circulation. 1991;84:583–93.

33. Almenar L, Osa A, Palencia M, Flores A, Sanchez E. Effects of fosinopril on the blood pressure and lipid profile of patients undergoing heart transplantation. J Heart Lung Transplant. 1997;16:454–9.
34. Braith RW, Mills RM, Wilcox CS, Mitchell MJ, Hill JA, et al. High dose angiotensin-converting enzyme inhibition prevents fluid volume expansion in heart transplant recipients. J Am Coll Cardiol. 2000;36:487–92.
35. Singer DR, Markandu ND, Buckley MG, Miller MA, Sagnella GA, et al. Blood pressure and endocrine responses to changes in dietary sodium intake in cardiac transplant recipients. Implications for the control of sodium balance. Circulation. 1994;89:1153–9.
36. Costanzo MR, Dipchand A, Starling R, Anderson A, Chan M, et al. The International Society of Heart and Lung Transplantation Guidelines for the care of heart transplant recipients. J Heart Lung Transplant. 2010;29:914–56.
37. Ojo AO, Held PJ, Port FK, Wolfe RA, Leichtman AB, et al. Chronic renal failure after transplantation of a nonrenal organ. N Engl J Med. 2003;349:931–40.
38. Ruster C, Wolf G. Renin-angiotensin-aldosterone system and progression of renal disease. J Am Soc Nephrol. 2006;17:2985–91.
39. Sugimoto T, Haneda M, Sawano H, Isshiki K, Maeda S, et al. Endothelin-1 induces cyclooxygenase-2 expression via nuclear factor of activated T-cell transcription factor in glomerular mesangial cells. J Am Soc Nephrol. 2001;12:1359–68.
40. Klintmalm GB, Iwatsuki S, Starzl TE. Nephrotoxicity of cyclosporin A in liver and kidney transplant patients. Lancet. 1981;1:470–1.
41. Kershner RP, Fitzsimmons WE. Relationship of FK506 whole blood concentrations and efficacy and toxicity after liver and kidney transplantation. Transplantation. 1996;62:920–6.
42. Bunke M, Ganzel B. Effect of calcium channel antagonists on renal function in hypertensive heart transplant recipients. J Heart Lung Transplant. 1992;11:1194–9.
43. Chan C, Maurer J, Cardella C, Cattran D, Pei Y. A randomized controlled trial of verapamil on cyclosporine nephrotoxicity in heart and lung transplant recipients. Transplantation. 1997;63:1435–40.
44. Inigo P, Campistol JM, Lario S, Piera C, Campos B, et al. Effects of losartan and amlodipine on intrarenal hemodynamics and TGF-beta(1) plasma levels in a crossover trial in renal transplant recipients. J Am Soc Nephrol. 2001;12:822–7.
45. Costanzo MR, Dipchand A, Starling R, Anderson A, Chan M, et al. The International Society of Heart and Lung Transplantation Guidelines for the care of heart transplant recipients. T J Heart Lung Transplant. 2010;29(8):914–56. 4.
46. Angermann CE, Stork S, Costard-Jackle A, Dengler TJ, Siebert U, et al. Reduction of cyclosporine after introduction of mycophenolate mofetil improves chronic renal dysfunction in heart transplant recipients – the IMPROVED multi-centre study. Eur Heart J. 2004;25:1626–34.
47. Tedoriya T, Keogh AM, Kusano K, Savdie E, Hayward C, et al. Reversal of chronic cyclosporine nephrotoxicity after heart transplantation-potential role of mycophenolate mofetil. J Heart Lung Transplant. 2002;21:976–82.
48. Rice JE, Shipp AT, Carlin JB, Vidmar SI, Weintraub RG. Late reduction in cyclosporine dosage does not improve renal function in pediatric heart transplant recipients. J Heart Lung Transplant. 2002;21:1109–12.
49. Rice JE, Shipp AT, Vidmar S, Weintraub RG. Is renal function in paediatric heart transplant recipients influenced by late reduction in cyclosporine dosage? J Heart Lung Transplant. 2001;20:232.
50. Groetzner J, Kaczmarek I, Landwehr P, Mueller M, Daebritz S, et al. Renal recovery after conversion to a calcineurin inhibitor-free immunosuppression in late cardiac transplant recipients. Eur J Cardiothorac Surg. 2004;25:333–41.
51. Hunt J, Lerman M, Magee MJ, Dewey TM, Herbert M, et al. Improvement of renal dysfunction by conversion from calcineurin inhibitors to sirolimus after heart transplantation. J Heart Lung Transplant. 2005;24:1863–7.
52. Meiser B, Reichart B, Adamidis I, Uberfuhr P, Kaczmarek I. First experience with de novo calcineurin-inhibitor-free immunosuppression following cardiac transplantation. Am J Transplant. 2005;5:827–31.

53. Kushwaha SS, Khalpey Z, Frantz RP, Rodeheffer RJ, Clavell AL, et al. Sirolimus in cardiac transplantation: use as a primary immunosuppressant in calcineurin inhibitor-induced nephrotoxicity. J Heart Lung Transplant. 2005;24:2129–36.
54. Zuckermann A, Keogh A, Crespo-Leiro MG, Mancini D, Vilchez FG, et al. Randomized controlled trial of sirolimus conversion in cardiac transplant recipients with renal insufficiency. Am J Transplant. 2012;12:2487–97.
55. Ganschow R, Schulz T, Meyer T, Broering DC, Burdelski M. Low-dose immunosuppression reduces the incidence of post-transplant lymphoproliferative disease in pediatric liver graft recipients. J Pediatr Gastroenterol Nutr. 2004;38:198–203.
56. Mehra MR, Kobashigawa J, Starling R, Russell S, Uber PA, et al. Listing criteria for heart transplantation: International Society for Heart and Lung Transplantation guidelines for the care of cardiac transplant candidates – 2006. T J Heart Lung Transplant. 2006;25:1024–42.
57. Randhawa P, Brennan DC. BK virus infection in transplant recipients: an overview and update. Am J Transplant. 2006;6:2000–5.
58. Coopersmith CM, Brennan DC, Miller B, Wang C, Hmiel P, et al. Renal transplantation following previous heart, liver, and lung transplantation: an 8-year single-center experience. Surgery. 2001;130:457–62.
59. Katz MR, Barnhart GR, Szentpetery S, Rider S, Thompson JA, et al. Are steroids essential for successful maintenance of immunosuppression in heart transplantation? J Thermophys Heat Transf. 1987;6:293–7.
60. Depczynski B, Daly B, Campbell LV, Chisholm DJ, Keogh A. Predicting the occurrence of diabetes mellitus in recipients of heart transplants. Diabet Med. 2000;17:15–9.
61. Ye X, Kuo HT, Sampaio MS, Jiang Y, Reddy P, et al. Risk factors for development of new-onset diabetes mellitus in adult heart transplant recipients. Transplantation. 2010;89:1526–32.
62. Martinez-Dolz L, Almenar L, Martinez-Ortiz L, Arnau MA, Chamorro C, et al. Predictive factors for development of diabetes mellitus post-heart transplant. Transplant Proc. 2005;37:4064–6.
63. Nieuwenhuis MG, Kirkels JH. Predictability and other aspects of post-transplant diabetes mellitus in heart transplant recipients. J Heart Lung Transplant. 2001;20:703–8.
64. Marelli D, Laks H, Patel B, Kermani R, Marmureanu A, et al. Heart transplantation in patients with diabetes mellitus in the current era. J Heart Lung Transplant. 2003;22:1091–7.
65. Klingenberg R, Gleissner C, Koch A, Schnabel PA, Sack FU, et al. Impact of pre-operative diabetes mellitus upon early and late survival after heart transplantation: a possible era effect. J Heart Lung Transplant. 2005;24:1239–46.
66. Russo MJ, Chen JM, Hong KN, Stewart AS, Ascheim DD, et al. Survival after heart transplantation is not diminished among recipients with uncomplicated diabetes mellitus: an analysis of the United Network of Organ Sharing database. Circulation. 2006;114:2280–7.
67. Ladowski JS, Kormos RL, Uretsky BF, Lee A, Curran M, et al. Posttransplantation diabetes mellitus in heart transplant recipients. J Thermophys Heat Transf. 1989;8:181–3.
68. Gao SZ, Schroeder JS, Alderman EL, Hunt SA, Silverman JF, et al. Clinical and laboratory correlates of accelerated coronary artery disease in the cardiac transplant patient. Circulation. 1976;76:V56–61.
69. Ekstrand A, Ahonen J, Gronhagen-Riska C, Groop L. Mechanisms of insulin resistance after kidney transplantation. Transplantation. 1989;48:563–8.
70. Jindal RM, Sidner RA, Milgrom ML. Post-transplant diabetes mellitus. The role of immunosuppression. Drug Saf. 1997;16:242–57.
71. Kobashigawa JA, Patel J, Furukawa H, Moriguchi JD, Yeatman L, et al. Five-year results of a randomized, single-center study of tacrolimus vs microemulsion cyclosporine in heart transplant patients. J Heart Lung Transplant. 2006;25:434–9.
72. Ye F, Ying-Bin X, Yu-Guo W, Hetzer R. Tacrolimus versus cyclosporine microemulsion for heart transplant recipients: a meta-analysis. J Heart Lung Transplant. 2009;28:58–66.
73. Lizak MK, Zakliczynski M, Jarosz A, Zembala M, Kalarus Z. Early steroid withdrawal – impact on diabetes mellitus and kidney function in heart transplant recipients. Ann Transplant. 2001;16:92–8.

74. Dunn GP, Bruce AT, Ikeda H, Old LJ, Schreiber RD. Cancer immunoediting: from immunosurveillance to tumor escape. Nat Immun. 2002;3:991–8.
75. Martinez OM, de Gruijl FR. Molecular and immunologic mechanisms of cancer pathogenesis in solid organ transplant recipients. Am J Transplant. 2008;8:2205–11.
76. Koehl GE, Andrassy J, Guba M, Richter S, Kroemer A, et al. Rapamycin protects allografts from rejection while simultaneously attacking tumors in immunosuppressed mice. Transplantation. 2004;77:1319–26.
77. Kauffman HM, Cherikh WS, Cheng Y, Hanto DW, Kahan BD. Maintenance immunosuppression with target-of-rapamycin inhibitors is associated with a reduced incidence of de novo malignancies. Transplantation. 2005;80:883–9.
78. Euvrard S, Morelon E, Rostaing L, Goffin E, Brocard A, et al. Sirolimus and secondary skin-cancer prevention in kidney transplantation. N Engl J Med. 2012;367:329–39.
79. Alam M, Brown RN, Silber DH, Mullen GM, Feldman DS, et al. Increased incidence and mortality associated with skin cancers after cardiac transplant. Am J Transplant. 2011;11:1488–97.
80. Jiang Y, Villeneuve PJ, Wielgosz A, Schaubel DE, Fenton SS, et al. The incidence of cancer in a population-based cohort of Canadian heart transplant recipients. Am J Transplant. 2010;10:637–45.
81. Na R, Grulich AE, Meagher NS, McCaughan GW, Keogh AM, et al. Comparison of de novo cancer incidence in Australian liver, heart and lung transplant recipients. Am J Transplant. 2013;13:174–83.
82. Collett D, Mumford L, Banner NR, Neuberger J, Watson C. Comparison of the incidence of malignancy in recipients of different types of organ: a UK Registry audit. Am J Transplant. 2010;10:1889–96.
83. Adami J, Gabel H, Lindelof B, Ekstrom K, Rydh B, et al. Cancer risk following organ transplantation: a nationwide cohort study in Sweden. Br J Cancer. 2003;89:1221–7.
84. Kasiske BL, Snyder JJ, Gilbertson DT, Wang C. Cancer after kidney transplantation in the United States. Am J Transplant. 2004;4:905–13.
85. Dharnidharka VR, Lamb KE, Gregg JA, Meier-Kriesche HU. Associations between EBV serostatus and organ transplant type in PTLD risk: an analysis of the SRTR National Registry Data in the United States. Am J Transplant. 2012;12:976–83.
86. Cohen JI. Epstein-Barr virus infection. N Engl J Med. 2000;343:481–92.
87. Kirk R, Dipchand AI, Edwards LB, Kucheryavaya AY, Benden C, et al. The registry of the International Society for Heart and Lung Transplantation: fifteenth pediatric heart transplantation report – 2012. J Heart Lung Transplant. 2012;31:1065–72.
88. Chinnock R, Webber SA, Dipchand AI, Brown RN, George JF. A 16-year multi-institutional study of the role of age and EBV status on PTLD incidence among pediatric heart transplant recipients. Am J Transplant. 2012;12:3061–8.
89. Swinnen LJ, Costanzo-Nordin MR, Fisher SG, O'Sullivan EJ, Johnson MR, et al. Increased incidence of lymphoproliferative disorder after immunosuppression with the monoclonal antibody OKT3 in cardiac-transplant recipients. N Engl J Med. 1990;323:1723–8.
90. Vincenti F, Charpentier B, Vanrenterghem Y, Rostaing L, Bresnahan B, et al. A phase III study of belatacept-based immunosuppression regimens versus cyclosporine in renal transplant recipients (BENEFIT study). Am J Transplant. 2010;10:535–46.
91. Caillard S, Lamy FX, Quelen C, Dantal J, Lebranchu Y, et al. Epidemiology of posttransplant lymphoproliferative disorders in adult kidney and kidney pancreas recipients: report of the French registry and analysis of subgroups of lymphomas. Am J Transplant. 2012;12:682–93.
92. Green MM, Michaels MG. Epstein–Barr Virus Infection and Posttransplant Lymphoproliferative Disorder. Am J Transplant. 2013;13(Suppl 3):41–54.
93. Green M. Management of Epstein-Barr virus-induced post-transplant lymphoproliferative disease in recipients of solid organ transplantation. Am J Transplant. 2001;1(2):103–8.
94. Lee TC, Savoldo B, Rooney CM, Heslop HE, Gee AP, et al. Quantitative EBV viral loads and immunosuppression alterations can decrease PTLD incidence in pediatric liver transplant recipients. Am J Transplant. 2005;5:2222–8.

95. Kauffman HM, Cherikh WS, McBride MA, Cheng Y, Hanto DW. Deceased donors with a past history of malignancy: an organ procurement and transplantation network/united network for organ sharing update. Transplantation. 2007;84:272–4.
96. Garrido G, Matesanz R. The Spanish National Transplant Organization (ONT) tumor registry. Transplantation. 2008;85:S61–3.
97. Nalesnik MA, Woodle ES, Dimaio JM, Vasudev B, Teperman LW, et al. Donor-transmitted malignancies in organ transplantation: assessment of clinical risk. Am J Transplant. 2011;11:1140–7.
98. Oechslin E, Kiowski W, Schneider J, Follath F, Turina M, et al. Pretransplant malignancy in candidates and posttransplant malignancy in recipients of cardiac transplantation. Ann Oncol. 1996;7:1059–63.
99. Dillon TA, Sullivan M, Schatzlein MH, Peterson AC, Scheeringa RH, et al. Cardiac transplantation in patients with preexisting malignancies. Transplantation. 1991; 52:82–5.
100. Sigurdardottir V, Bjortuft O, Eiskjaer H, Ekmehag B, Gude E, et al. Long-term follow-up of lung and heart transplant recipients with pre-transplant malignancies. J Heart Lung Transplant. 2012;31:1276–80.
101. Eschenhagen T, Force T, Ewer MS, de Keulenaer GW, Suter TM, et al. Cardiovascular side effects of cancer therapies: a position statement from the Heart Failure Association of the European Society of Cardiology. Eur J Heart Fail. 2011;13:1–10.
102. Singal PK, Iliskovic N. Doxorubicin-induced cardiomyopathy. N Engl J Med. 1998;339:900–5.
103. Goldberg MA, Antin JH, Guinan EC, Rappeport JM. Cyclophosphamide cardiotoxicity: an analysis of dosing as a risk factor. Blood. 1986;68:1114–8.
104. Yeh ET, Bickford CL. Cardiovascular complications of cancer therapy: incidence, pathogenesis, diagnosis, and management. J Am Coll Cardiol. 2009;53:2231–47.
105. Uraizee I, Cheng S, Moslehi J. Reversible cardiomyopathy associated with sunitinib and sorafenib. N Engl J Med. 2011;365:1649–50.
106. Oliveira GH, Hardaway BW, Kucheryavaya AY, Stehlik J, Edwards LB, et al. Characteristics and survival of patients with chemotherapy-induced cardiomyopathy undergoing heart transplantation. J Heart Lung Transplant. 2012;31:805–10.
107. Bexton RS, Nathan AW, Hellestrand KJ, Cory-Pearce R, Spurrell RA, et al. Sinoatrial function after cardiac transplantation. J Am Coll Cardiol. 1984;3:712–23.
108. Jacquet L, Ziady G, Stein K, Griffith B, Armitage J, et al. Cardiac rhythm disturbances early after orthotopic heart transplantation: prevalence and clinical importance of the observed abnormalities. J Am Coll Cardiol. 1990;16:832–7.
109. Bertolet BD, Eagle DA, Conti JB, Mills RM, Belardinelli L. Bradycardia after heart transplantation: reversal with theophylline. J Am Coll Cardiol. 1996;28:396–9.
110. Zhang R, Bobylev D, Stiefel P, Haverich A, Bara C. Lasting reduction of heart transplant tachycardia with ivabradine is effective and well tolerated: results of 48-month study. Clin Res Cardiol. 2012;101:631–6.
111. Doesch AO, Celik S, Ehlermann P, Frankenstein L, Zehelein J, et al. Heart rate reduction after heart transplantation with beta-blocker versus the selective If channel antagonist ivabradine. Transplantation. 2007;84:988–96.
112. Olmetti F, Pinna GD, Maestri R, D'Armini A, Pellegrini C, et al. Heart rate and cardiac allograft vasculopathy in heart transplant recipients. J Heart Lung Transplant. 2011;30:1368–73.
113. Doesch AO, Ammon K, Konstandin M, Celik S, Kristen A, et al. Heart rate reduction for 12 months with ivabradine reduces left ventricular mass in cardiac allograft recipients. Transplantation. 2009;88:835–41.
114. Nof E, Stevenson WG, Epstein LM, Tedrow UB, Koplan BA. Catheter ablation of atrial arrhythmias after cardiac transplantation: findings at EP study utility of 3-D mapping and outcomes. J Cardiovasc Electrophysiol. 2013;24:498–502.
115. Vaseghi M, Boyle NG, Kedia R, Patel JK, Cesario DA, et al. Supraventricular tachycardia after orthotopic cardiac transplantation. J Am Coll Cardiol. 2008;51:2241–9.

116. Anderson TJ, Ryan Jr TJ, Mudge GH, Selwyn AP, Ganz P, et al. Sinoatrial and atrioventricular block caused by intracoronary infusion of adenosine early after heart transplantation. J Heart Lung Transplant. 1993;12:522–4.
117. Elsik M, Teh A, Ling LH, Virdee M, Parameshwar J, et al. Supraventricular arrhythmias late after orthotopic cardiac transplantation: electrocardiographic and electrophysiological characterization and radiofrequency ablation. Europace. 2012;14:1498–505.
118. Tsai VW, Cooper J, Garan H, Natale A, Ptaszek LM, et al. The efficacy of implantable cardioverter-defibrillators in heart transplant recipients: results from a multicenter registry. Circ Heart Fail. 2009;2:197–201.
119. World Health Organization Study Group on Assessment of Fracture Risk and Its Application to Screening and Postmenopausal Osteoporosis. Report of a WHO Study Group. Technical Report Series (No 84). 1994.
120. Muchmore JS, Cooper DK, Ye Y, Schlegel V, Pribil A, et al. Prevention of loss of vertebral bone density in heart transplant patients. J Heart Lung Transplant 1995;11:959–63; discussion 963–4.
121. Sambrook PN, Kelly PJ, Keogh AM, Macdonald P, Spratt P, et al. Bone loss after heart transplantation: a prospective study. J Heart Lung Transplant 1994;13:116–20; discussion 121.
122. Shane E, Rivas M, McMahon DJ, Staron RB, Silverberg SJ, et al. Bone loss and turnover after cardiac transplantation. J Clin Endocrinol Metab. 1997;82:1497–506.
123. Rich GM, Mudge GH, Laffel GL, LeBoff MS. Cyclosporine A and prednisone-associated osteoporosis in heart transplant recipients. J Heart Lung Transplant. 1992;11:950–8.
124. Shane E, Rivas MC, Silverberg SJ, Kim TS, Staron RB, et al. Osteoporosis after cardiac transplantation. Am J Med. 1993;94:257–64.
125. Shane E, Rivas M, Staron RB, Silverberg SJ, Seibel MJ, et al. Fracture after cardiac transplantation: a prospective longitudinal study. J Clin Endocrinol Metab. 1996;81:1740–6.
126. Lee AH, Mull RL, Keenan GF, Callegari PE, Dalinka MK, et al. Osteoporosis and bone morbidity in cardiac transplant recipients. Am J Med. 1994;96:35–41.
127. Canalis E, Delany AM. Mechanisms of glucocorticoid action in bone. Ann N Y Acad Sci. 2002;966:73–81.
128. Muchmore JS, Cooper DK, Ye Y, Schlegel VT, Zuhdi N. Loss of vertebral bone density in heart transplant patients. Transplant Proc. 1991;23:1184–5.
129. Movsowitz C, Epstein S, Fallon M, Ismail F, Thomas S. Cyclosporin-A in vivo produces severe osteopenia in the rat: effect of dose and duration of administration. Endocrinology. 1988;123:2571–7.
130. Lowik CW, van der Pluijm G, Bloys H, Hoekman K, Bijvoet OL, et al. Parathyroid hormone (PTH) and PTH-like protein (PLP) stimulate interleukin-6 production by osteogenic cells: a possible role of interleukin-6 in osteoclastogenesis. Biochem Biophys Res Commun. 1989;162:1546–52.
131. Epstein S, Dissanayake IR, Goodman GR, Bowman AR, Zhou H, et al. Effect of the interaction of parathyroid hormone and cyclosporine a on bone mineral metabolism in the rat. Calcif Tissue Int. 2001;68:240–7.
132. Movsowitz C, Schlosberg M, Epstein S, Ismail F, Fallon M, et al. Combined treatment with cyclosporin A and cortisone acetate minimizes the adverse bone effects of either agent alone. J Orthop Res. 1990;8:635–41.
133. Fukunaga J, Yamaai T, Yamachika E, Ishiwari Y, Tsujigiwa H, et al. Expression of osteoclast differentiation factor and osteoclastogenesis inhibitory factor in rat osteoporosis induced by immunosuppressant FK506. Bone. 2004;34:425–31.
134. JA O'C, LE L, MacFie H. The influence of strain rate on adaptive bone remodeling. J Biomech. 1982;15:767–81.
135. Rubin CT, Lanyon LE. Regulation of bone mass by mechanical strain magnitude. Calcif Tissue Int. 1985;37:411–7.
136. Chow JW. Role of nitric oxide and prostaglandins in the bone formation response to mechanical loading. Exerc Sport Sci Rev. 2000;28:185–8.

137. Lean JM, Mackay AG, Chow JW, Chambers TJ. Osteocytic expression of mRNA for c-fos and IGF-I: an immediate early gene response to an osteogenic stimulus. Am J Phys. 1996;270:E937–45.
138. Braith RW, Mills RM, Welsch MA, Keller JW, Pollock ML. Resistance exercise training restores bone mineral density in heart transplant recipients. J Am Coll Cardiol. 1996;28:1471–7.
139. Sambrook PN, Kotowicz M, Nash P, Styles CB, Naganathan V, et al. Prevention and treatment of glucocorticoid-induced osteoporosis: a comparison of calcitriol, vitamin D plus calcium, and alendronate plus calcium. J Bone Miner Res. 2003;18:919–24.
140. Van Cleemput J, Daenen W, Geusens P, Dequeker P, Van De Werf F, et al. Prevention of bone loss in cardiac transplant recipients. A comparison of biphosphonates and vitamin D. Transplantation. 1996;61:1495–9.
141. Sambrook P, Birmingham J, Kelly P, Kempler S, Nguyen T, et al. Prevention of corticosteroid osteoporosis. A comparison of calcium, calcitriol, and calcitonin. N Engl J Med. 1993;328:1747–52.
142. Sambrook P, Henderson NK, Keogh A, MacDonald P, Glanville A, et al. Effect of calcitriol on bone loss after cardiac or lung transplantation. J Bone Miner Res. 2000;15:1818–24.
143. Braith RW, Magyari PM, Fulton MN, Lisor CF, Vogel SE, et al. Comparison of calcitonin versus calcitonin + resistance exercise as prophylaxis for osteoporosis in heart transplant recipients. Transplantation. 2006;81:1191–5.
144. Henderson K, Eisman J, Keogh A, MacDonald P, Glanville A, et al. Protective effect of short-tem calcitriol or cyclical etidronate on bone loss after cardiac or lung transplantation. J Bone Miner Res. 2001;16:565–71.
145. Shane E, Addesso V, Namerow PB, McMahon DJ, Lo SH, et al. Alendronate versus calcitriol for the prevention of bone loss after cardiac transplantation. N Engl J Med. 2004;350:767–76.
146. Wolpowitz A, Barnard CN. Impotence after heart transplantation. S Afr Med J. 1978;53:693.
147. Lough ME, Lindsey AM, Shinn JA, Stotts NA. Life satisfaction following heart transplantation. J Thermophys Heat Transf. 1985;4:446–9.
148. Harvison A, Jones BM, McBride M, Taylor F, Wright O, et al. Rehabilitation after heart transplantation: the Australian experience. J Thermophys Heat Transf. 1988;7:337–41.
149. Bunzel B, Grundbock A, Laczkovics A, Holzinger C, Teufelsbauer H. Quality of life after orthotopic heart transplantation. J Heart Lung Transplant. 1991;10:455–9.
150. Phan A, Ishak WW, Shen BJ, Fuess J, Philip K, et al. Persistent sexual dysfunction impairs quality of life after cardiac transplantation. J Sex Med. 2010;7:2765–73.
151. Tabler JB, Frierson RL. Sexual concerns after heart transplantation. J Thermophys Heat Transf. 1990;9:397–403.
152. Stiefel P, Malehsa D, Bara C, Strueber M, Haverich A, et al. Symptom Experiences in Patients after Heart Transplantation. J Health Psychol. 2013;18:680–92.
153. Mulligan T, Sheehan H, Hanrahan J. Sexual function after heart transplantation. J Heart Lung Transplant. 1991;10:125–8.
154. MacAdams MR, White RH, Chipps BE. Reduction of serum testosterone levels during chronic glucocorticoid therapy. Ann Intern Med. 1986;104:648–51.
155. Huyghe E, Zairi A, Nohra J, Kamar N, Plante P, et al. Gonadal impact of target of rapamycin inhibitors (sirolimus and everolimus) in male patients: an overview. Transpl Int. 2007;20:305–11.
156. Donaldson DS, Fuselier HA. Urologic experience in 48 heart transplant recipients. South Med J. 1997;90:1084–6.

Chapter 25
Patient Selection

Sharven Taghavi and Abeel A. Mangi

Introduction

Heart failure remains a growing problem worldwide [1, 2]. This is especially true in the Western World, where its prevalence is estimated around 1–2 % [1, 3–6]. For patients with advanced heart failure, quality of life is poor and mortality is as high as 50 % at 1 year after only one hospitalization [1, 3–6]. Heart transplantation remains the gold standard for end stage heart failure. It results in improved quality of life and a 10-year survival of up to 60 % [7]. However, a shortage of organ donors and increasing waiting times means many transplant candidates will not receive donor hearts [7]. In addition, many patients with end stage heart failure are ineligible for heart transplantation due to various contraindications [8].

Left ventricular assist device (LVAD) therapy for patients in end-stage heart failure results in improved quality of life and better survival [9–14]. Newer generation, continuous-flow LVAD have resulted in improved outcomes with decreased complications when compared to first generation pulsatile-flow devices [15, 16]. Studies have estimated that there are as many as 200,000 patients in the United States that would benefit from such therapy [17, 18]. Careful patient selection remains the most important process in obtaining a successful outcome with LVAD implantation.

S. Taghavi, MD, MPH
Washington University School of Medicine, Division of Cardiothoracic Surgery,
660 South Euclid Avenue, Campus Box 8234, St. Louis, MO 63110, USA
e-mail: taghavis@wudosis.wustl.edu

A.A. Mangi, MD, FACC, FACS (✉)
Yale University School of Medicine, Section of Cardiac Surgery, Yale New Haven Hospital,
Boardman 204, 330 Cedar Street, New Haven, CT 06520, USA
e-mail: abeel.mangi@yale.edu

H. Eisen (ed.), *Heart Failure*, DOI 10.1007/978-1-4471-4219-5_25

Indications to Left Ventricular Assist Device

In 2006, the International Society for Heart and Lung Transplantation released the Guidelines for the Care of Cardiac Transplant Candidates, in which recommendations for the institutional of MCS were made [19]. These guidelines recommended that patients be considered for MCS when they are no longer able to sustain adequate oxygen delivery for normal end-organ function, despite maximal medical therapy and/or intra-aortic balloon pump support [19]. The hemodynamic criteria for LVAD placement described at that time included a systolic blood pressure less than 80 mmHG, mean arterial pressure (MAP) less than 65 mmHG, or a systemic vascular resistance (SVR) greater than 2100 dynes.sec/cm [19]. However, as experience with MCS devices increased the indications for LVAD implantation has evolved. Results of the REMATCH trial lead to coverage of HM-2 implantation by the Centers for Medicare and Medicaid Services (CMS) when certain criterion was met. This included patients with New York Heart Association Class IV heart failure without response to optimal medical management for at least 45 of the past 60 days, a left ventricular ejection fraction of less than 25 %, and peak oxygen consumption of less than or equal to 14/ml/kg/min unless balloon pump or inotrope dependent [20, 21].

Contraindications and Other Considerations to Left Ventricular Assist Device

In addition to hemodynamic parameters, many additional factors must be assessed to determine if a patient is a candidate for LVAD therapy [19]. While age is not an absolute contraindication to LVAD placement, ISHLT guidelines recommend a thorough evaluation of other clinical risk factors in patients over the age of 60 [19]. In addition, guidelines recommend that patients have a body surface area greater than 1.5 m^2 [19].

An overall assessment of end-organ function is also a necessary component of patient selection for LVAD [19]. Patients with CHF commonly have some degree of renal dysfunction and renal failure is a predictor of poor outcomes in patients undergoing LVAD implantation [22, 23]. A serum creatinine greater than 3.0 mg/dl and the need for dialysis have typically been considered contraindications for LVAD. However, renal function has been shown to improve in heart failure patients after implementation of LVAD [12, 24, 25]. Therefore, an assessment of the reversibility of renal dysfunction is an integral component of the patient selection process. Similarly, hepatic dysfunction and the potential for recovery of function must be evaluated [19]. Liver dysfunction is an marker of poor outcomes in patients with LVAD [26]. ISHLT guidelines recommend exuding caution in patients with alanine aminotransferase (ALT) or aspartate aminotransferase (AST) values over three time greater than control values or with an INR over 2.5 [19]. Studies have shown that elevated bilirubin is also a predictor of poor outcomes in LVAD placement [26].

Liver function can improve after the implementation of LVAD [12, 25, 27, 28] and this must be a consideration when evaluating hepatic dysfunction.

Pulmonary function should be assessed with a 1 s forced expiratory volume (FEV1) less than 1 considered a contraindication for LVAD [19]. Mechanical ventilation is also a risk factor for poor outcomes in LVAD patients [29, 30]. Candidates for LVAD should also be thoroughly assessed for clinical evidence of infection as sepsis is a common cause of death after institution of MCS [29–32] and an elevated white blood cell count has been identified as a risk factor for mortality in LVAD patients [33].

A neurological and psychological evaluation is also an important aspect of patient selection. Any post-stroke motor deficits should be identified to determine if the patient is physically capable of taking care of the LVAD. Neurological dysfunction can effect outcomes post-implantation of LVAD [29, 30, 32]. Psychiatric history and/or the presence of substance abuse should also be assessed. Patients with a psychiatric history or concerning symptoms should be referred to a psychiatrist for evaluation prior to device implantation [19].

Other factors that should be considered include nutritional status and the presence of active malignancy. A study has shown that a pre-albumin level less than 15 mg/dL results in increased mortality in LVAD patients [34]. Cachexia is also a clear contraindication to LVAD [35]. While active malignancy can be a contraindication to LVAD implantation, the use of MCS in certain situations may allow for prolongation of life to allow treatment of the malignancy followed by transplantation, or for destination therapy.

Assessment of Overall Outcomes

Proper patient selection remains the most critical step to implementation of mechanical circulatory support (MCS) as patients who are less sick at the time of implantation have superior outcomes [36]. Numerous risk assessment scores have been developed in order to help physicians quantify risk of mechanical circulatory support to patients. Most risk assessment scores were established in older generation pulsatile LVADs and their utilization in new generation common flow LVAD still needs validation. Furthermore, these risk assessment scores are based on retrospective analyses of small, single-institutional studies [37]. However, they remain as valuable tools in predicting patient risk in implementing mechanical circulatory support.

The National Institutes of Health (NIH) sponsored Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) scale was developed to improve patient selection and improve outcomes [6]. The INTERMACS scale divides patients into 7 levels according to their hemodynamic status prior to implantation of LVAD. A summary of the INTERMACS scale is shown in Table 25.1 [38]. The INTERMACS scale has been validated in a previous single-institutional study [39], however, it has not been tested or validated in prospective fashion. Yet, it

Table 25.1 Overview of INTERMACS classification

Profile	Description	1-year survival %	Time frame for intervention
Profile 1: Critical cardiogenic shock	Life-threatening hypotension despite rapidly increasing inotropic support. Critical organ hypoperfusion confirmed by worsening acidosis or high lactate levels	65	Within hours
Profile 2: Progressive decline	Declining function despite inotropic support. May see worsening renal or hepatic function	72	Within a few days
Profile 3: Stable but inotrope dependent	Stable hemodynamics and organ function while on inotropic support but unable to wean from support	82	Elective intervention over a period of weeks to months
Profile 4: Resting symptoms	Hemodynamically stable but with daily symptoms at rest or during activities of daily living. Usually require high doses of diuretics	75	Elective intervention over a period of weeks to months
Profile 5: Exertion intolerant	Comfortable at rest or during activities of daily living but unable to perform other activities	72	Variable, depends on maintenance of nutrition, organ function, symptoms and activity
Profile 6: Exertion limited	Comfortable at rest and is able to perform other activities outside the home but fatigues after a few minutes	72	Variable, depends on maintenance of nutrition, organ function, symptoms and activity
Profile 7: Advanced NYHA III	Stable without current or recent episodes of unstable fluid balance	73	LVAD may not be currently indicated

remains a useful tool for overall clinical assessment of patients requiring mechanical circulatory support.

The Columbia University/Cleveland Clinic risk factor selection scale (RFSS) was the first scoring system to examine risk of mechanical circulatory support. This study examined 56 patients with the HeartMate (HM) implantable pneumatic (IP) and HM vented electric (VE) devices. While too small for a multivariate analysis, this study identified five risk factors for death: oliguria, ventilator dependence, elevated central venous pressure (CVP), elevated prothrombin time (PT), and reoperation status [40]. This scoring system was later revised based on data from 130 patients receiving the HM VE. A summary of the revised scoring system (RSS) is shown in Table 25.2. While mechanical ventilation, elevated CVP and PT remained a part of the risk scoring system, post-cardiotomy shock and pre-operative LVAD were also found to be important factors. A score greater than 5 was estimated to have an operative mortality risk of 46 % [41].

Lietz et al. examined 45 baseline laboratory, hemodynamic, and clinical parameters and outcomes in destination therapy (DT) patients. The authors devised a score

Table 25.2 Predicting overall outcomes [37, 40–42]

Scoring system	Number of patients	Device studied	Predictors of mortality (Points per risk factor)	Scoring
Columbia University/ Cleveland Clinic Risk Factor Selection Scale (RFSS) [37]	56	HM XVE HM IP	Urine output <30 cc/hr (1) Elevated CVP (1) Mechanical ventilation (1) Elevated prothrombin time (1) Redo sternotomy (1)	>5 points: operative mortality 67 %
Columbia University/ Cleveland Clinic Revised Screening Scale (RSS) [40]	130	HM VE	Mechanical ventilation (3) Cardiogenic shock (2) Pre-operative LVAD (2) Elevated CVP (2) Elevated prothrombin time (1)	1 year survival: ≤5 points: 46 % >5 points: 12 %
Lietz-Miller Destination Therapy Risk Score (DTRS) [41]	222	HM XVE	Platelet Count ≤148,000/uL (7) Albumin ≤3.3 g/dL (5) INR >1.1 (4) Vasodilator therapy (4) Mean pulmonary artery pressures ≤25 mmHg (3) Aspartate aminotransferase >45 U/mL (2) Hematocrit ≤34 % (2) Blood urea nitrogen >51 U/dL (2) No intravenous inotropes (2)	1 year survival: 0–8 points: 81 % 9–16 points: 62 % 17–19 points: 28 % >19 points: 11 %
Muenster University Medical Center [42]	241	Variable	Pre-operative transfusion of >10 units RBC and/or 10 units FFP (6) Inotropes (5) Lactate >3 mg/dL (5) LDH >500 and/or CK >200 and/or troponin I >20 ng/mL (5) C-reactive protein >8 and/or WBC >13 (4) Re-do sternotomy (4) Pre-operative mechanical ventilation (3) Creatinine >1.5 mg/dL and/or BUN >40 and/or CVVH(d) (3) Emergency implant (3) Pre-operative CPR (2) Ischemic etiology (2) Heart rate >100 (1) Hemoglobin <12 g/dL and/or hematocrit <35 % (1) Age >50	ICU mortality: ≥15 points: 15.8 % 16–30 points: 48.2 % >30 points: 65.2

that stratified patients in low-, medium-, and high-risk categories. Estimated 1 year survival for patients in the low-, medium-, high, and very high-risk categories was 81.2, 62.4, 27.8 and 10.7 %. It is important to note that this study did not include patients requiring mechanical ventilation or intra-aortic balloon pump (IABP). Furthermore, when this risk assessment score was tested in continuous flow LVADs, it was shown to be a poor predictor of mortality in bridge to transplant (BTT) patients and only of modest use in DR patients [37]. Klotz et al. at Muenster University Medical Center identified several pre-operative risk factors for mortality in an analysis of 241 patients with variable devices. Using a weighted risk score, this study divided patients into low-, medium, and high-risk groups [42]. A summary of risk factors predicting death in LVAD patients for this study is shown in Table 25.2.

Holman et al. used the INTERMACS database to determine predictors of mortality for patients on mechanical circulatory support [43]. Predictors of death included older patient age, cardiogenic shock with hemodynamic compromise described by assignment of INTERMACS level 1, and clinical indicators of right ventricular failure such as ascites and hyperbilirubinemia.

Assessment of Right Ventricular Function

Right ventricular (RV) dysfunction is common in congestive heart failure [44]. Implantation of LVAD results in increased cardiac output and venous return, which can exacerbate severe RV failure [45]. In addition, unloading of the left ventricle can shift the interventricular septum to the left, decreasing the septal contribution to RV output [46, 47]. As many as 20–35 % of LVAD patients will develop severe RV failure and this directly increases mortality [48]. RV dysfunction after institution of MCS leads to longer lengths of stay, higher morbidity and mortality, and worse post-transplant outcomes [28, 49–51]. For this reason, assessment of RV function prior to LVAD implantation is essential.

An assessment of RV function should include an echocardiogram and invasive hemodynamics [19]. A low RV systolic pressure with elevated right atrial pressure and low RV stroke volume is a marker of severe RV impairment with decreased potential for reversibility [52]. Echocardiographic parameters that may be helpful in predicting post-LVAD RV failure include tricuspid annular plane systolic excursion (TAPSE) less than 1.5 cm, right to left ventricular end-diastolic diameter greater than 0.72, and RV stroke volume index [53]. It must be kept in mind that an RV that appears dysfunctional on echocardiogram may still be capable of generating high pulmonary pressures, therefore, invasive hemodynamics are a critical component of RV assessment. A pulmonary artery systolic pressure of less than 50 mmHg is thought to be associated with a high RV failure risk [48]. In addition, a RV stroke work index (RVSWI) of less than 450 mmHG × ml/m^2 is predictive of RV failure [48]. For patients with borderline RV function, an extended assessment period using a Swan-Ganz catheter in an ICU setting may be beneficial in determining if the patient can be managed with LVAD implantation alone [48].

Table 25.3 Scoring scales to predict RV failure after LVAD implantation [48, 54, 55]

Scoring system	Number of patients	Device studied	Predictors of mortality (Points per risk factor)	Scoring
University of Pennsylvania RV Failure Risk Score [54]	266	Variable	Cardiac index ≤2.2 L/min/m^2 (18) RVSWI ≤250 mmHG × ml/m^2 (18) Severe RV dysfunction (17) Previous cardiac surgery (16) Systolic BP <96 mmHG (13)	Need for RV support: <30 points: 4 % ≥65 points: 89 %
University of Michigan Risk Score [48]	197	Variable	Vasopressor requirement (4) AST ≥80 IU/L (2) Bilirubin ≥2 mg/dL (2.5) Serum creatinine ≥2.3 mg/dL (3)	Likelihood of RV failure: ≤3 points: 0.49 4–5 points: 2.8 ≥7.6
Kormos et al. [55]	484	Heartmate II	CVP/PCWP >0.63 (RR: 2.3) Mechanical ventilation (RR: 5.5) BUN >39 mg/dL (RR: 2.1)	Relative risk for RV failure

Risk factor scores have been devised to help quantify the risk of RV failure as seen in Table 25.3. Fitzpatrick et al. from the University of Pennsylvania identified several risk factors for needing right ventricular assist device (RVAD) support. Independent predictors of RVAD support included cardiac index less than 2.2 L/m^2, RVSWI less than 250 mmHG × ml/m^2, severe RV dysfunction, serum creatinine greater than 1.9 mg/dL, previous cardiac surgery, and systolic blood pressure less than or equal to 96 mmHg. An important limitation of this study was that a small minority of the patients (less than 4 %) had continuous flow LVAD [54]. The University of Michigan risk score also identified several risk factors for RV failure. However, only 15 % of the devices in this study were continuous flow devices. Risk factors for RV failure in this study included vasopressor requirement, AST greater than 80 IH/L, bilirubin over 2.0 mg/dL, and serum creatinine greater than 2.3 mg/dL [48].

Kormos et al. carried out the largest study to date examining RV failure after implantation of a continuous-flow LVAD. In this study, numerous clinical, echocardiographic, and hemodynamic parameters were assessed. The University of Michigan RV failure score was also examined. Of the 484 patients in this study to receive the Heartmate-2 (HM-2) as a bridge to transplantation, 6 % required RVAD, 7 % required prolonged inotropic support, and 7 % required late initiation of inotropic support. The parameters found to predict RV failure on multivariate

analysis included the need for mechanical ventilation, a central venous pressure/wedge pressure ratio greater than 0.63, and a blood urea nitrogen (BUN) over 39 mg/dL [55].

Timing of Implantation

While mechanical circulatory support was once reserved for patients in New York Heart Association class IV heart failure in impending cardiogenic shock [29, 56], the benefits of implanting less critically ill patients is coming to light. Earlier device implantation, before end organ damage and right ventricular failure, leads to improved outcomes. Yet the estimated 5–10 % perioperative mortality [11, 57] for device implantation must be considered when implanting less severely ill patients. For example, a patient with a short estimated waiting time for cardiac transplantation in good clinical state might benefit from awaiting transplantation. However, for DT patients who reach inotrope dependence, LVAD implementation should not be delayed [58].

The two most common indications for LVAD placement are cardiogenic shock (INTERMACS level 1) and worsening symptoms in inotropic dependent patients (INTERMACS level 2). These two classes of patients account for 60 % of all MCS patients [10]. For stable, but inotropic-dependent patients (INTERMACS level 3), true dependence should be verified with a trial to withdraw inotropes. Once dependence has been verified, the patient should be considered for LVAD implantation as these patients have been shown to obtain the most benefit from institution of LVAD [58, 59].

For patients meeting INTERMACS levels 4–6 criterion, the timing of LVAD implantation remains controversial. Subgroup analysis of the REMATCH trial showed no survival benefit with implantation of LVAD in non-inotropic dependent patients. However, all clinical factors should be considered as up to 40 % of ambulatory heart transplantation candidates will deteriorate and require upgrade to high-urgency status or require emergency MCS [60]. For these non-inotrope dependent patients, cardiopulmonary testing is considered to be the best indicator of long-term outcomes [61, 62] and may be a useful tool in determining if patients will have a desirable outcome without LVAD support. Other risk scores such as the Heart Failure Survival Score [63] or the Seattle Heart Failure Risk Score [64] may also be useful adjuncts.

Total Artificial Heart

The total artificial heart (TAH) provides biventricular support and replaces the patient's native ventricles and all four valves orthotopically. A large proportion of patients with LVAD will go on to develop right heart failure. The TAH can maintain these patients and provide complete replacement of the failing heart. The TAH has other additional advantages. It can be useful in patients whom LVAD and BIVAD is contraindicated, such as those with aortic regurgitation, cardiac

arrhythmias, left ventricular thrombus, an aortic prosthesis, or an acquired ventricular septal defect [65, 66].

The largest study to date examining the use of the TAH demonstrated that in patients with irreversible biventricular failure, TAH implantation results in improved survival. Implantation of the TAH improved outcomes by providing immediate hemodynamic restoration and recovery of end-organ damage. This allowed a greater number of patients to reach cardiac transplantation [65, 66]. As experience with the TAH has increased, outcomes have improved [66]. Continued research and device improvement will lead to better results and decreased adverse events.

Summary

Implantation of LVAD results in better quality of life and improved survival for select patients with congestive heart failure [9–14]. However, perioperative mortality remains high and appropriate patient selection is the most critical step to ensuring successful device implantation [11, 57]. Patients should undergo a thorough clinical examination, including echocardiographic and invasive hemodynamic assessment, to determine if there is an indication for LVAD. Numerous risk factors have been identified to risk-stratify patients and these factors should be considered and conveyed to the patient in the decision making process. In addition, because LVAD implantation can unmask RV dysfunction and result in severe RV failure, an assessment of RV function and potential need for RVAD should be made. Finally, one must determine the optimal timing for device implantation. Some patients, due to severe hemodynamic instability, will clearly need emergent LVAD therapy. However, other may benefit from medical optimization and elective implantation.

References

1. Cowie M, Mosterd A, Wood D, Deckers J, Poole-Wilson P, Sutton G, et al. The epidemiology of heart failure. Eur Heart J. 1997;18(2):208–25.
2. Lund LH, Matthews J, Aaronson K. Patient selection for left ventricular assist devices. Eur J Heart Fail. 2010;12(5):434–43.
3. Deng MC. Orthotopic heart transplantation: highlights and limitations. Surg Clinics N Am. 2004;84(1):243–55.
4. Lund LH, Mancini D. Heart failure in women. Med Clin N Am. 2004;88(5):1321.
5. Schocken DD, Arrieta MI, Leaverton PE, Ross EA. Prevalence and mortality rate of congestive heart failure in the United States. J Am Coll Cardiol. 1992;20(2):301–6.
6. Stevenson LW. Evolving role of mechanical circulatory support in advanced heart failure. In: Frazier OH, Kirklin JK, editors. Mechanical Circulatory Support. Philadelphia, PA: Elsevier, 2006:181–283.
7. Taylor DO, Edwards LB, Boucek MM, Trulock EP, Aurora P, Christie J, et al. Registry of the International Society for Heart and Lung Transplantation: twenty-fourth official adult heart transplant report – 2007. J Heart Lung Transplant Rev. 2007;26(8):769–81.
8. Deng MC, Edwards LB, Hertz MI, Rowe AW, Keck BM, Kormos R, et al. Mechanical circulatory support device database of the International Society for Heart and Lung Transplantation: third annual report – 2005. J Heart Lung Transplant 2005;24(9):1182–7.

9. Frazier O, Rose EA, McCarthy P, Burton NA, Tector A, Levin H, et al. Improved mortality and rehabilitation of transplant candidates treated with a long-term implantable left ventricular assist system. Ann Surg. 1995;222(3):327.
10. Kirklin JK, Naftel DC, Kormos RL, Stevenson LW, Pagani FD, Miller MA, et al. Third INTERMACS annual report: the evolution of destination therapy in the United States. J Heart Lung Transplant. 2011;30(2):115–23.
11. Miller LW, Pagani FD, Russell SD, John R, Boyle AJ, Aaronson KD, et al. Use of a continuous-flow device in patients awaiting heart transplantation. N Engl J Med. 2007;357(9):885–96.
12. Pagani FD, Miller LW, Russell SD, Aaronson KD, John R, Boyle AJ, et al. Extended mechanical circulatory support with a continuous-flow rotary left ventricular assist device. J Am Coll Cardiol. 2009;54(4):312–21.
13. Rogers JG, Aaronson KD, Boyle AJ, Russell SD, Milano CA, Pagani FD, et al. Continuous flow left ventricular assist device improves functional capacity and quality of life of advanced heart failure patients. J Am Coll Cardiol Res Support Non-US Gov't. 2010;55(17):1826–34.
14. Rose EA, Gelijns AC, Moskowitz AJ, Heitjan DF, Stevenson LW, Dembitsky W, et al. Long-term use of a left ventricular assist device for end-stage heart failure. N Engl J Med. 2001;345(20):1435–43.
15. Boyle AJ, Russell SD, Teuteberg JJ, Slaughter MS, Moazami N, Pagani FD, et al. Low thromboembolism and pump thrombosis with the heartMate II left ventricular assist device: analysis of outpatient anti-coagulation. J Heart Lung Transplant. 2009;28(9):881–7.
16. John R, Kamdar F, Liao K, Colvin-Adams M, Boyle A, Joyce L. Improved survival and decreasing incidence of adverse events with the HeartMate II left ventricular assist device as bridge-to-transplant therapy. Ann Thorac Surg. [Comparative Study]. 2008;86(4):1227–34; discussion 34–5.
17. Ammar KA, Jacobsen SJ, Mahoney DW, Kors JA, Redfield MM, Burnett Jr JC, et al. Prevalence and prognostic significance of heart failure stages. Circulation. 2007;115(12):1563–70.
18. Baughman KL, Jarcho JA. Bridge to life – cardiac mechanical support. N Engl J Med 2007;357(9):846–9.
19. Gronda E, Bourge RC, Costanzo MR, Deng M, Mancini D, Martinelli L, et al. Heart rhythm considerations in heart transplant candidates and considerations for ventricular assist devices: International Society for Heart and Lung Transplantation guidelines for the care of cardiac transplant candidates – 2006. J Heart Lung Tranplant. 2006;25(9):1043–56.
20. Slaughter MS, Meyer AL, Birks EJ. Destination therapy with left ventricular assist devices: patient selection and outcomes. Curr Op Cardiol. 2011;26(3):232.
21. Slaughter MS, Pagani FD, Rogers JG, Miller LW, Sun B, Russell SD, et al. Clinical management of continuous-flow left ventricular assist devices in advanced heart failure. J Heart Lung Transplant. 2010;29(4):S1–S39.
22. Butler J, Geisberg C, Howser R, Portner PM, Rogers JG, Deng MC, et al. Relationship between renal function and left ventricular assist device use. Ann Thorac Surg. 2006;81(5):1745–51.
23. Sandner SE, Zimpfer D, Zrunek P, Rajek A, Schima H, Dunkler D, et al. Renal function and outcome after continuous flow left ventricular assist device implantation. Ann Thorac Surg. 2009;87(4):1072–8.
24. Radovancevic B, Vrtovec B, de Kort E, Radovancevic R, Gregoric ID, Frazier O. End-organ function in patients on long-term circulatory support with continuous-or pulsatile-flow assist devices. J Heart Lung Transplant. 2007;26(8):815–8.
25. Letsou GV, Myers TJ, Gregoric ID, Delgado R, Shah N, Robertson K, et al. Continuous axial-flow left ventricular assist device (Jarvik 2000) maintains kidney and liver perfusion for up to 6 months. Ann Thorac Surg. 2003;76(4):1167–70.
26. Reinhartz O, Farrar DJ, Hershon JH, Avery GJ, Haeusslein EA, Hill JD. Importance of preoperative liver function as a predictor of survival in patients supported with Thoratec ventricular assist devices as a bridge to transplantation. J Thorac Cardiovasc Surg. 1998;116(4):633–40.
27. Farrar DJ, Hill J. Recovery of major organ function in patients awaiting heart transplantation with Thoratec ventricular assist devices. Thoratec Ventricular Assist Device Principal Investigators. J Heart Lung Transplant. 1994;13(6):1125.

28. Frazier O, Rose EA, Oz MC, Dembitsky W, McCarthy P, Radovancevic B, et al. Multicenter clinical evaluation of the HeartMate vented electric left ventricular assist system in patients awaiting heart transplantation. J Thorac Cardiovasc Surg. 2001;122(6):1186.
29. Aaronson KD, Patel H, Pagani FD. Patient selection for left ventricular assist device therapy. Ann Thorac Surg. 2003;75(6):S29–35.
30. Miller LW. Patient selection for the use of ventricular assist devices as a bridge to transplantation. Ann Thorac Surg. 2003;75(6):S66–71.
31. Frazier O, Delgado RM. Mechanical circulatory support for advanced heart failure. Circulation. 2003;108(25):3064–8.
32. Williams MR, Oz MC. Indications and patient selection for mechanical ventricular assistance. Ann Thorac Surg. 2001;71(3):S86–91.
33. Deng MC, Edwards LB, Hertz MI, Rowe AW, Keck BM, Kormos R, et al. Mechanical circulatory support device database of the International Society for Heart and Lung Transplantation: second annual report – 2004. J Heart Lung Transplant. 2004;23(9):1027–34.
34. Lockard K, Degore L, Schwarm P, Winowich S, O'Shea G, Siegenthaler M, et al. 5: lack of improvement in prealbumin at two weeks predicts a poor outcome after mechanical circulatory support. J Heart Lung Transplant. 2009;28(2):S66.
35. Butler J, Howser R, Portner PM, Pierson RN. Body mass index and outcomes after left ventricular assist device placement. Ann Thorac Surg. 2005;79(1):66–73.
36. Boyle AJ, Ascheim DD, Russo MJ, Kormos RL, John R, Naka Y, et al. Clinical outcomes for continuous-flow left ventricular assist device patients stratified by pre-operative INTERMACS classification. J Heart Lung Transplant. 2011;30(4):402–7.
37. Teuteberg JJ, Ewald GA, Adamson RM, Lietz K, Miller LW, Tatooles AJ, et al. Risk assessment for continuous flow left ventricular assist devices: does the destination therapy risk score work? An analysis of over 1,000 patients. J Am Coll Cardiol. 2012;60(1):44–51.
38. Stevenson LW, Pagani FD, Young JB, Jessup M, Miller L, Kormos RL, et al. INTERMACS profiles of advanced heart failure: the current picture. J Heart Lung Transplant. 2009;28(6):535–41.
39. Alba AC, Rao V, Ivanov J, Ross HJ, Delgado DH. Usefulness of the INTERMACS scale to predict outcomes after mechanical assist device implantation. J Heart Lung Transplant. 2009;28(8):827–33.
40. Oz MC, Goldstein DJ, Pepino P, Weinberg AD, Thompson SM, Catanese KA, et al. Screening scale predicts patients successfully receiving long-term implantable left ventricular assist devices. Circulation. 1995;92(9):169–73.
41. Rao V, Oz MC, Flannery MA, Catanese KA, Argenziano M, Naka Y. Revised screening scale to predict survival after insertion of a left ventricular assist device. J Thorac Cardiovasc Surg. 2003;125(4):855–62.
42. Klotz S, Vahlhaus C, Riehl C, Reitz C, Sindermann JR, Scheld HH. Pre-operative prediction of post-VAD implant mortality using easily accessible clinical parameters. J Heart Lung Transplant. 2010;29(1):45–52.
43. Holman WL, Kormos RL, Naftel DC, Miller MA, Pagani FD, Blume E, et al. Predictors of death and transplant in patients with a mechanical circulatory support device: a multi-institutional study. J Heart Lung Transplant. 2009;28(1):44–50.
44. Feldman D, Menachemi DM, Abraham WT, Wexler RK. Management strategies for stage-D patients with acute heart failure. Clin Cardiol. 2008;31(7):297–301.
45. Lietz K, Miller LW. Patient selection for left-ventricular assist devices. Curr Opin Cardiol. 2009;24(3):246–51.
46. Farrar D. Ventricular interactions during mechanical circulatory support. Sem Thoracic Cardiovasc Surg. 1994;6(3):163–8.
47. Farrar DJ, Compton PG, Hershon JJ, Fonger JD, Hill JD. Right heart interaction with the mechanically assisted left heart. World J Surg. 1985;9(1):89–102.
48. Matthews JC, Koelling TM, Pagani FD, Aaronson KD. The right ventricular failure risk score: a pre-operative tool for assessing the risk of right ventricular failure in left ventricular assist device candidates. J Am Coll Cardiol. 2008;51(22):2163–72.

49. Dang NC, Topkara VK, Mercando M, Kay J, Kruger KH, Aboodi MS, et al. Right heart failure after left ventricular assist device implantation in patients with chronic congestive heart failure. J Heart Lung Transplant. 2006;25(1):1.
50. Kavarana MN, Pessin-Minsley MS, Urtecho J, Catanese KA, Flannery M, Oz MC, et al. Right ventricular dysfunction and organ failure in left ventricular assist device recipients: a continuing problem. Ann Thorac Surg. 2002;73(3):745–50.
51. Ochiai Y, McCarthy PM, Smedira NG, Banbury MK, Navia JL, Feng J, et al. Predictors of severe right ventricular failure after implantable left ventricular assist device insertion: analysis of 245 patients. Circulation. 2002;106(12 suppl 1):I-198–202.
52. Morgan JA, John R, Lee BJ, Oz MC, Naka Y. Is severe right ventricular failure in left ventricular assist device recipients a risk factor for unsuccessful bridging to transplant and post-transplant mortality. Ann Thorac Surg. 2004;77(3):859–63.
53. Kukucka M, Stepanenko A, Potapov E, Krabatsch T, Redlin M, Mladenow A, et al. Right-to-left ventricular end-diastolic diameter ratio and prediction of right ventricular failure with continuous-flow left ventricular assist devices. J Heart Lung Transplant. 2011;30(1):64–9.
54. Fitzpatrick III JR, Frederick JR, Hsu VM, Kozin ED, O'Hara ML, Howell E, et al. A risk score derived from preoperative data analysis predicts the need for biventricular mechanical circulatory support. J Heart Lung Transplantation Off J Heart Lung Transplant. 2008;27(12):1286.
55. Kormos RL, Teuteberg JJ, Pagani FD, Russell SD, John R, Miller LW, et al. Right ventricular failure in patients with the HeartMate II continuous-flow left ventricular assist device: incidence, risk factors, and effect on outcomes. J Thorac Cardiovasc Surg. 2010;139(5):1316.
56. Stevenson LW, Shekar P. Ventricular assist devices for durable support. Circulation. 2005;112(9):e111–e5.
57. Pal JD, Klodell CT, John R, Pagani FD, Rogers JG, Farrar DJ, et al. Low operative mortality with implantation of a continuous-flow left ventricular assist device and impact of concurrent cardiac procedures. Circulation. 2009;120(11 suppl 1):S215–S9.
58. Stevenson LW, Miller LW, Desvigne-Nickens P, Ascheim DD, Parides MK, Renlund DG, et al. Left ventricular assist device as destination for patients undergoing intravenous inotropic therapy. Circulation. 2004;110(8):975–81.
59. Lietz K, Long JW, Kfoury AG, Slaughter MS, Silver MA, Milano CA, et al. Outcomes of left ventricular assist device implantation as destination therapy in the post-REMATCH era. Circulation. 2007;116(5):497–505.
60. Lietz K, Miller LW. Improved survival of patients with end-stage heart failure listed for heart transplantation: analysis of organ procurement and transplantation network/US United Network of Organ Sharing data, 1990 to 2005. J Am Coll Cardiol. 2007;50(13):1282–90.
61. Mancini D, Eisen H, Kussmaul W, Mull R, Edmunds Jr L, Wilson J. Value of peak exercise oxygen consumption for optimal timing of cardiac transplantation in ambulatory patients with heart failure. Circulation. 1991;83(3):778–86.
62. Mehra MR, Kobashigawa J, Starling R, Russell S, Uber PA, Parameshwar J, et al. Listing criteria for heart transplantation: International Society for Heart and Lung Transplantation guidelines for the care of cardiac transplant candidates – 2006. J Heart Lung Transplant. 2006;25(9):1024.
63. Aaronson KD, Schwartz JS, Chen TM, Wong KL, Goin JE, Mancini DM. Development and prospective validation of a clinical index to predict survival in ambulatory patients referred for cardiac transplant evaluation. Circulation. 1997;95(12):2660–7.
64. Levy WC, Mozaffarian D, Linker DT, Sutradhar SC, Anker SD, Cropp AB, et al. The seattle heart failure model prediction of survival in heart failure. Circulation. 2006;113(11):1424–33.
65. Copeland JG, Smith RG, Arabia FA, Nolan PE, Sethi GK, Tsau PH, et al. Cardiac replacement with a total artificial heart as a bridge to transplantation. N Engl J Med. 2004;351(9):859–67.
66. Gray NA, Selzman CH. Current status of the total artificial heart. Am Heart J. 2006;152(1):4–10.

Chapter 26
Acute Mechanical Circulatory Support

Michael M. Koerner and Aly El-Banayosy

Abbreviations

ACCF	American College of Cardiology Foundation
ACLS	Advanced Cardiovascular Life Support
AHA	American Heart Association
BVAD	Biventricular Assist Device
CPR	Cardiopulmonary Resuscitation
CS	Cardiogenic Shock
ECMO	ExtraCorporeal Membrane Oxygenation
IABP	Intra-aortic Balloon Pump
LVAD	Left Ventricular Assist Device
MI	Myocardial Infarction
pVAD	Percutaneous Ventricular Assist Device
ROSC	Return of Spontaneous Circulation
RVAD	Right Ventricular Assist Device
SCAI	Society for Cardiovascular Angiography and Intervention
STEMI	ST-Elevation Myocardial Infarction
VAD	Ventricular Assist Device

M.M. Koerner, MD, PhD (✉)
Adj. Clinical Professor Medicine/Cardiology, Oklahoma State University
Center for Health Sciences, Director Critical Care, Nazih Zudhi Transplant Institute/
Advanced Cardiac Care, Integris Baptist Medical Center, 3400 NW Expressway,
Bldg C, Suite 300, Oklahoma City, OK 73112, USA
e-mail: michael.koerner@integrisok.com

A. El-Banayosy, MD, PhD
Executive Director Critical Care, Nazih Zudhi Transplant Institute/Advanced Cardiac Care,
Integris Baptist Medical Center, 3400 NW Expressway,
Bldg C, Suite 300, Oklahoma City, OK 73112, USA
e-mail: aly.elbanayosy@integrisok.com

H. Eisen (ed.), *Heart Failure*, DOI 10.1007/978-1-4471-4219-5_26

Introduction

This chapter provides clinical facts of cardiac arrest (CA) and cardiogenic shock (CS) mostly caused by acute myocardial infarction (AMI), as well as prognostic aspects if refractory to conventional therapy and beyond treatment with an intra-aortic balloon pump (IABP). CS had a high mortality due to limited options for patients who did not respond to traditional treatment algorithms [1]. Now more than a decade later with the more sophisticated mechanical circulatory support devices even patients with advanced CS states have better chances for survival [2]. Specific emphasis is given to the evolving role of acute mechanical circulatory support devices (aMCS) which can be used interdisciplinary and usually do not require surgical presence and/or immediate access to a catheterization laboratory (cath lab). Some remarks about the history of extracorporeal membrane oxygenation (ECMO) which nowadays can be placed peripherally percutaneously as first line aMCS in the emergency department (ED), at the patient's bedside in the hospital or wherever needed: being placed when and where needed outside a cath lab or operating room (OR): without a time demanding transport, a surgical cut down or central placement with a thoracotomy. Being placed when and where needed as a percutaneous peripheral femoro-femoral veno-arterial (pVA-ECMO) when an IABP is or is expected not to be sufficient. Devices which will require the patient's transfer to another location and/or imaging during their placement like fluoroscopy, a transesophageal echocardiogram, a cath lab or primarily even a atrioseptostomy before sufficient hemodynamics can be established for necessary brain and organ protection are considered here as subacute mechanical circulatory support devices (sMCS) and will not be described in detail in this chapter, as well as the armamentarium of devices available to be placed with the need of a sternotomy or thoracotomy. Beside the risk of losing crucial time securing or reestablishing sufficient brain/organ perfusion and so potentially minimizing a patient's chances by using any sMCS in acute life-threatening situations like CA and therapy-refractory CS one has also to be aware of the sMCS possible additional side effects and/or possible sMCS specific complications. A pVA-ECMO device is serving in the majority of patients as a percutaneous heart-lung machine. If the patient's left ventricle will not eject sufficiently after restoring cardiopulmonary circulation for brain and organ perfusion under pVA-ECMO support with this specific aMCS additional options have to be considered in individual patients. So some of the most common aMCS will be described because all of them can be placed outside an OR, cath lab or intensive care unit by trained physicians without surgical background the moment a patient is suffering from witnessed CA without appropriate resumption of spontaneous circulation (ROSC) and/or therapy-refractory CS.

CA in an out-of hospital setting has still a mortality of 92 % [3]. CS is the leading cause of death for patients suffering from AMI who reach the hospital alive [4], and mortality in affected patients remains high (50–70 %) despite advances of reperfusion therapy [5–8].

CS is a complex, self-perpetuating pathological process of end-organ hypoperfusion caused by left, right or biventricular myocardial injury with decreased coronary blood flow in the presence of adequate intravascular volume and left ventricular filling pressure resulting in systolic and/or diastolic myocardial pump failure, a degen-

Table 26.1 Aetiologies of advanced CS: a lethal condition like CA if not reversible as soon as possible "time is tissue": **Indications for an aMCS with a percutaneous VA-ECMO** if refractory to conventional medical therapy, IAPB or resuscitation non-responsive to ACLS (<30 min) [15–18]

By low-output syndromes:
Cardiac arrest and cardiogenic shock acute decompensation of pre-existing chronic heart failure: non-ischemic: congenital, iron overload, amyloidosis, postviral, metabolic or ischemic cardiomyopathy, VAD failure (mechanical, electrical, pump thrombus)
Acute myocardial infarction with right, left or biventricular pump failure
Mechanical complications of acute myocardial infarction with CA and advanced CS before diagnose and treatment can be established: tamponade, papillary muscle rupture, stunning with severe mitral valve regurgitation, post-infarct ventricular septal defect, left ventricular free wall rupture
Arrhythmias refractory to medications and electrotherapy: ventricular fibrillation, tachycardia, intractable atrial fibrillation with rapid rate response of supraventricular tachycardia
Pacer refractory electrical mechanical dissociation: post myocardial infarct, intoxication, electrolyte imbalance, severe hypothermia
Decompensated severe aortic stenosis, ventricular outflow tract obstruction before cath lab or OR can be reached or is ready to be used
Prosthetic valve failure: fracture, thrombosis, paravalvular leak
Restriction of ventricular filling: restrictive pericarditis, myxomas
Valvular regurgitation: endocarditis, rheumatic, traumatic, congenital
Cardiac tamponade: posttraumatic:stab or gun shoot wounds, autoimmune disease, infection, neoplasm with good 1-year life expectancy
Acute severe myocarditis /−necrosis: viral, carbon monoxide intoxication, sarcoidosis, autoimmune: post- partum, lupus, giant cell myocarditis
Prolonged cardiopulmonary bypass, post cardiotomy syndrome (early, late)
Intoxication: iatrogenic, accidental or suicide related: beta-blocker, cocaine, chemotherapy, smoke
Cytokine storm (brain damage, sepsis immune response syndrome, chemotherapy)
Graft failure after heart or heart lung transplantation: donor related etiology, insufficient preservation, rejection related failure (early, late)
Hypothermia
Hypoxemia
Drowning
Hypertension
Pheocromocytoma [16]
Takotsubo syndrome [17, 18]
Pulmonary hypertension
Acute right heart/biventricular failure due to pulmonary embolism

Reproduced with permission from Koerner and Jahanyar [15], Lippincott Williams & Wilkins

erating clinical spiral of multi organ dysfunction that begins when the heart is no longer able to provide sufficient resting pressure and flow that frequently causes death [4, 9–14]. The etiology of CS can result from several types of cardiac dysfunction: acute coronary insufficiency due to systolic or diastolic dysfunction, valvular dysfunction, cardiac arrhythmias, acute or chronic coronary artery disease, metabolic or mechanical complications. Major pathological conditions are listed in Table 26.1 [15–18]. All of those are causing advanced CS. CS which very soon will cause irreversible brain and organ damage. Both are leading to an extreme high mortality

Table 26.2 Contraindications for peripheral percutaneous aMCS VA-ECMO support over femoral vessels to treat CS and/or CA

High cardiac output syndromes: overwhelming proven septicemia, thyrotoxicosis, anemia, shunt syndromes
Aortic dissection
Severe aortic regurgitation
Severe known peripheral vascular occlusive disease
Intolerance to anticoagulants (including: cerebral hemorrhage, active gastrointestinal bleeding)
Do **N**ot **R**esuscitate orders
Expected mortality >95 % (including: unrecoverable heart/lung disease while not being already identified as a transplant or VAD candidate

similar to CA if not reversed immediately. If advanced CS and CA are refractory to conventional therapy one has to be proactive by providing immediate sufficient cardiopulmonary support to stabilize the patient's circulation and tissue oxygenation. Proactive means first things first: first restoration of cardiopulmonary circulation and tissue oxygenation whenever and wherever needed with the help of an aMCS to beat the running time and not to lose organ function, as well as and finally the patient. After the patient has been stabilized ("time is tissue") a transport to a cath lab or operating room can safely be done for further diagnostic and therapeutic measures. Major contraindications for the use of a peripheral percutaneous aMCS VA-ECMO using the femoral vessels as access to treat CS and CA are listed in Table 26.2.

Prognosis of CS

Incidence and treatment of CS in a 10-year period [19], as well as 30-year trends in the magnitude of, management of, and hospital death rates associated with CS in patients with AMI and acute coronary syndrome have been analyzed recently [20–22]. The systolic blood pressure, creatinine clearance, and number of vasopressors are significant predictors of mortality in patients with persistent vasopressor-dependent CS following AMI, despite a patent infarct artery. These prognostic variables may be useful for risk stratification and in selecting patients for investigation of additional therapies [23], and pro- and anti- inflammatory markers like interleukin −6, −7, −8 and −10 predict outcome in AMI complicated by CS [24].

CS is a serious disorder with a high early death rate, but one that is treatable and that, if approached proactively ("aggressively"), can result in full recovery [13, 22]. VA-ECMO is capable to obtain rapid resuscitation, stabilization, and subsequent triage to a more permanent treatment strategy [25]: "bridge-to-decision" means until neurological recovery, cardiac recovery will occur or as "bridge-to-bridge" in case a heart replacement (cardiac transplantation, total artificial heart or biventricular assist device) or LVAD may be indicated after neurological recovery, but irreversible myocardial failure, or until withdrawal of care will be requested or organ donation [26].

The results of the Intraaortic Balloon Pump in Cardiogenic Shock II (IABP-SHOCK II) trial show that in patients with AMI and hemodynamic compromise who undergo revascularization, the routine use of an IABP, as compared with standard therapy, does not improve survival [27]. On the basis of the findings of the IABP-SHOCK II trial one has to move forward with the understanding that a cardiovascular condition with 40 % mortality at 30 days remains unacceptable [28]. The overall 6-month-mortality of CS patients remained 50 % in accordance with other reports [29]. In case the revascularization with PCI is not successful the mortality had been described as high as 85 % [30]. The immediate use of aMCS may even become equally important as opening the occluded artery in STEMI patients with CS. Eventually, the focus of these patients may therefore shift from door-to-balloon time to door to-sufficient circulatory support time, but only in the light of clinical evidence [31]. Mitral regurgitation is an independent predictor of 1-year mortality in ST-elevation myocardial infarction patients presenting in CS on admission [32].

In regard to post-cardiotomy heart failure otherwise established markers of renal and hepatic failure seem not to be appropriate to predict mortality in the acute stage before extracorporeal life support implantation [33].

History

Based on the pioneering work of Gibbon who developed the first heart-lung machine facilitating open-heart surgery [34], Dennis reported 10 years later about the clinical use of a cannula for left heart bypass without thoracotomy in 1962 [35] followed by Kennedy reporting the use of a pump oxygenator in clinical heart failure by "femoral-vein-to-femoral-artery cannulation in 1966 [36], whereas Hill reported first clinical experience in patients assisted with extracorporeal veno-arterial and veno-venous circulation starting in 1968 [37, 38]. A battery-powered portable cardiopulmonary bypass machine had been used by Mattox in 39 patients whose condition precluded their transport to the OR [39]. Among others Dembitsky used portable ECMO devices for emergency resuscitation and trained a team of in-house personnel to emergently prepare, apply, and temporarily manage cardiopulmonary bypass until personnel with greater specialty training arrived [40].

The 2011 ACCF/AHA/SCAI guidelines present recommendations for circulatory support: "A hemodynamic support device is recommended for patients with CS after STEMI who do not quickly stabilize with pharmacological therapy." [41] (Level of Evidence B) [13, 29, 42–44]. The 2013 ACCF/AHA guidelines for the management of ST-Elevation Myocardial Infarction are stating for the treatment of CS as a Class IIa (Level of Evidence B):

> "1. The use of IABP counter pulsation can be useful for patients with CS after STEMI who do not quickly stabilize with pharmacologically therapy", and as a Class IIa (Level of Evidence C): "alternative LVADs for circulatory support may be considered in patients with refractory CS." [45]

Indications for AMCS

An aMCS is indicated in CA (witnessed, not longer than 20 min without ROSC) and therapy-refractory CS despite conservative treatment including volume load, inotropes and IABP. The principal benefit of left ventricular assist devices (LVADs) (which encompass pVADs, as well as surgical VADs is to compensate for the loss of myocardial pump function, normalizing cardiac output and thus allowing physiologic perfusion of vital organs, especially if this can be achieved where the CA and/or CS manifested first [15, 46–48]. Some pVads can only be placed with additional imaging inside a hospital or even require always a cath lab due to the need of additional imaging [49, 50]—therefore they are called here sMCS not aMCS. Peripheral VA-ECMO are shown to improve survival in AMI with CS [51–54] or CA [55–57].

Guidelines

Important especially for cardiologists focusing on Critical Care Cardiology [58] the 2011 ACCF/AHA/SCAI guidelines presenting straight forward recommendations for acute mechanical circulatory support: "A hemodynamic support device is recommended for patients with CS after STEMI who do not quickly stabilize with pharmacological therapy." [41] (Level of Evidence B) [13, 29, 42–44], and the 2013 ACCF/AHA guidelines for the management of ST-Elevation Myocardial Infarction are stating for the treatment of CS as a Class IIa (Level of Evidence B): "1. The use of IABP counter pulsation can be useful for patients with CS after STEMI who do not quickly stabilize with pharmacologically therapy.", and as a Class IIb (Level of Evidence C): "alternative LVADs for circulatory support may be considered in patients with refractory CS." [45].

Required and expected features for an excellent peripheral insertable aMCS to beat the "time is tissue" reality: easy to assemble, fast to apply, and easy, effective, as well as safe to use where and when needed ("KISS" keep it stupid simple: no paralytics, no cath lab).

Cardiac Arrest

It is being estimated that 300,000 CA occur each year in the United States, with 50 % happening out-of hospital and the other half to patients in a hospital setting [3, 59]. Based on the findings of Goldberger's observational study which suggest that efforts to systematically increase the duration of resuscitation could improve survival in high-risk patient [60] we suggest in addition that patients who having a witnessed in-hospital CA and who do not achieve ROSC after a duration of 10 min

of Advanced Cardiovascular Life Support (ACLS) based high-quality CPR should always additionally be presented to an ECMO team for possible placement of percutaneous VA-ECMO in the absence of contraindication for ECMO.

Out-of-Hospital Cardiac Arrest: Prognostic Aspects

Approximately 92 % of persons who experience a out-of-hospital CA in the US die [3]. Predictors of survival from out-of-hospital CA have been evaluated in a systematic review and meta-analysis [61]. ECMO has been proposed as the ultimate heroic rescue in prolonged CA unresponsive to conventional CPR [55–57, 62, 63]. The effectiveness of ECMO in out-of-hospital CA remains debated [64, 65]. A rule for termination of CPR in out-of-hospital CA has been validated prospectively to get an universal prehospital termination of resuscitation clinical prediction rule for advanced and basic life support providers [66], but Morrison did not report that the use of an aMCS like a percutaneous VA-ECMO for some of the patients with CA had been considered to be a therapeutic option at any point before the termination of resuscitation or transport to a hospital [67].

ROSC after prolonged, complete, whole-body ischemia is an unnatural pathophysiological state created by successful CPR [68, 69]. Modest, but significant predictors of neurological outcome and mortality in patients after CA as compared to neuron-specific enolase seem circulating microRNAs to be [70]. In addition procalcitonin might be an ancillary marker for outcome prediction after CA treated by induced hypothermia [71–73]. Clinical predictors for in-hospital mortality are unsuccessful angioplasty, asystole or pulse less electrical activity before ECMO introduction, and ECMO-related complications [8].

Rescue by temporary aMCS like VA-ECMO provides an ultimate therapeutic option with good outcomes in patient after a period of prolonged CA [63].

Out-of hospital percutaneous VA-ECMO implantation during refractory CA after witnessed drowning [47] (Fig. 26.1) or asystolic CA in a half-marathon runner [46] (Fig. 26.1) demonstrate the clinical potential and could be considered for protocol based prospective multicenter studies [74].

Out-of hospital CA with in-hospital ECMO implantation was found to have poor outcome suggesting that the implantation and use of ECMO should be more restricted following out-of-hospital refractory CA [75]. $SpvO_2$ was found to be useful in witnessed refractory in-or-out-of hospital CA to predict the inability of maintaining refractory CA victims on ECMO without detrimental capillary leak and multi organ failure until neurological evaluation [76]. The level of lactic acid at 48 h after CA is an independent predictor of mortality and unfavorable neurologic outcome. Persisting elevated lactic acid over 48 h predicts a poor prognosis [77]. At this point in time it is still recommended that a multimodal approach to neurologic prognostication post CA has to be utilized [78]. The ethical appropriateness of out-of-hospital use of aMCS like percutaneous VA-ECMO especially if it carries the potential not only to achieve full recovery of the patient in CA and/or CS, but also

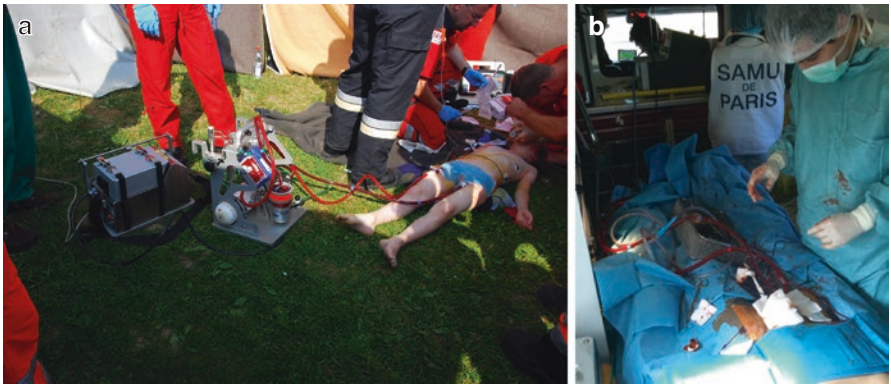


Fig. 26.1 Rescue by temporary aMCS like VA-ECMO provides an ultimate therapeutic option with good outcomes in patient after a period of prolonged CA [63]. Out-of hospital percutaneous VA-ECMO implantation during refractory CA after witnessed drowning (Reprinted from Arltet al. [47] © 2011, with permission from Elsevier) (**a**) or asystolic CA in a half-marathon runner (Reprinted from Lebreton et al. [46] © 2011, with permission from Elsevier) (**b**) demonstrate the clinical potential and could be considered for protocol based prospective multicenter studies [74]

to prolong life for possible organ donation in case the individual patient may become brain dead or decease due to withdrawal of care (cardiac or circulatory death), Controlled Donation after Circulatory Death needs to be discussed [79–81].

Acute Ischemic Myocardial Infarction with CS

Left main coronary artery transradial rescue percutaneous coronary intervention for AMI complicated by CS with Impella® ventricular mechanical support [82], advanced heart failure, therapy-refractory cardiogenic shock.

Right Heart Failure

As an aMCS a percutaneous centrifugal pump [83] or as sMCS the TandemHeart® [84–86] or when FDA approved for sale the Impella RP RV® support system (Abiomed, Danvers, MA, USA).

Allograft Failure

Percutaneous mechanical circulatory support to treat severe allograft failure [87–90].

Pulmonary Embolism

Percutaneous VA-ECMO improves prognosis of hemodynamic instable patients with massive pulmonary embolism [91] and such treated additionally with catheter-based interventions [92].

Trauma

Extracorporeal life support in patients with severe trauma evolved as an advanced treatment strategy for refractory clinical settings [93, 94].

Poisoning Induced CA and Therapy-Refractory CS

ECMO may improve survival of critically ill poisoned patients who experiencing CA and severe CS refractory to conventional treatment [63, 95, 96].

Peri- and Postpartum

Percutaneous aMCS VA-ECMO here are also lifesaving tools [97, 98].

Acute and Subacute Mechanical Circulatory Support Devices

Intra-Aortic Balloon Counter Pulsation

IABP was introduced in 1968 [99] into clinical practice. IABP has long been the mainstay of mechanical therapy in the treatment of infarction-related CS [13, 99–105] and was considered to be capable to lower mortality [44], but in the randomized IABP SHOCK Trial IABP did not reduce elevated levels of IL-6 levels which is known to be a strong predictor of adverse outcome [102]. Also the results of the Counterpulsation to Reduce Infarct Size Pre-PCI Acute Myocardial Infarction (CRISP AMI) [106] are helping to clarify the existing controversy about observation of lack of IABP effectiveness in high-risk percutaneous coronary interventions without CS [27, 105, 107, 108].

Devices being used as aMCS and sMCS and some of their specifics are listed in Table 26.3 such as:

Table 26.3 Percutaneous placeable aMCD and sMCD to treat therapy-refractory CS and CA

Device	Pump	Pump location	Flow type (l/min)	Assisted ventricle	Comment	Duration	
Impella LP 2.5® Impella 5.0®	Axial flow	Left ventricle over transaortic valve passage	Non pulsatile (2–5)	LVAD (possible use as RVAD)	TEE, exact positioning hemolysis, hyperglycemia	Days	
TandemHeart®	Centrifugal	Extracorporeal over femoral vein with transseptal insertion into left atrium	Nonpulsatile (2–4)	LVAD (possible use as RVAD)	cath lab, left atrial perforation/ tamponade	Days	
Biomedicus®	Centrifugal	Extracorporeal over femoral vessels possible	Nonpulsatile (5–10)	LVAD (possible use as RVAD)	Portable, hemolysis	Days	
CentriMags®	Centrifugal	Extracorporeal over femoral vessels possible	Nonpulsatile (4–9)	LVAD (possible use as RVAD)	Portable	Weeks	
Rotaflow®	Centrifugal	Extracorporeal over femoral vessels possible	Non pulsatile (4–5)	VA-ECMO	Portable	Weeks	
CardioHelp®	Centrifugal	Extracorporeal over femoral vessels possible	Non pulsatile (4–5)	VA-ECMO	Portable	Days	
LifeBridge®	Centrifugal	Extracorporeal over femoral vessels possible	Non pulsatile (4–5)	VA-ECMO	Portable	Days	

Centrifugal Pumps Centrifugal pumps like the Revolution Centrifugal Blood Pump® (Sorin Group Italia S.r.l.TM, Milano, Italy), the Biomedicus ® (Medtronic Inc., Minneapolis, MN, USA) [40, 46, 55, 109–112], Rotaflow® pump (Maquet, Wayne, NJ, USA) [22, 63, 90] or Sarns Delphin® pump (Terumo Inc., Ann Arbor, MI) [8] are lifesaving tools which allow the time saving percutaneous placement of VA-cannulas in the femoral vessels out-of-hospitals or out-of-cath-lab to establish the necessary circulatory support.

Portable Mobile aMCS ECMO Systems There are currently two FDA approved portable mobile aMCS ECMO systems for percutaneous use available: the CardioHelp System® (Maquet, Wayne, NJ, USA), and the LifeBridge B2T® (Lifebridge North America Inc., San Antonio, TX) [113].

CentriMag® The CentriMag® ECMO device: The CentriMag® (Thoratec Inc., Pleasanton, CA, USA) ECMO device consists of a single use centrifugal pump, a motor, a console and a flow probe. The low-pressure drop Quadrox D® oxygenator (Maquet, Wayne, NJ, USA) is attached in the circuit [2, 114, 115]. In a multicenter trial the short-term support for patients with CS with this device demonstrated a low incidence of device-related complications and no device failures [116]. It can also be used as an aMCS as pLVAD [97] or percutaneous RVAD [83].

Devices (sMCS)

Impella® The Impella LV® support device (Abiomed Inc., Danvers, MA, USA) uses a miniaturized axial flow pump and can be used alone [117–119], combined with IABP [120, 121] or other ventricular assist devices [83, 122]. The Impella RP RV® support system design is based on the Impella 5.0® and can be used as a percutaneously applicable RVAD.

Tandem Heart® The Tandem Heart® (Cardiac Assist Inc., Pittsburgh, PA, USA) is a useful tool in selected patients who are already hospitalized and a cath lab or an operating room is available [123, 124]. This sMCS has clearly an indication as pLVAD as a bridge to recovery from myocarditis when sufficient left ventricular unloading may not be achievable by percutaneous aMCS VA-ECMO without atrioseptostomy [125], the patient does not present with therapy-refractory CS and no concerns for relevant perforation during the atrioseptostomy due to acute inflammatory changes with possible fragile myocardium exist. Variations of placement of the TandemHeart® e.g. as pLVAD [126] or as pRVAD [84–86] in combination with e.g. the Impella 2.5® percutaneous device for left ventricular unloading have been reported [89].

Future Trends

The worldwide successful use of aMCS which are peripherally percutaneously applicable as VA-ECMO to rescue patients in CA and/or therapy-refractory CS even in out-of-hospital scenarios has been performed already years ago, but evolved more within the last 5 years, passing the visionary and pioneering stage [15, 40].

A wet-primed ECMO circuit with hollow-fiber membrane oxygenator can be stored for up to 2 weeks if prepared according to the protocol recently published by Karimova [127]. Based on this information the access to rapid-response to provide an aMCS like a percutaneous VA- ECMO support for patients in CA and/or CS in a hospital, emergency room or ambulance is feasible.

Mobile ECMO teams being trained and competent in: assessing / triaging patients' medical indication for aMCS could cover metropolitan areas 24/7, capable to insert percutaneous arterial and venous femoral cannulas to establish sufficient access: in hospital based Emergency Departments [128] or even under out-of-hospital conditions in the field (Fig. 26.1) [47], within an ambulance (Fig. 26.1) [46] where and when needed, capable to start the circuit, to adjust respirator settings and IV medications.

The availability and targeted use of aMCS like percutaneous VA-ECMO as a bridge to decision has been effective to promptly restore adequate systemic perfusion, allowing further time to evaluate cerebral and myocardial recovery or candidacy for long-term VAD, TAH, heart transplantation [129], withdrawal of care and/or donor organ preservation [130, 131]. Beside re-establishing sufficient brain and organ perfusion in a short period of time while keeping the odds and chances for neurological and organ recovery high, a safe transport of these critical ill patients on percutaneous VA-ECMO support to a regional ECMO center can be done [40, 110, 132, 133]. If necessary these transports can be performed across oceans and continents while the patients remains hemodynamically safe on VA-ECMO In case the left ventricle is not going to eject or may stop to eject under the aMCS like the VA-ECMO and developing relevant therapy-refractory pulmonary congestion and edema a percutaneous balloon atrioseptostomy can be performed. This can be done fast as needed, effective and by using minimal invasive techniques for offloading the left heart of patients with the chance of a reversible cardiac dysfunction under VA-ECMO suffering from refractory pulmonary edema [134].

Not FDA approved, but in clinical use in Europe: a minimal invasive technique for decompressing the left ventricle if high left-heart filling pressures during peripheral VA-ECMO continue to exist by using the pulsatile paracorporeal assist device, the iVAC® (PulseCath, Groningen, The Netherlands), which will be implantable through the right axillary artery with a subclavicular incision [135, 136].

Bridge to Decision

The compelling purpose of use an aMCS like a percutaneous VA-ECMO is to prevent hypoxemia and lack of organ perfusion as long as the window of opportunity is existing to prevent or minimize brain and organ dysfunction. Again "time is

tissue" and an aMCS is capable to reestablish and secure cardiopulmonary function, as well as to serve as a bridge to decision in patients with refractory acute CS and CA: to decide if cardiac recovery will take place [137], if heart replacement (LVAD, BVAD, TAH, HTx) may be necessary and an appropriate option, if withdrawal of care is justified or eventually organ donation will be possible [26, 130, 131, 138]. Randomized controlled trials in the intensive care unit are lacking, but should be abandoned [139] and other study designs may be considered [74].

> "To live is not merely to breathe; it is to act; it is to make use of our organs, senses, faculties – of all those parts of ourselves which give us the feeling of existence"

Jean-Jacques Rousseau 1712–1778 (French philosopher and writer whose novels inspired the leaders of the French Revolution).

References

1. Hochman JS, Sleeper LA, Webb JG, et al. Early revascularization in acute myocardial infarction complicated by cardiogenic shock. N Engl J Med. 1999;341(9):625–34.
2. Aziz TA, Singh G, Popjes E, et al. Initial experience with CentriMag extracorporal membrane oxygenation for support of critically ill patients with refractory cardiogenic shock. J Heart Lung Transplant. 2010;29(1):66–71.
3. McNally B, Robb R, Mehta M, et al. Out-of-hospital cardiac arrest surveillance – Cardiac Arrest Registry to Enhance Survival (CARES), United States, October 1, 2005–December 31, 2010. MMWR Surveill Summ. 2011;60(8):1–19 . Epub 2011/07/29.
4. Hasdai D, Harrington RA, Hochman JS, et al. Platelet glycoprotein IIb/IIIa blockade and outcome of cardiogenic shock complicating acute coronary syndromes without persistent ST-segment elevation. J Am Coll Cardiol. 2000;36(3):685–92.
5. Goldberg RJ, Samad NA, Yarzebski J, et al. Temporal trends in cardiogenic shock complicating acute myocardial infarction. N Engl J Med. 1999;340(15):1162–8 . Epub 1999/04/15.
6. Hochman JS, Butler CE, Sleeper LA, et al. Cardiogenic shock complicating acute myocardial infarction–etiologies, management and outcome: a report from the SHOCK Trial Registry. SHould we emergently revascularize Occluded Coronaries for cardiogenic shocK? J Am Coll Cardiol. 2000;36(3 Suppl A):1063–70.
7. Hochman JS, Sleeper LA, White HD, et al. One-year survival following early revascularization for cardiogenic shock. JAMA. 2001;285(2):190–2 . Epub 2001/02/15.
8. Sakamoto S, Taniguchi N, Nakajima S, et al. Extracorporeal life support for cardiogenic shock or cardiac arrest due to acute coronary syndrome. Ann Thorac Surg. 2012;94(1):1–7.
9. Hasdai D, Topol EJ, Califf RM, et al. Cardiogenic shock complicating acute coronary syndromes. Lancet. 2000;356(9231):749–56 . Epub 2000/11/21.
10. Westaby SKR, Banning AP. Cardiogenic shock in ACS. Part 1: prediction, presentation and medical therapy. Nat Rev Cardiol. 2011;9(3):158–71.
11. Westaby S, Anastasiadis K, Wieselthaler GM. Cardiogenic shock in ACS. Part 2: role of mechanical circulatory support. Nat Rev Cardiol. 2012;9(4):195–208.
12. Topalian SGF, Parrillo JE. Cardiogenic shock. Crit Care Med. 2008;36(1 Suppl):S66–74.
13. Reynolds HR, Hochman JS. Cardiogenic shock: current concepts and improving outcomes. Circulation. 2008;117(5):686–97.
14. Holmes Jr DR. Cardiogenic shock: a lethal complication of acute myocardial infarction. Rev Cardiovasc Med. 2003;4(3):131–5 . Epub 2003/09/02.
15. Koerner MM, Jahanyar J. Assist devices for circulatory support in therapy-refractory acute heart failure. Curr Opin Cardiol. 2008;23(4):399–406 . Epub 2008/06/04.
16. Sojod G, Diana M, Wall J, et al. Successful extracorporeal membrane oxygenation treatment for pheochromocytoma-induced acute cardiac failure. Am J Emerg Med. 2012;30(6):1017.e1–3.

17. Donker DW, Pragt E, Weerwind PW, et al. Rescue extracorporeal life support as a bridge to reflection in fulminant stress-induced cardiomyopathy. Int J Cardiol. 2012;154(3):e54–6. doi:10.1016/j.ijcard.2011.06.037 . Epub 2011 Jun 24.
18. Vernick WJ, Hargrove WC, Augoustides JG, Horak J. Takotsubo cardiomyopathy associated with cardiac arrest following cardiac surgery: new variants of an unusual syndrome. J Card Surg. 2010;25:654–93.
19. Jeger RV, Radovanovic D, Hunziker PR, et al. Ten-year trends in the incidence and treatment of cardiogenic shock. Ann Intern Med. 2008;149(9):618–26 . Epub 2008/11/05.
20. Goldberg RJ, Spencer FA, Gore JM, et al. Thirty-year trends (1975 to 2005) in the magnitude of, management of, and hospital death rates associated with cardiogenic shock in patients with acute myocardial infarction: a population-based perspective. Circulation. 2009;119(9):1211–9 . Epub 2009/02/25.
21. Awad HH, Anderson Jr FA, Gore JM, et al. Cardiogenic shock complicating acute coronary syndromes: insights from the Global Registry of Acute Coronary Events. Am Heart J. 2012;163(6):963–71.
22. Combes A, Leprince P, Luyt CE, et al. Outcomes and long-term quality-of-life of patients supported by extracorporeal membrane oxygenation for refractory cardiogenic shock. Crit Care Med. 2008;36(5):1404–11 . Epub 2008/04/25.
23. Katz JN, Stebbins AL, Alexander JH, et al. Predictors of 30-day mortality in patients with refractory cardiogenic shock following acute myocardial infarction despite a patent infarct artery. Am Heart J. 2009;158(4):680–7.
24. Prondzinsky R, Unverzagt S, Lemm H, et al. Interleukin-6, −7, −8 and −10 predict outcome in acute myocardial infarction complicated by cardiogenic shock. Clin Res Cardiol. 2012;101(5):375–84 . Epub 2012/01/04.
25. Bermudez CA, Rocha RV, Toyoda Y, et al. Extracorporeal membrane oxygenation for advanced refractory shock in acute and chronic cardiomyopathy. Ann Thorac Surg. 2011;92(6):2125–31.
26. Vivien B, Deye N, Mégarbane B, et al. Extracorporeal life support in a case of fatal flecainide and betaxolol poisoning allowing successful cardiac allograft. Ann Emerg Med. 2010;56(4):409–12.
27. Thiele H, Zeymer U, Neumann FJ, et al. Intraaortic balloon support for myocardial infarction with cardiogenic shock. N Engl J Med. 2012;367(14):1287–96 . Epub 2012/08/28.
28. O'Connor CM, Rogers JG. Evidence for overturning the guidelines in cardiogenic shock. N Engl J Med. 2012;367(14):1349–50 . Epub 2012/08/28.
29. Hochman JS, Sleeper LA, Webb JG, et al. Early revascularization in acute myocardial infarction complicated by cardiogenic shock. SHOCK Investigators. Should We Emergently Revascularize Occluded Coronaries for Cardiogenic Shock. N Engl J Med. 1999;341(9):625–34 . Epub 1999/08/26.
30. Webb JG, Lowe AM, Sanborn TA, et al. Percutaneous coronary intervention for cardiogenic shock in the SHOCK trial. J Am Coll Cardiol. 2003;42(8):1380–6 . Epub 2003/10/18.
31. Ouweneel DM, Henriques JPS. Percutaneous cardiac support devices for cardiogenic shock: current indications and recommendations. Heart. 2012;98(16):1246–54.
32. Engstrom AE, Vis MM, Bouma BJ, et al. Mitral regurgitation is an independent predictor of 1-year mortality in ST-elevation myocardial infarction patients presenting in cardiogenic shock on admission. Acute Card Care. 2010;12(2):51–7 . Epub 2010/05/21.
33. Heilmann C, Trummer G, Berchtold-Herz M, et al. Established markers of renal and hepatic failure are not appropriate to predict mortality in the acute stage before extracorporeal life support implantation. Eur J Cardiothorac Surg. 2012;42(1):135–41.
34. Stokes TL, Gibbon Jr JH. Experimental maintenance of life by a mechanical heart and lung during occlusion of the venae cavae followed by survival. Surg Gynecol Obstet. 1950;91(2):138–56 . Epub 1950/08/01.
35. Dennis C, Carlens E, Senning A, et al. Clinical use of a cannula for left heart bypass without thoracotomy: experimental protection against fibrillation by left heart bypass. Ann Surg. 1962;156:623–37.

36. Kennedy J, Bailas N, Barnard P, et al. USe of a pump oxygenator in clinical cardiac failure. JAMA. 1966;195(2):61–6.
37. Hill JD, Branson ML, Hackel A, et al. Laboratory and clinical studies during prolonged partial extracorporeal circulation using the Bramson membrane lung. Circulation. 1968;37(4 Suppl):II 139–5.
38. Hill JD, Branson ML, Rapaport E, et al. Experimental and clinical experiences with prolonged oxygenation and assisted circulation. Ann Surg. 1969;170(3):448–59.
39. Mattox KL, Beall Jr AC. Resuscitation of the moribund patient using portable cardiopulmonary bypass. Ann Thorac Surg. 1976;22(5):436–42.
40. Dembitsky WP, Moreno-Cabral RJ, Adamson RM, Daily PO. Emergency resuscitation using portable extracorporeal membrane oxygenation. Ann Thorac Surg. 1993;55(1):304–9.
41. Levine GN, Bates ER, Blankenship JC, et al. 2011 ACCF/AHA/SCAI Guideline for Percutaneous Coronary Intervention: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Society for Cardiovascular Angiography and Interventions. Circulation. 2011;124(23):e574–651.
42. Sanborn TA, Sleeper LA, Bates ER, et al. Impact of thrombolysis, intra-aortic balloon pump counterpulsation, and their combination in cardiogenic shock complicating acute myocardial infarction: a report from the SHOCK Trial Registry. SHould we emergently revascularize Occluded Coronaries for cardiogenic shocK? J Am Coll Cardiol. 2000;36(3 Suppl A):1123–9.
43. Chen EW, Canto JG, Parsons LS, et al. Relation between hospital intra-aortic balloon counterpulsation volume and mortality in acute myocardial infarction complicated by cardiogenic shock. Circulation. 2003;108(8):951–7.
44. Barron HV, Every NR, Parsons LS, et al. The use of intra-aortic balloon counterpulsation in patients with cardiogenic shock complicating acute myocardial infarction: data from the National Registry of Myocardial Infarction 2. Am Heart J. 2001;141(6):933–9.
45. O'Gara PT, Kushner FG, Ascheim DD, et al. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: executive summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation. 2013;127(4):529–55 . Epub 2012/12/19.
46. Lebreton G, Pozzi M, Luyt CE, et al. Out-of-hospital extra-corporeal life support implantation during refractory cardiac arrest in a half-marathon runner. Resuscitation. 2011;82(9):1239–42 . Epub 2011/05/04.
47. Arlt M, Philipp A, Voelkel S, et al. Out-of-hospital extracorporeal life support for cardiac arrest-A case report. Resuscitation. 2011;822(9):1243–5. doi:10.1016/j.resuscitation.2011.03.022 . Epub 2011 Mar 31.
48. Cook S, Windecker S. Percutaneous ventricular assist devices for cardiogenic shock. Curr Heart Fail Rep. 2008;5(3):163–9 . Epub 2008/08/30.
49. Kar B, Gregoric ID, Basra SS, et al. The percutaneous ventricular assist device in severe refractory cardiogenic shock. J Am Coll Cardiol. 2011;57(6):688–96 Epub 2010/10/19.
50. Kar B, Basra SS, Shah NR, et al. Percutaneous circulatory support in cardiogenic shock: interventional bridge to recovery. Circulation. 2012;125(14):1809–17.
51. Tang gH, Malekan R, Kai M, et al. Peripheral venoarterial extracorporeal membrane oxygenation improves survival in myocardial infarction with cardiogenic shock. J Thorac Cardiovasc Surg. 2013;145(3):e32–3.
52. Takayama H, Truby L, Koekort M, et al. Clinical outcome of mechanical circulatory support for refractory cardiogenic shock in the current era. J Heart Lung Transplant. 2013;32(1):106–11 . Epub 2012/12/25.
53. Formica F, Avalli L, Colagrande L, et al. Extracorporeal membrane oxygenation to support adult patients with cardiac failure: predictive factors of 30-day mortality. Interact Cardiovasc Thorac Surg. 2010;10(5):721–6 . Epub 2010/02/04.
54. Tanaka K, Sato N, Yamamoto T, et al. Measurement of end-tidal carbon dioxide in patients with cardiogenic shock treated using a percutaneous cardiopulmonary assist system. J Nippon Med Sch. 2004;71(3):160–6 . Epub 2004/07/01.

55. Schwarz B, Mair P, Margreiter J, et al. Experience with percutaneous venoarterial cardiopulmonary bypass for emergency circulatory support. Crit Care Med. 2003;31(3):758–64 . Epub 2003/03/11.
56. Mégarbane B, Leprince P, Deye N, et al. Emergency feasibility in medical intensive care unit of extracorporeal life support for refractory cardiac arrest. Intensive Care Med. 2007;33(5):758–64.
57. Chen Y-S, Lin J-W, Yu H-Y, et al. Cardiopulmonary resuscitation with assisted extracorporeal life-support versus conventional cardiopulmonary resuscitation in adults with in-hospital cardiac arrest: an observational study and propensity analysis. Lancet. 2008;372:554–61.
58. Morrow DA, Fang JC, Fintel DJ, et al. Evolution of critical care cardiology: transformation of the cardiovascular intensive care unit and the emerging need for new medical staffing and training models: a scientific statement from the American Heart Association. Circulation. 2012;126(11):1408–28 . Epub 2012/08/16.
59. Travers AH, Rea TD, Bobrow BJ, et al. Part 4: CPR overview: 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Circulation. 2010;122(18 Suppl 3):S676–84 . Epub 2010/10/22.
60. Goldberger ZD, Chan PS, Berg RA, et al. Duration of resuscitation efforts and survival after in-hospital cardiac arrest: an observational study. Lancet. 2012;380(9852):1473–81. doi:10.1016/S0140-6736(12)60862-9 . Epub 2012 Sep 5.
61. Sasson C, Rogers MAM, Dahl J, et al. Predictors of survival from out-of-hospital cardiac arrest: a systematic review and meta-analysis. Circ Cardiovasc Qual Outcomes. 2010;3(1):63–81.
62. Chen J-S, Ko W-J, Yu H-Y, et al. Analysis of the outcome for patients experiencing myocardial infarction and cardiopulmonary resuscitation refractory to conventional therapies necessitating extracorporeal life support rescue *. Crit Care Med. 2006;34(4):950–7. doi:10.1097/01.CCM.0000206103.35460.1F.
63. Massetti M, Tasle M, Le Page O, et al. Back from irreversibility: extracorporeal life support for prolonged cardiac arrest. Ann Thorac Surg. 2005;79(1):178–83 ; discussion 83–4.
64. Morimura N, Sakamoto T, Nagao K, et al. Extracorporeal cardiopulmonary resuscitation for out-of-hospital cardiac arrest: a review of the Japanese literature. Resuscitation. 2011;82(1):10–4 . Epub 2010/10/12.
65. Maekawa K, Tanno K, Hase M, et al. Extracorporeal cardiopulmonary resuscitation for patients with out-of-hospital cardiac arrest of cardiac origin: a propensity-matched study and predictor analysis. Crit Care Med. 2013;41(5):1186–96 . Epub 2013/02/08.
66. Morrison LJ, LM V, Kiss A, TOR Investigators, et al. Validation of a rule for termination of resuscitation in out-of-hospital cardiac arrest. N Engl J Med. 2006;355(5):478–87.
67. Morrison LJ, Verbeek PR, Zhan C, et al. Validation of a universal prehospital termination of resuscitation clinical prediction rule for advanced and basic life support providers. Resuscitation. 2009;80(3):324–8 . Epub 2009/01/20.
68. Neumar RW, Nolan JP, Adrie C, et al. Post–cardiac arrest syndrome: epidemiology, pathophysiology, treatment, and prognostication A Ccnsensus statement from the International Liaison Committee on Resuscitation (American Heart Association, Australian and New Zealand Council on Resuscitation, European Resuscitation Council, Heart and Stroke Foundation of Canada, InterAmerican Heart Foundation, Resuscitation Council of Asia, and the Resuscitation Council of Southern Africa); the American Heart Association Emergency Cardiovascular Care Committee; the Council on Cardiovascular Surgery and Anesthesia; the Council on Cardiopulmonary, Perioperative, and Critical Care; the Council on Clinical Cardiology; and the Stroke Council. Circulation. 2008;118(23):2452–83.
69. Negovsky VA. The second step in resuscitation–the treatment of the ‘post-resuscitation disease’. Resuscitation. 1972;1(1):1–7 . Epub 1972/03/01.
70. Stammet P, Goretti E, Vausort M, et al. Circulating microRNAs after cardiac arrest. Crit Care Med. 2012;40(12):3209–14 . Epub 2012/08/15.
71. Stammet P, Devaux Y, Azuaje F, et al. Assessment of procalcitonin to predict outcome in hypothermia-treated patients after cardiac arrest. Crit Care Res Pract. 2011;2011:631062 . Epub 2011/11/24.

72. Hayashida H, Kaneko T, Kasaoka S, et al. Comparison of the predictability of neurological outcome by serum procalcitonin and glial fibrillary acidic protein in postcardiac-arrest patients. Neurocrit Care. 2010;12(2):252–7.
73. Engel H, Ben Hamouda N, Portmann K, et al. Serum procalcitonin as a marker of post-cardiac arrest syndrome and long-term neurological recovery, but not of early-onset infections, in comatose post-anoxic patients treated with therapeutic hypothermia. Resuscitation. 84(6):776–81.
74. (ROC) ROC. Website homepage. https://roc.uwctc.org/. Accessed June 2013.
75. Le Guen M, Nicolas-Robin A, Carreira S, et al. Extracorporeal life support following out-of-hospital refractory cardiac arrest. Crit Care. 2011;15(1):R29 . Epub 2011/01/20.
76. Mégarbane B, Deve N, Aout M, et al. Usefulness of routine laboratory parameters in the decision to treat refractory cardiac arrest with extracorporeal life support. Resuscitation. 2011;82(9):1154–61. doi:10.1016/j.resuscitation.2011.05.007 . Epub 2011 May 19.
77. Kliegel A, Losert H, Sterz F, et al. Serial lactate determinations for prediction of outcome after cardiac arrest. Medicine. 2004;83(5):274–9.
78. Tisherman SA, Rittenberger J. Should our crystal ball after cardiac arrest include one of the building blocks of life? Crit Care Med. 2012;40(12):3321–3. doi:10.1097/CCM.0b013e31826536c9.
79. Lippert FK, Raffay V, Georgiou M, et al. European Resuscitation Council Guidelines for Resuscitation 2010 Section 10. The ethics of resuscitation and end-of-life decisions. Resuscitation. 2010;81(10):1445–51 . Epub 2010/10/20.
80. Flannigan C, Bourke TW, Chisakuta A. Out-of-hospital extracorporeal life support—when is it appropriate? Resuscitation. 2012;83(3):e85.
81. JM H. Open letter to JR Lake, president OPTN/UNOS, Nov 11, 2011. www.ncbcenter.org/documentdoc?id=368. 2011.
82. Dahdouh Z, Roule V, Lognoné T, et al. Left main coronary artery transradial rescue percutaneous coronary intervention for acute myocardial infarction complicated by cardiogenic shock with Impella ventricular mechanical support. Cardiovasc Revasc Med. 2012;13(2):142.e1–4.
83. Takayama H, Naka Y, Kodali SK, et al. A novel approach to percutaneous right-ventricular mechanical support. Eur J Cardiothorac Surg. 2012;41(2):423–6 . Epub 2011/07/09.
84. Atiemo AD, Conte JV, Heldman AW. Resuscitation and recovery from acute right ventricular failure using a percutaneous right ventricular assist device. Catheter Cardiovasc Interv. 2006;68(1):78–82 . Epub 2006/06/10.
85. Giesler GM, Gomez JS, Letsou G, et al. Initial report of percutaneous right ventricular assist for right ventricular shock secondary to right ventricular infarction. Catheter Cardiovasc Interv. 2006;68(2):263–6 . Epub 2006/07/05.
86. Kapur NK, Paruchuri V, Korabathina R, et al. Effects of a percitaneous mechanical circulatory support device for medically refreactory right ventricular failure. J Heart Lung Transplant. 2011;30(12):1360–7.
87. Arpesella G, Loforte A, Mikus E, et al. Extracorporeal membrane oxygenation for primary allograft failure. Transplant Proc. 2008;40(10):3596–7 . Epub 2008/12/23.
88. Chandola R, Cusimano R, Osten M, et al. Postcardiac transplant transcatheter core valve implantation for aortic insufficiency secondary to Impella device placement. Ann Thorac Surg. 2012;93(6):e155–7 . Epub 2012/05/29.
89. Rajagopal V, Steahr G, Wilmer CI, et al. A novel percutaneous mechanical biventricular bridge to recovery in severe cardiac allograft rejection. J Heart Lung Transplant. 2010;29(1):93–5.
90. D'Alessandro C, Aubert S, Golmard JL, et al. Extra-corporeal membrane oxygenation temporary support for early graft failure after cardiac transplantation. Eur J Cardiothorac Surg. 2010;37(2):343–9.
91. Maggio P, Hemmila M, Haft J, et al. Extracorporeal life support for massive pulmonary embolism. J Trauma. 2007;62(3):570–6 . Epub 2007/04/07.
92. Munakata R, Yamamoto T, Hosokawa Y, et al. Massive pulmonary embolism requiring extracorporeal life support treated with catheter-based interventions. Int Heart J. 2012;53(6):370–4. Epub 2012/12/22.

93. Bonacchi M, Spina R, Torracchi L, et al. Extracorporeal life support in patients with severe trauma: an advanced treatment strategy for refractory clinical settings. J Thorac Cardiovasc Surg. 2013;145(6):1617–26 . Epub 2012 Sep 13.
94. Arlt M, Philipp A, Voelkel S, et al. Extracorporeal membrane oxygenation in severe trauma patients with bleeding shock. Resuscitation. 2010;81(7):804–9.
95. Massetti M, Bruno P, Babatasi G, et al. Cardiopulmonary bypass and severe drug intoxication. J Thorac Cardiovasc Surg. 2000;120(2):424–5 . Epub 2000/08/05.
96. Masson R, Colas V, Parienti J-J, et al. A comparison of survival with and without extracorporeal life support treatment for severe poisoning due to drug intoxication. Resuscitation. 2012;83(11):1413–7.
97. Palanzo D, Baer L, El-Banayosy A, et al. Successful treatment of peripartum cardiomyopathy with extracorporeal membrane oxygenation. Perfusion. 2009;24(2):75–9.
98. Sim SS, Chou HC, Chen JW, et al. Extracorporeal membrane oxygenation in maternal arrhythmic cardiogenic shock. Am J Emerg Med. 2012;30.
99. Kantrowitz A, Tjonneland S, Freed PS, et al. Initial clinical experience with intraaortic balloon pumping in cardiogenic shock. JAMA. 1968;203(2):113–8 . Epub 1968/01/08.
100. Cheng JM, den Uil CA, Hoeks SE, et al. Percutaneous left ventricular assist devices vs. intra-aortic balloon pump counterpulsation for treatment of cardiogenic shock: a meta-analysis of controlled trials. Eur Heart J. 2009;30(17):2102–8.
101. Nordhaug D, Steensrud T, Muller S, et al. Intraaortic balloon pumping improves hemodynamics and right ventricular efficiency in acute ischemic right ventricular failure. Ann Thorac Surg. 2004;78(4):1426–32.
102. Prondzinsky R, Lemm H, Swyter M, et al. Intra-aortic balloon counterpulsation in patients with acute myocardial infarction complicated by cardiogenic shock: The prospective, randomized IABP SHOCK Trial for attenuation of multiorgan dysfunction syndrome. Crit Care Med. 2010;38(1):152–60. doi:10.1097/CCM.0b013e3181b78671.
103. Buerke M, Prondzinsky R, Lemm H, et al. Intra-aortic balloon counterpulsation in the treatment of infarction-related cardiogenic shock—review of the current evidence. Artif Organs. 2012;36(6):505–11.
104. Bahekar A, Singh M, Singh S, et al. Cardiovascular outcomes using intra-aortic balloon pump in high-risk acute myocardial infarction with or without cardiogenic shock: a meta-analysis. J Cardiovasc Pharmacol Ther. 2012;17(1):44–56.
105. Ndrepepa G, Kastrati A. Need for critical reappraisal of intra-aortic balloon counterpulsation. JAMA. 2011;306(12):1376–7 . Epub 2011/09/01.
106. Patel MR, Smalling RW, Thiele H, et al. Intra-aortic balloon counterpulsation and infarct size in patients with acute anterior myocardial infarction without shock: the CRISP AMI randomized trial. JAMA. 2011;306(12):1329–37 . Epub 2011/09/01.
107. Romeo F, Acconcia MC, Sergi D, et al. Lack of intra-aortic balloon pump effectiveness in high-risk percutaneous coronary interventions without cardiogenic shock: a comprehensive meta-analysis of randomised trials and observational studies. Int J Cardiol. 2013;167(5):1783–93 . Epub 2013/01/09.
108. Sjauw KD, Engström AE, Vis MM, et al. A systematic review and meta-analysis of intra-aortic balloon pump therapy in ST-elevation myocardial infarction: should we change the guidelines? Eur Heart J. 2009;30(4):459–68.
109. Minami K, El-Banayosy A, Posival H, et al. Improvement of survival rate in patients with cardiogenic shock by using nonpulsatile and pulsatile ventricular assist device. Int J Artif Organs. 1992;15(12):715–21 . Epub 1992/12/01.
110. El-Banayosy A, Posival H, Hartmann D, et al. Transport of patients in cardiogenic shock with mobile femoral-femoral cardiopulmonary bypass. J Cardiothorac Vasc Anesth. 1995;9(3):301–3.
111. Reiss N, El-Banayosy A, Mirow N, et al. Implantation of the biomedicus centrifugal pump in post-transplant right heart failure. J Cardiovasc Surg (Torino). 2000;41(5):691–4 . Epub 2001/01/10.

112. Kutty RS, Parameshwar J, Lewis C, et al. Use of centrifugal left ventricular assist device as a bridge to candidacy in severe heart failure with secondary pulmonary hypertension. Eur J Cardiothorac Surg. 2013;43(6):1237–42.
113. Mehlhorn U, Brieske M, Fischer UM, et al. LIFEBRIDGE: a portable, modular, rapidly available "plug-and-play" mechanical circulatory support system. Ann Thorac Surg. 2005;8(5):1887–92.
114. De Robertis F, Birks EJ, Rogers P, et al. Clinical performance with the Levitronix Centrimag short-term ventricular assist device. J Heart Lung Transplant. 2006;25(2):181–6.
115. Mueller JP, Kuenzli A, Reuthebuch O, et al. The CentriMag: a new optimized centrifugal blood pump with levitating impeller. Heart Surg Forum. 2004;7(5):E477–80 . Epub 2005/04/02.
116. John R, Long JW, Massey HT, et al. Outcomes of a multicenter trial of the Levitronix CentriMag ventricular assist system for short-term circulatory support. J Thorac Cardiovasc Surg. 2011;141(4):932–9.
117. Meyns B, Dens J, Sergeant P, et al. Initial experiences with the Impella device in patients with cardiogenic shock – Impella support for cardiogenic shock. Thorac Cardiovasc Surg. 2003;51(6):312–7 . Epub 2003/12/12.
118. Siegenthaler MP, Brehm K, Strecker T, et al. The Impella Recover microaxial left ventricular assist device reduces mortality for postcardiotomy failure: a three-center experience. J Thorac Cardiovasc Surg. 2004;127(3):812–22 . Epub 2004/03/06.
119. Engström AE, Cocchieri R, Driessen AH, et al. The Impella 2.5 and 5.0 devices for ST-elevation myocardial infarction patients presenting with severe and profound cardiogenic shock: the Academic Medical Center intensive care unit experience. Crit Care Med. 2011;39(9):2072–9. doi:10.1097/CCM.0b013e31821e89b5.
120. Cubeddu RJ, Lago R, Horvath SA, et al. Use of the Impella 2.5 system alone, after and in combination with an intra-aortic balloon pump in patients with cardiogenic shock: case description and review of the literature. EuroIntervention. 2012;7(12):1453–60. doi:10.4244/EIJV7I12A226.
121. Gupta A, Allaqaband S, Bajwa T. Combined use of Impella device and intra-aortic balloon pump to improve survival in a patient in profound cardiogenic shock post cardiac arrest. Catheter Cardiovasc Interv. 2009;74(6):975–6 . Epub 2009/06/13.
122. Koeckert MS, Jorde UP, Naka Y, et al. Impella LP 2.5 for left ventricular unloading during venoarterial extracorporeal membrane oxygenation support. J Card Surg. 2011;26(6):666–8.
123. Gregoric ID, Loyalka P, Radovancevic R, et al. TandemHeart as a rescue therapy for patients with critical aortic valve stenosis. Ann Thorac Surg. 2009;88:1822–7.
124. Loebe M, Zade Asfahani WH, Petrov GP, et al. Surgical considerations on the use of the percutaneous ventricular assist device TandemHeart® in critical aortic valve stenosis. Thorac Cardiovasc Surg. 2009;57(01):50–2.
125. Chandra D, Kar B, Idelchik G, et al. Usefulness of percutaneous left ventricular assist device as a bridge to recovery from myocarditis. Am J Cardiol. 2007;99(12):1755–6 . Epub 2007/06/15.
126. Idelchik GM, Loyalka P, Kar B. Percutaneous ventricular assist device placement during active cardiopulmonary resuscitation for severe refractory cardiogenic shock after acute myocardial infarction. Tex Heart Inst J (From the Texas Heart Institute of St Luke's Episcopal Hospital, Texas Children's Hospital). 2007;34(2):204–8 . Epub 2007/07/12.
127. Karimova A, Robertson A, Cross N, et al. A wet-primed extracorporeal membrane oxygenation circuit with hollow-fiber membrane oxygenator maintains adequate function for use during cardiopulmonary resuscitation after 2 weeks on standby. Crit Care Med. 2005;33(7):1572–6.
128. Bellezzo JM, Shinar Z, Davis DP, et al. Emergency physician-initiated extracorporeal cardiopulmonary resuscitation. Resuscitation. 2012;83(8):966–70.
129. Russo CF, Cannata A, Lanfranconi M, et al. Veno-arterial extracorporeal membrane oxygenation using Levitronix centrifugal pump as bridge to decision for refractory cardiogenic shock. J Thorac Cardiovasc Surg. 2010;140(6):1416–21.

130. Englesbe MJ, Woodrum D, Debroy M, et al. Salvage of an unstable brain dead donor with prompt extracorporeal support. Transplantation. 2004;78(12):1815. doi:10.097/01.TP.0000141360.74374.A1.
131. Magliocca JF, Magee JC, Rowe SA, et al. Extracorporeal support for organ donation after cardiac death effectively expands the donor pool. J Trauma Acute Care Surg. 2005;58(6):1095–102.
132. Javidfar J, Brodie D, Takayama H, et al. Safe transport of critically ill adult patients on extracorporeal membrane oxygenation support to a regional extracorporeal membrane oxygenation center. ASAIO J. 2011;57(5):421–5 . Epub 2011/08/27.
133. Formica F, Avalli L, Redaelli G, et al. Interhospital stabilization of adult patients with refractory cardiogenic shock by veno-arterial extracorporeal membrane oxygenation. Int J Cardiol. 2011;147(1):164–5.
134. Bignon M, Roule V, Dahdouh Z, et al. Percutaneous balloon atrioseptostomy for left heart discharge in extracorporeal life support patients with persistent pulmonary edema. J Interv Cardiol. 2012;25(1):62–7. doi:10.1111/j.1540-8183.2011.00681.x . Epub 2011 Nov 4.
135. Anastasiadis K, Chalvatzoulis O, Antonitsis P, et al. Left ventricular decompression during peripheral extracorporeal membrane oxygenation support with the use of the novel iVAC pulsatile paracorporeal assist device. Ann Thorac Surg. 2011;92(6):2257–9.
136. Anastasiadis K, Antonitsis P, Chalvatzoulis O, et al. Use of a novel short-term mechanical circulatory support device for cardiac recovery. J Heart Lung Transplant. 2011;30(6):732–3.
137. Koerner M, Brehm C, El-Banayosy A. Venous-arterial extracorporeal membraneoxygenation is more than life support: it has the capacity to facilitate myocardial recovery. Crit Care Med. 2012;40(12 (suppl) abstract 567):1–328.
138. Santise G, Sciacca S, D'Ancona G, et al. Circulatory support system as a bridge to decision in patients with refractory acute cardiogenic shock: is there a space for extracorporeal membrane oxygenation? J Thorac Cardiovasc Surg. 2008;135(3):717.
139. Vincent J. We should abandon randomized controlled trials in the intensive care unit. Crit Care Med. 2010;38(10 (suppl)):534–8.

Chapter 27
Mechanical Circulatory Support as a Bridge to Heart Transplantation

Antoine H. Chaanine and Sean P. Pinney

Introduction

Heart failure (HF) is a worldwide pandemic. According to the latest American Heart Association Heart Disease and Stroke Statistics 2011 Update, HF affects approximately 5.7 million Americans with an incidence of 670,000 new HF cases ≥45 years of age [1]. It is estimated that HF affects more than 23 million people worldwide [2]. HF is associated with a process known as remodeling that consists of adverse cellular, structural, and functional changes in the myocardium. Clinically, this results in progressive enlargement of the ventricle, reduction in contractility, and increases in intracardiac filling pressures [3]. As a consequence of the reduced contractility, decreased cardiac output occurs, resulting in the syndrome of HF. The remodeling process is often initiated after an initial insult, such as myocardial infarction or prolonged and uncontrolled hypertension, and is also associated with increases in the left ventricular (LV) muscle mass, LV end diastolic and end systolic volumes, and a change in LV sphericity [3]. At the cellular level, histological changes include cardiomyocyte hypertrophy [4, 5], cardiomyocyte slippage [6], increased interstitial fibrosis, myocyte lengthening, and apoptosis [7–9]. The initiators of the remodeling process remain incompletely understood. Medical therapy with angiotensin-converting-enzyme inhibitors, β-blockers [10–13], aldosterone antagonists [14, 15], and angiotensin-receptor blockers [16, 17] has significantly improved morbidity and mortality in patients with HF. Advanced HF affects 10 % of the HF population and is associated with a dismal quality of life, recurrent hospitalizations and a mortality up to 50 % per year. Medical arms in left ventricular

A.H. Chaanine, MD • S.P. Pinney, MD (✉)
Icahn School of Medicine at Mount Sinai,
One Gustave L. Levy Place, Box, 1030 New York, NY, USA

Department of Cardiology, Mount Sinai Hospital,
One Gustave L. Levy Place, Box 1030, New York, NY 10029, USA
e-mail: antoine.chaanine@mssm.edu; sean.pinney@mssm.edu

H. Eisen (ed.), *Heart Failure*, DOI 10.1007/978-1-4471-4219-5_27

assist device (LVAD) trials have generally been inotrope dependent and have had 1-year mortality of over 75 % [18–20].

The traditional treatment for medically refractory HF has been heart transplantation. In spite of the increased number of HF patients, the total number of heart transplants in the United States has remained virtually unchanged in the range of 2200 transplants performed annually. Moreover, many patients with advanced HF are not eligible for heart transplantation due to existing comorbidities or advanced age. A major advancement in the treatment of HF has been the emergence of LVADs both as a bridge to transplantation (BTT) and as destination therapy (DT), which has revolutionized and improved the care of the sickest HF patients. The first use of a ventricular assist device is attributed to Michael DeBakey to support a patient in post-cardiotomy shock. Over the ensuing decades, with the support of the NIH Artificial Heart Program, the types and applications of LVADs were broadened to act as a BTT. In fact, the original indication for which implantable LVADs were granted approval by the US FDA was as a BTT. However, due to a high rate of device-related complications, the widespread use of LVADs, both as a BTT and DT did not occur until after the publication of the Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure REMATCH trial in 2001 [18].

This chapter provides up to date overview of the various LVAD generations, LVAD indications and clinical outcomes, as well as the current utilization and future potential of this technology.

Classification and Description of Devices

A mechanical circulatory support pump may be positioned extracorporeally or intracorporeally as a biventricular assist device (BiVAD), a right ventricular assist device (RVAD), or more commonly as a LVAD. Moreover, the pump characteristic further substratifies it into a pulsatile or nonpulsatile device. The three different generations of LVADs are described below and are shown in Fig. 27.1. LVADs FDA approved for BTT are highlighted in Table 27.1.

First-Generation LVADs

The first-generation of implantable devices are classified as pulsatile pumps. Examples of this class are the HeartMate XVE® (Thoratec Corp., Pleasanton, CA), Thoratec PVAD™ (Thoratec Corp., Pleasanton, CA), and Novacor N100 (World Heart, Inc., Oakland, CA). First-generation devices had larger tissue and blood contacting surfaces as well as multiple moving parts [21]. Their implantation requires a median sternotomy, with inflow and outflow cannulation insertions made at the left ventricular apex and ascending aorta, respectively. Due to its large size, the pumping chamber is located entirely within the abdomen or preperitoneal space with the

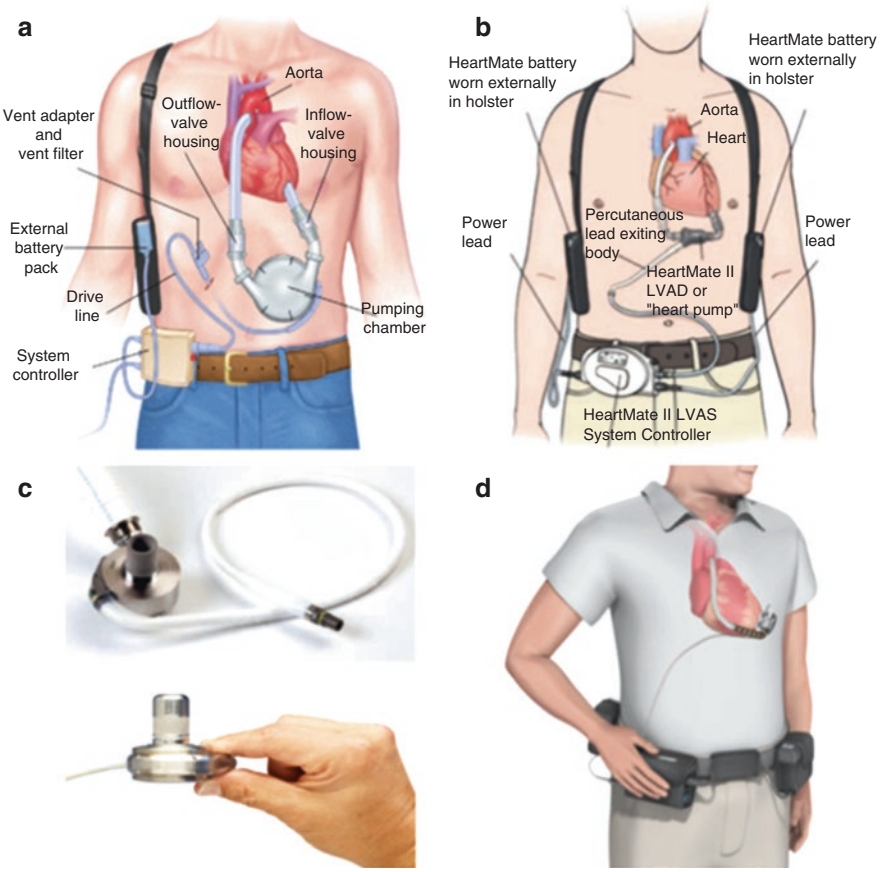


Fig. 27.1 Generations of left ventricular assist devices. (**a**) Schematic drawing of the implanted first-generation LVAD HeartMate XVE. (**b**) Schematic drawing of the implanted second-generation LVAD HeartMate II. (**c**) Third-generation LVADs. Upper image HeartMate III and lower image HeartWare HVAD. (**d**) Schematic drawing of the implanted HeartWare HVAD ((**a**) Adapted with permission from the Wilson et al. [21], © 2009, with permission from Elsevier. (**b**) and (**c**) (*upper*): Adapted with permission from Thoratec incorporation. (**c**) (*lower*) and (**d**)**:** Adapted with permission from HeartWare incorporation)

Table 27.1 Left ventricular assist devices approved by FDA for BTT

LVAD	Manufacturer	Generation	Portable
Thoratec PVAD	Thoratec	1st generation	Yes
Novacor	World Heart	1st generation	Yes
HeartMate XVE	Thoratec	1st generation	Yes
HeartMate II	Thoratec	2nd generation	Yes
HeartWare HVAD	HeartWare	3rd generation	Yes

transcutaneous driveline exiting the abdominal wall. The major disadvantage of these pumps was their lack of durability, mostly due to failure of the inflow valve after about 18 months of support. Furthermore, high risk of infection, thrombus formation, and blood trauma were significant complications that needed to improve, especially if long-term support was to be achieved with LVAD therapy.

Second-Generation LVADs

The second-generation LVADs are continuous flow (CF) devices that are smaller in size with better efficiency and durability than the first-generation pumps. Examples of the second-generation LVADs include the HeartMate II® (Thoratec Corp., Pleasanton, CA), Jarvik 2000 (Jarvik Heart, Inc., New York, NY), and Micromed DeBakey® (MicroMed Cardiovascular, Inc., Houston, TX). Historically, some questioned whether these CF-LVADs could support long-term end-organ function. It has been well demonstrated that pulsatile blood flow primarily occurs at large arteries as compared to capillary flow, where pulsatile flow is markedly reduced and the average velocity of blood flow in capillaries is about one-thousandth of that of the aorta [22]. Subsequently, large animal studies were able to demonstrate successful long-term end-organ perfusion with CF [23, 24]. The key mechanical difference was the implementation of a valveless axial pump with a rotary motor as the only moving part in the system. This was accomplished by the introduction of an internal rotor in the axial path of flow that was suspended by blood-immersed bearings [25]. The idea behind this design was further reduction of prothrombotic sites and minimization of wear and tear associated with multiple moving parts. Efficiency was further enhanced with elimination of the reservoir chamber and inflow/outflow valves. The blood contacting surfaces were designed with textured titanium as an additional antithrombotic measure.

Its current configuration consists of an inlet cannula placed in the left ventricle, and an outflow cannula which is anastomosed to the aorta via a Dacron graft. A single driveline exits the abdominal wall just below the costal margin. The impeller blade is powered by an electromagnetic motor, which is driven by an external battery source similar to first-generation devices. The second-generation LVADs are designed to provide high-level cardiac output, with rotary speeds of 8000 to a maximum of 15,000 rpm. The benchmark predicted mechanical life of second-generation LVADs is 5 years, but longer support has been well documented. Long-term anticoagulation is still required, with emphasis on individual patient needs as discussed below.

Third-Generation LVADs

The critical difference between the second and third-generation LVADs is that the latter utilizes non-contact bearings to support its impellar which allows for rotation without friction or wear [26]. The goal of this design is to further minimize

prothrombotic sites while enhancing efficiency and durability. Examples of the third-generation devices include DuraHeart™ (Terumo Heart, Inc., Ann Arbor, MI), HeartWare HVAD® (HeartWare International, Inc., Framingham MA), Incor® (Berlin Heart, Inc., Berlin, Germany), Levacor® (World Heart Inc., Salt Lake City, UT), and HeartMate III (Thoratec Corp., Pleasanton, CA). Third-generation LVADs are CF pumps that can be broadly differentiated as follows: (1) centrifugal versus axial flow pumps, and (2) magnetically levitated impeller +/− hydrodynamic support [27]. The primary difference between centrifugal flow and axial flow pumps lies in the design of their rotating elements. The rotating element of a centrifugal pump acts as a spinning disk with blades that can be viewed as a 'thrower'; fluid is captured and then thrown tangentially off the blade tips. In contrast, the rotating element of an axial pump operates like an Archimedes screw and can be viewed as a 'pusher'. Advantages of centrifugal pumps include lower rotational speeds, higher efficiency, and further enhanced anatomic design. Moazami et al. describes in detail differences in pump mechanics between axial and centrifugal CF pumps and its translation into clinical practice [28]. The Incor is the only third-generation axial pump under active clinical investigation, with the remaining pumps being centrifugal. In terms of levitation, the DuraHeart employs a dual hydrodynamic and magnetic system for levitation compared to the Levacor, which is completely magnetically levitated. Unique to the HeartWare, which was FDA approved for BTT in November 2012, is that implantation is completely intrapericardial due to the smaller pump size, eliminating the need for an abdominal pocket [29]. In terms of survival, reports demonstrate expected success with third-generation devices. One European single-center study reported very promising long-term outcomes in 68 patients implanted with the DuraHeart. Overall survival at 3, 6, 12, and 24 months was 87 %, 81 %, 77 %, and 61 %, respectively [30]. The HeartWare Ventricular Assist Device (HVAD) BTT ADVANCE trial enrolled, in a non-randomized fashion, 140 patients who received the HVAD investigational pump versus 499 patients who received a commercially available pump, most controls had received the HeartMate II LVAD. The study showed that the HVAD was non-inferior to the commercially available pumps. Survival in patients receiving the HVAD was 91 % at 6 months and 84 % at 1 year. The disease specific and global quality-of-life scores improved significantly, adverse event rates remained low and the median 6-min walk distance improved by 128.5 m at 6 months after HVAD implantation [31, 32] which is almost a three-fold greater than the improvement achieved in the cardiac resynchronization therapy (CRT) COMPANION trial that enrolled patients with class IV of NYHA [33]. These outcomes reflect incremental improvement since the initial European BTT trial of the same device [34]. Infection, right heart failure, device replacement, stroke, kidney dysfunction, hemolysis and arrhythmia rates were similar to those reported previously for the HeartMate II [35]. Electromagnetic interference between the HVAD and an implantable defibrillator occurred in two patients and thus evaluation for electromagnetic interference before discharge is recommended. The majority of third-generation devices are either in clinical trials, under development or only available in Europe.

Molecular Changes After LVAD Implantation and Their Correlation to Clinical Recovery

Patients with chronic advanced HF can show near-normalization of nearly all of the structural abnormalities of the myocardium or reverse remodeling after LVAD support due to near-total unloading of the ventricle. However, reverse remodeling does not always equate with clinical recovery. In spite of the reversal of structural changes in most patients after a period of support, only a small percentage of patients have shown significant associated improvement in their myocardial function. This improvement in myocardial function can be significant enough to allow the device to be removed, known as myocardial recovery. The molecular changes occurring after LVAD support, both in patients bridged to transplantation and in patients who have recovered enough myocardial function to have the device removed, have been studied [36]. Reverse remodeling may be attributable to a reversal of the pathological mechanisms that occur in remodeling or the generation of new pathways. A reduction in myocardial cell size occurs after LVAD unloading, which does not necessarily correlate with improved cardiac function [37, 38]. However, some of the changes in both the cardiac myocyte and the matrix after LVAD support have been shown to correlate with myocardial recovery. In the myocyte, increases in the cytoskeletal proteins and improvements in the Ca^{2+} handling pathway seem to be specifically associated with myocardial recovery [39]. Changes in the matrix are complex, but excessive scarring appears to limit the ability for recovery, and the degree of fibrosis in the myocardium at the time of implantation may predict the ability to recover [40–42]. However, translation of structural recovery to sustainable function permitting device removal remains uncertain. In the series by Dandel and coworkers, 32 nonischemic patients who were weaned demonstrated a survival rate of 78 % at 5 years after device explantation. Clinical heart failure recurred during the first 3 years after weaning in 31.3 %, and two died of heart failure. More recently, the same group has updated their experience and defined parameters likely to be associated with successful long-term survival after LVAD explantation. They entertained that left ventricular ejection fraction >45 % at an end-diastolic diameter of <55 mm carries a predictive value of 87.5 % for 5-year cardiac stability. More meaningful and sustained recovery after LVAD explantation is seen in patients who develop HF in the context of myocarditis, peripartum cardiomyopathy, and post cardiac surgery [43]. Birks and colleagues implanted LVADs in 15 patients with severe HF due to nonischemic cardiomyopathy. The patients were treated with lisinopril, carvedilol, spironolactone, and losartan to enhance reverse remodeling. Once regression of left ventricular enlargement had been achieved, the β_2-adrenergic receptor agonist clenbuterol was administered to prevent myocardial atrophy. Of the 15 patients, 11 had sufficient myocardial recovery to undergo explantation of the LVAD at 10 months after implantation of the device. One patient died of intractable arrhythmias 24 h after explantation; another died of carcinoma of the lung 27 months after explantation. The cumulative rate of freedom from recurrent heart failure among the surviving patients was

100 % and 88.9 % at 1 year and 4 years, respectively [44]. This investigation suggested long-term recovery with pharmacologic support; however, the absence of a control group precludes conclusive statements about the precise role of quadruple therapy and particularly raises doubts about the true impact of the agent clenbuterol. These data require further confirmation in randomized controlled trials.

Patient Selection and Clinical Outcomes with LVADS

Critical factors in order to achieve optimal outcomes after implantation of a LVAD include patient's illness, underlying comorbidity and timing of device implantation. It is very important that surgery take place at the right time when the patient is neither too sick nor too early in the course of the patient's illness.

The Heart Failure Survival Score and the Seattle Heart Failure Model can be used to estimate a heart failure patient's expected survival during the next 1 to 2 years with medical management and to identify patients at high risk of death who might benefit from LVAD support. Before consideration for LVAD implantation, patients should be evaluated at specialized centers, where they receive aggressive medical management for advanced heart disease. If they remain refractory to standard therapy, they should be assessed and, if appropriate, listed for cardiac transplantation. Patients who have prolonged waitlist time, especially if they are inotrope dependent, should be considered for LVAD implantation as a BTT as the waitlist mortality for transplant exceeds by far that of LVAD mortality [45]. Other indications for LVAD implantation include individuals who require temporary circulatory support and are expected to recover after a cardiac insult (Bridge to recovery) or those who need long-term support but have a relative or absolute contraindication to cardiac transplantation (DT). About 80–90 % of LVADs are implanted in transplant candidates who are not expected to survive until transplant or who are deemed too sick for transplant or who have potentially reversible transplant contraindications [46]. On the contrary, up to 17 % of DT patients subsequently undergo heart transplantation [47] and many BTT patients subsequently become ineligible for heart transplantation. Despite that recommendations for mechanical circulatory support have been implemented [48], patient selection usually relies on certain criteria such as patient clinical status, inotrope dependence and invasive hemodynamic parameters. It is noteworthy to mention that with worsening clinical status, the need for LVAD increases but so does the peri-operative risk and thus optimal operative timing becomes difficult. Another key consideration for LVAD implantation is the expected waiting time for heart transplantation, which is highly variable between different regions and is dependent on body size, blood type and panel reactive antibodies. The main goals of LVAD therapy are to improve symptoms, quality of life and prognosis. Other goals include stabilization or reversal of organ dysfunction and lowering pulmonary vascular resistance which may then allow subsequent successful heart transplantation. Table 27.2 highlights the indications and contraindications of LVAD implantation.

Table 27.2 Indications and contraindications for LVAD implantation

Indications
NYHA class IV symptoms and failure to respond to OMT for at least 45 days of the last 60 days
Chronic inotrope dependence and life expectancy <2 years (more than 50 % 1-year mortality)
Left ventricular ejection fraction <25 %
Peak oxygen consumption ≤12 ml/kg/min with significant cardiac limitation
Refractory cardiogenic shock or failure (SBP ≤80–90 mmHg, PCWP ≥ 20 mmHg, CI ≤ 2.2 L/min/m^2) or declining renal or right ventricular function.
Recurrent sustained ventricular tachycardia in the setting of an untreatable arrhythmogenic substrate
Body surface area >1.5 m^2
Contraindications to heart transplant or PVR >5 Woods.unit or GFR <25–30 ml/min/1.73 m^2 that is likely to improve after LVAD implantation.
Relative contraindications
Age >65, unless minimal or no other risk factors
Chronic kidney disease with Cr >3 mg/dL
Severe chronic malnutrition (BMI <21 kg/m^2, in males and <19.21 kg/m^2 in females)
Morbid Obesity (BMI >40.21 kg/m^2)
Mechanical ventilation
Severe mitral stenosis or moderate to severe aortic insufficiency or uncorrectable mitral regurgitation
Absolute contraindications
Potentially reversible cause of heart failure or high surgical risk for successful implantation
Neurological deficits impairing the ability to manage device, or lack of psychosocial support or new evolving stroke
Severe multiorgan failure, severe pulmonary hypertension and severely reduced RV function
Active systemic infection or terminal illness (such as metastatic cancer and cirrhosis)
Inability to tolerate systemic anticoagulation and heparin induced thrombocytopenia
Impending renal or hepatic failure or severe pulmonary dysfunction (FEV1 <1 L)

Patient risk factors that are associated with worse outcomes after LVAD implantation or preclude LVAD implantation include deficiencies in nutritional status, hematologic abnormalities, presence of hepatic and renal insufficiency, right ventricular dysfunction, lung disease and neuropsychiatric and psychological considerations [48–50]. A clinical algorithm that takes into account a patient's risk factors is shown in Fig. 27.2. Various composite risk scores have been devised from hemodynamic parameters and measures of end-organ function to help identify predictors of survival and guide patient selection. Examples of these risk scores are the Columbia University/Cleveland Clinic risk factor selection scale (RFSS) [51], The Columbia University/Cleveland Clinic revised screening scale (RSS) [52], the Lietz-Miller Destination Therapy Risk Score (DTRS) [47] and most recently the HeartMate II risk score (HMRS) [53]. Although useful in clinical decision-making, none of the risk scores, except for the HMRS, have been prospectively validated. They are derived from small selected populations and are limited to specific mechanical devices. The HMRS has been prospectively validated and included 1122 patients

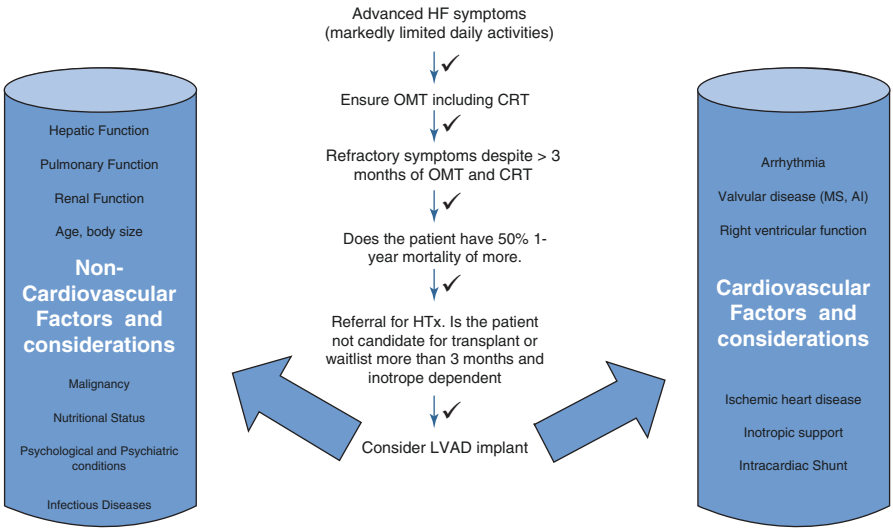


Fig. 27.2 Clinical algorithm to initiate mechanical circulatory support and factors involved in determining outcomes and appropriateness of LVAD implantation. *OMT* optimal medical therapy, *CRT* cardiac resynchronization therapy, *HTx* heart transplant, *MS* mitral stenosis, *AI* aortic insufficiency

who have received HeartMate II as a BTT or DT. The limitation of the HMRS is that clinical trial patient population is not representative of many non-trial patients. Moreover, the applicability of the HMRS to patients undergoing implant of other types of CF devices is not known.

The INTERMACS registry [54] has defined patient profiles which distinguish various categories of risk among the subset of advanced HF patients. The INTERMACS risk levels, Table 27.3**,** range from 1–7 and in general level 1–5 fall under NYHA class IV, with level 1 classifying as the worst state, known as cardiogenic shock or Crash and Burn. Levels 6–7 are patients in the advanced NYHA class III subset and can be viewed as relatively low risk. Patients receiving implantable ventricular assist devices were frequently in profiles 1 and 2 and experienced relatively high perioperative mortality. This lead to the gradual shift towards implanting less sick individuals with INTERMACS profiles level 3–4 as reported in the second INTERMACS report that analyzed 1092 primary LVAD implants including 48 % pulsatile-flow and 52 % CF pumps [55]. An emerging issue in BTT is whether to implant an LVAD before the institution of chronic inotrope support. The vast majority of patients implanted to date have been inotrope dependent. Inotrope dependence is associated with more than 50 % mortality at 6 months [56] and the medical arm in the REMATCH [18] and INTrEPID [19] had 76 % and 89 % mortality at 1-year, respectively. Moreover, earlier implantation, before right ventricular and multiorgan failure, leads to better outcomes. This is a favored strategy for DT. It is also important to realize that poor tolerance of evidence-based pharmacologic therapy, repeat hospitalizations, escalating inotrope or pressor needs and end-organ

Table 27.3 Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) clinical profiles [54]

Level	Definition	Description
1	Critical cardiogenic shock	"***Crash and burn***". Patients with cardiogenic shock despite escalating inotropic support resulting in critical organ hypoperfusion. Definitive intervention needed within hours.
2	Progressive decline	"***Sliding fast"***. Patients with clinical status declining despite being on inotropes or are unable to tolerate inotropic therapy. Definitive intervention needed within few days.
3	Stable but inotrope dependent	***"Dependent stability"***. Patients whose clinical status (blood pressure, organ function) is stable with continuous intravenous inotropic support or a temporary support device but are unable to be weaned off. Definitive intervention during a period of weeks to few months.
4	Resting symptoms	***"Resting symptoms"***. Patient experiences daily symptoms at rest and require high doses of diuretics. Definitive intervention elective within a period of weeks to few months.
5	Exertion intolerant	***"Housebound"***. Patient asymptomatic at rest but is unable to engage with any other activity. May consider for LVAD implantation.
6	Exertion limited	***"Walking wounded"***. Patient with no evidence of fluid overload and is comfortable at rest and with activities of daily living but gets fatigued within the first few minutes of any meaningful activity. May consider for LVAD implantation.
7	Advanced NYHA III	***"Advanced NYHA III"***. Patients without evidence of fluid overload who are living comfortably with meaningful activity limited to mild physical exertion. Advanced HF therapies may not currently be indicated.

Modified from Stevenson et al. [54], © 2009, with permission from Elsevier

dysfunction are more integrated criteria for LVAD than single hemodynamic parameters. In general, outcomes are better for stable patients entering an operative procedure than for subjects who are in extremis.

The effects of LVAD support as a BTT on heart transplantation outcomes have been conflicting in different trials. In the ISHLT registry, patients with pre-heart transplant LVAD fared worse after heart transplantation [57]. This registry did not account for selection bias, era of implant, patient characteristics and other confounding factors. In fact other studies suggested a neutral [58] or favorable [59] effect. Moreover, it has been shown that the HeartMate II® device reduces wait list mortality and improves post-transplant survival as opposed to inotrope therapy and other mechanical assist device therapy [60]. The duration of support with HeartMate II LVAD did not affect early and long-term post-transplant survival when compared to that of conventional transplantation [61, 62]. However, device infections and the increased need for blood transfusions during LVAD support were associated with significant reduction in 1 year and 10 years post-transplant survival [61, 62]. The frequent need for blood transfusions during LVAD support may provoke HLA sensitization, which can impact heart transplant candidacy. Complications other than those listed above did not seem to have significant impact on post-transplant survival in HeartMate II trials [61].

The REMATCH trial, a multicenter study that compared long-term implantation of LVADs with optimal medical management for patients with refractory heart failure, was conducted to test the hypothesis of destination therapy for patients ineligible for transplantation [18]. This trial demonstrated that compared with best medical therapy device implanted patients had an average extension of life of 8 months, of which 3 months were spent in the hospital. This particular trial demonstrated that when patients were appropriately selected, even patients with a futile outlook could achieve clinically meaningful benefits. However, patients with devices were more than twice as likely to develop an adverse event than the medical therapy group and had a higher median number of days spent in and out of the hospital. Thus, at 2 years, only 23 % in the ventricular assist device group were alive compared with 8 % in the medical group. The probability of infection with the device was 28 %; bleeding, 42 %; and device failure, 35 %, requiring device replacement. This early proof-of-concept trial did not result in an aggressive widespread translation into community application because of concerns of cost, lack of device durability, and complications related to infection and thromboembolism.

To date, the only CF-LVAD approved for both BTT and DT is the HeartMate II. The HMII BTT clinical trial was a prospective, multicenter study without a concurrent control group that included 133 patients with end-stage heart failure who were awaiting heart transplantation. The principal competing outcomes were the number of patients bridged to transplantation; who experienced myocardial recovery or continued to be supported while remaining eligible for transplantation at 180 days after LVAD implantation. The principal outcome occurred in 100 patients and the median duration of support was 126 days. The survival rate was 75 % and 68 % at 6 and 12 months, respectively. The therapy resulted in significant improvement in functional status and in quality of life at 3 months after LVAD implantation. Major adverse events included postoperative bleeding, stroke, right heart failure and percutaneous lead infection. Pump thrombosis occurred in two patients. This study resulted in market approval of the HeartMate II as a BTT by the FDA in April 2008 [63]. The pivotal DT trial with the HeartMate II, is the largest published, randomized clinical trial of DT. The trial evaluated the use of the second-generation CF axial pump, the HeartMate II. The study was conducted between March 2005 and May 2007and enrolled 200 patients with advanced HF not eligible for heart transplant at 38 United States hospitals. The trial entry criteria were similar to that of the REMATCH trial. The study randomized patients in a 2:1 fashion; 134 patients received CF axial flow device, the HeartMate II, and 66 patients received the first-generation pulsatile device HeartMate XVE. The study demonstrated that the HeartMate II had a significantly greater percentage of patients who reached the primary endpoint of survival at 2 years, free of disabling stroke and reoperation for pump replacement, compared with the XVE [64]. Survival rates were 68 % and 58 % at 1 year and 2 years, as compared to 55 % and 24 % for the HeartMate XVE, respectively (Fig. 27.3). These results led to FDA approval of HeartMate II® for destination therapy in January 2010.

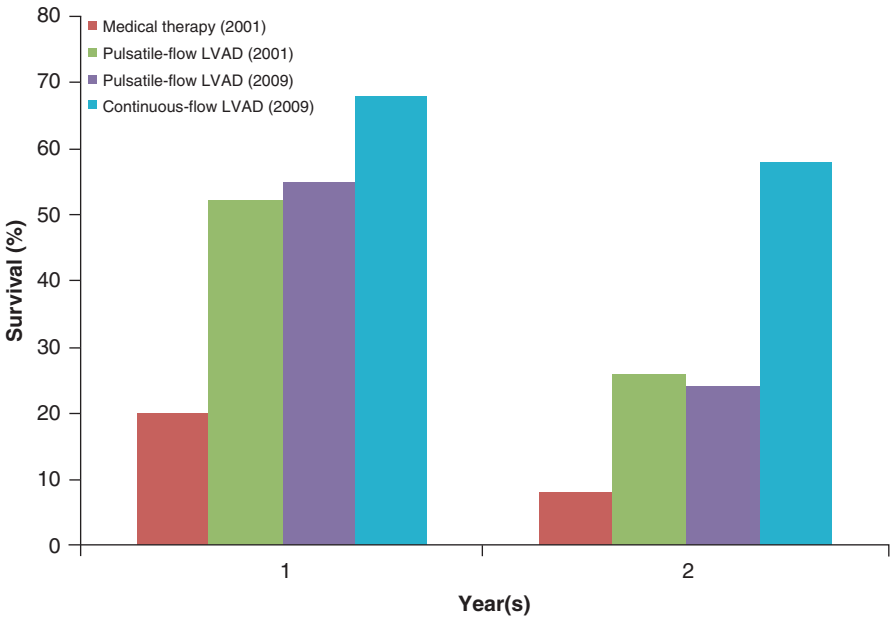


Fig. 27.3 Survival rates in two trials of left ventricular assist devices as a destination therapy. The *bars* labeled 2009 represent data reported by Slaughter et al. [60] and the *ones* labeled 2001 represent data reported in the REMATCH trial [18]

Current State of LVAD Utilization and Quality of Life Post LVAD Implantation

The choice of device largely depends on the indication for which it is being used and the anticipated duration of support. The most common indications for the use of LVADs are in patients with heart failure (BTT, DT or as a bridge to candidacy), cardiogenic shock (post-cardiotomy or post-myocardial infarction or myocarditis) or refractory ventricular arrhythmias. According to the latest INTERMACS annual report, 98 % of LVADs being implanted are second-generation [65]. In addition, the indications for device implantation between January 2009 and June 2010 were BTT (41 %), bridge to candidacy (43 %), DT (13.8 %), bridge to recovery (1.0 %), rescue therapy (0.5 %) and other (0.5 %). The area of biggest change over the previous 2 years was the increase of device implantation as DT. This trend can partly be attributed to the approval of the HeartMate II® in January 2010 as a device for destination therapy in patients deemed not eligible for transplantation. Nearly 30 % of patients receiving implantation as BTT were still on mechanical support at 2 years and 43 % of those patients were no longer listed for transplant after 2 years of mechanical support. Another significant finding of the INTERMACS data is the continued improvement in overall survival with LVAD implantation. The latest reported survival of 79 % at 1 year and 66 % at 2 years among all patients receiving

LVAD support is quite remarkable given the dismal prognosis with best medical therapy in this group of patients. A subgroup analysis of the data showed that patients receiving CF pumps, especially the HeartMate II LVAD, fared even better, with a survival rate of nearly 80 % at 1 year [65, 66]. DT continues to carry a slightly higher risk than BTT therapy. The survival difference in predicted 1-year survival, when adjusted for risk factor prevalence in each group, is approximately 5 %. The small survival difference is likely related to the ability of transplantation for some BTT patients in the event of device related complications [67]. However, it is noteworthy to mention that the mortality rate in patients with INTERMACS level 1 continues to be high.

Despite potential complications, LVADs significantly improved the quality of life (QOL) and functional capacity in patients with advanced HF. QOL in a diseased state is a multidimensional concept and includes aspects of physical, mental and social functioning. The Minnesota Living With Heart Failure Questionnaire (MLHFQ) and the Kansas City Cardiomyopathy Questionnaire (KCCQ) are reliable and validated health status questionnaires specific to patients living with HF [68, 69]. LVAD patients, when surveyed about lifestyle changes, were able to drive, exercise, travel, return to work or school and engage in hobbies [70]. The improvement in QOL can be seen as early as 1 to 3 months after LVAD implantation and is sustained for the duration of support. This QOL improvement surpasses that achieved with adjunctive pharmacologic or cardiac resynchronization therapy in patients with advanced HF [71, 72]. More recently, in BTT and DT patients, the HeartMate II CF device has improved QOL on multiple validated indexes such as the MLHFQ and KCCQ [18, 63]. Patients with HeartMate II LVAD had significantly higher peak VO2 at 6 months when compared with that at 3 months post LVAD implantation [73]. Additionally, there was significant increase in the distance that the patients could walk between baseline (43 m) and 3 months after HeartMate II implantation (292 m) [63]. These improvements were maintained but did not change significantly for the duration of the follow-up period [35]. The impact of different devices on QOL has not been compared directly in clinical trials to date. It is supposed that QOL may be even higher with the newer devices because of their smaller size, higher efficiency and durability and less associated complications. QOL outcome measures have become an integral part of all clinical trials and registries involving LVADs due to the evolution of the mechanical circulatory support devices.

Another emerging aspect is donor heart allocation in the present LVAD era. According to the United Network of Organ Sharing (UNOS), patients who are critically ill (class IA) who could not receive a heart transplant and instead ended up having a LVAD implant as a bridge to transplant, remained classified as class IA for the next 30 days after LVAD implantation. The rationale behind this is that LVAD supported patients remained at high risk for LVAD failure over time. However, this decision was implemented back when pulsatile flow devices were being incorporated. This prioritization has remained even after the emergence of continuous flow LVADs, which are less likely to fail and have produced higher survival rates. Because of that, there is a perception that stable patients are able to ‘jump the list’

ahead of other more critically ill patients and has raised a concern as to whether the UNOS donor heart allocation system in its present configuration is indeed fair [74]. The question that comes to the surface is whether clinically stable LVAD patients should continue to receive prioritization for donor hearts. Dardas et al. proposed that they should not as this action violates the justice principle. There is no utilitarian reason to prioritize stable LVAD patients because transplant outcomes are not superior in this group compared with other class IA and class IB subgroups [75]. In the Eurotransplant system, there is no prioritization for stable LVAD patients unless they develop a device complication [76]. The solution to this problem would perhaps be by adapting a heart allocation score similar to that for end-stage liver disease. Another possibility is to expand the number of prioritization categories matching individual risk profiles [74].

Optimal Anticoagulation Regimen in Patients with LVAD

Patients with axial-flow LVADs develop substantial alterations in their prothrombotic profile and platelet function, which appears to be reversible after the removal of the device and are likely to be responsible for the non-surgical bleeding episodes [77–79]. Warfarin seems to offer a lower thromboembolic risk compared with unfractionated heparin or low molecular weight heparin [80]. There are reports which suggest that some axial-flow LVAD patients may be managed without anticoagulation, for example after major bleeding complications; however, these papers are subject to publication bias as poor outcomes are unlikely to have been reported [81, 82]. Antiplatelet and anticoagulant therapy must be started early, but only after meticulous control of postoperative bleeding has ensued. The use of warfarin (INR target 2–3), in association with aspirin at 81–325 mg/day, or with point-of-care tests titrated antiplatelet therapy to inhibit 70 %, is one strategy that can be used. Although HeartWare targets a higher INR, the target INR for the newer CF devices is in the range of 1.5 to 2.5, beyond which the risk of thrombosis and bleeding escalates [49, 83]. This is because gastrointestinal bleeding (GIB) is more commonly encountered with the newer CF pumps [84]. Although the exact reason for this occurrence is uncertain, one hypothesis implicates the development of acquired von Willebrand (vWF) factor deficiency caused by increased shear stress and reduced pulsatility of these devices with an increased prevalence of arteriovenous malformations (AVMs). An identical constellation of findings is described in Heyde's syndrome, namely, aortic stenosis with acquired vWF deficiency and GIB from AVMs. The rate of GIB ranges between 18–30 %. Importantly, these rates are significantly higher than that described in patients receiving Aspirin and Warfarin for mechanical valve prosthesis [85]. Recurrent bleeding after a first event is not uncommon and ranges between 21–44 %. However, available data suggests that GIB is associated with very low mortality (<1 %) [86, 87]. History of GIB, age, INR and platelet count were found as an independent predictors for GIB in a multivariate analysis. The risk/benefit of reducing or discontinuing anticoagulation should be thoroughly assessed and discussed with the patient. Lowering of the device power and

speed to decrease shear stress may decrease such bleeding episodes but remains to be proven as a viable treatment option. Higher degree of anticoagulation must be targeted in patients with atrial fibrillation, prior thromboembolic events, presence of atrial or ventricular thrombi and if low assist device flow rates of less than 3 L/min are anticipated. Patients who develop heparin-induced thrombocytopenia after LVAD implantation, which is verified by serotonin release assay [88], are at high risk of thromboembolism and should be treated with a direct thrombin inhibitor. Bivalirudin is the preferred agent as its elimination is enzymatic by thrombin and is not dependent on renal or liver functions, which are frequently impaired in patients at the time of LVAD implantation [88].

Impact of Adverse Events on LVAD Outcomes

Despite significant progress, even the latest generation LVADs are burdened by a significant long-term adverse events profile that will increasingly challenge physicians, especially now that LVADs are more frequently used as a destination therapy [89]. Only 30 % of CF-LVAD recipients survive the first year without experiencing a major adverse event. (Fig. 27.4). Below is a brief discussion of the most frequent or debilitating adverse events, their potential causes and future implications.

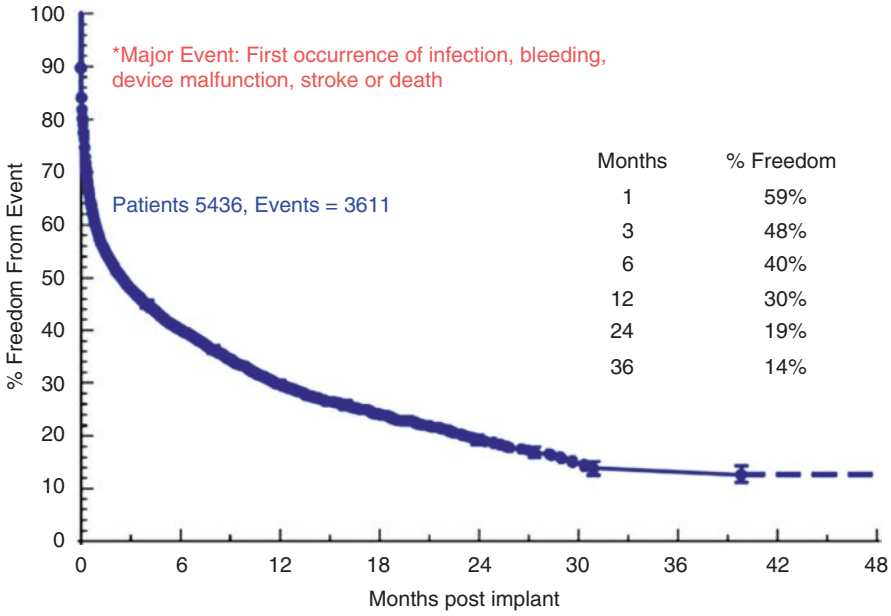


Fig. 27.4 Actuarial freedom from any adverse events as highlighted in figure above in adult primary CF LVADs and BIVADs implanted between June 2006 – June 2012 as DT and BTT. Error bars indicate ± standard error (Adapted from Kirklin et al. [67], © 2013, with permission from Elsevier)

Right Ventricular Failure

Right ventricular failure (RVF) after LVAD implantation is associated with significant morbidity and mortality. INTERMACS classifies severe RVF as those requiring RVAD placement and moderate RVF as those requiring prolonged inotropic support or pulmonary vasodilators. RVF post LVAD is also classified according to the period when it occurs, specifically intraoperative, early or late, i.e., greater than 14 days [90]. INTERMACS has implemented a set of criteria to help standardize the diagnosis of RVF following LVAD implantation. These diagnostic criteria include elevated central venous pressure (CVP) >18 mmHg with a cardiac index less than 2.2 L/min in the absence of elevated left atrial pressure of more than 18 mmHg along with the need for postoperative inotropic support more than 14 days and inhaled nitric oxide more than 48 h [91]. A number of complex mechanisms contribute to RVF in the early postoperative period. These include sudden increases in cardiac output leading to increases in venous return and RV preload; shifting of the interventricular septum towards the LV and the "suck down" effect caused by LV unloading which may subsequently increase RV wall stress; and increased pulmonary vasoreactivity in the setting of cardiopulmonary bypass, blood transfusions and inflammation leading to increased RV afterload [92]. The incidence of RVF ranges from 9–44 % depending on the diagnostic criteria used [93, 94]. Clinically, RVF may result in renal and hepatic dysfunction along with the formation of ascites and lower extremity edema. Reductions in RV stroke volume may dangerously underfill the LV risking the potential for suck down events, ventricular arrhythmias and cardiogenic shock. Not surprisingly, perioperative mortality increases from 19 to 43 % in the setting of RV failure.

Identifying which patients are susceptible to RVF following LVAD implantation has been challenging and is still a subject of ongoing investigation. Patients who require preoperative mechanical cardiac support are at increased risk of RVF. High CVP and CVP/PCWP ratio, decreased cardiac index ≤ 2.2 L/min/m^2, low right ventricular stroke work index ≤ 0.25 mmHg L/m^2 or high PVR have all been identified as potential risk factors for RVF [95]. Patients with multiorgan dysfunction are also at an increased risk for RVF. A preoperative risk score to predict RVF preoperatively and the need for BIVAD has been established by Alturi et al. Through a multivariate regression analysis, the authors show a **C**VP >15 mmHg, severe **R**VF, preoperative **I**ntubation, severe **T**ricuspid regurgitation and a heart rate >100-**T**achycardia (CRITT) carries an OR of 2, 3.7, 4.3, 4.1 and 2, respectively. Using these data, a highly sensitive and easy to use risk score can be performed to determine the need for biventricular support [96]. The RVF risk score (RVFRS) is also a sensitive risk score that can be used to predict RVF and death after LVAD implantation. Risk factors included in the RVFRS are: vasopressin requirements (4 points), aspartate aminotransferase ≥ 80 IU/L (2 points), Bilirubin ≥ 2 mg/dL (2.5 points) and creatinine ≥ 2.3 mg/dL (3 points). The OR for RVF for patients with RVFRS $\leq$3, 4–5, and $\geq$5.5 were 0.49, 2.8 and 7.6, and the 180-day survivals were 90 %, 80 % and 66 %, respectively [94]. RVF is typically treated by adjunctive inotropic support and a

decrease in the pumping power of the LVAD to prevent excessive suction pressure on the interventricular septum. When these measures are insufficient, reoperation for temporary or permanent RVAD support may be required.

Device Malfunction

INTERMACS categorizes device malfunction as pump failure and non-pump failure. Pump failure includes dysfunction of any blood contact part of the device and non-pump failure includes dysfunction of other device components. Pump thrombosis is a rare but potentially devastating complication of LVADs. Making a clinical diagnosis of pump thrombosis can be challenging and may be suggested by abnormal readings from the pump console (gradual or sudden sustained increases in the Power to maintain a preset speed), blood testing for hemolysis (lactate dehydrogenase (LDH) and plasma free hemoglobin), Doppler Echocardiography [97], CT imaging [98] and hemodynamic studies. There is no standardized approach to the management of pump thrombus. Various strategies have been implemented to treat suspected pump thrombus and avoid device exchange, such as using glycoprotein IIb/ IIIa inhibitors, direct thrombin inhibitors, systemic thrombolytic therapy and direct intraventricular delivery of thrombolytics. In the absence of acute hemodynamic compromise, an initial attempt at one of these conservative non-surgical measures is favored, since device exchange for thrombus has been associated with poor outcomes. Starling and his colleagues, in a recent multi-institutional study, have observed an increase in the rate of HeartMate II device thrombosis as compared with pre-approval clinical trial results and clinical experience. The occurrence of confirmed pump thrombosis at 3 months after transplantation has increased from 2.4 % in 2011 to 8.4 % by January 1, 2013. Elevated levels of LDH at 3 months after implantation mirrored that of device thrombosis. The mortality rate among patients who had pump thrombosis and did not undergo heart transplantation or pump replacement was 48.2 % in the ensuing 6 months after pump thrombosis [99].

Stroke

INTERMACS defines stroke as any new, temporary or permanent, focal or global neurological deficit. The HeartWare BTT trial employed the Modified Rankin Scale for evaluation of the degree of residual disability in those patients suffering stroke. Notably, this metric has been included in the primary endpoint of the proposed REVIVE-IT trial. The incidence of stroke in large studies is: ischemic stroke (4–8 %), hemorrhagic stroke (2–11 %), TIA (2–4 %), disabling stroke (3.6–11 %) and death from stroke (3.6–8.5 %). Ischemic strokes are considered to be thromboembolic events from the pump. Hemorrhagic strokes may be due to de novo cerebrovascular bleeds or hemorrhagic conversion of a prior

thromboembolic event. Investigators have recently reported an association between LVAD related blood stream infections and stroke, with a 20-fold elevation in risk for hemorrhagic stroke in a cohort of continuous flow LVAD patients who had a proven blood stream infection [100]. Management of LVAD related stroke presents unique challenges where the need for anticoagulation (AC) in patients suspected of thromboembolism must be balanced by the risk of hemorrhagic conversion. Further, withholding AC for hemorrhagic stroke must be balanced against the risk of pump thrombus. INTERMACS data will inform future guidelines for optimal AC regimens and blood pressure control that will be critical in stroke prevention.

Infection

INTERMACS differentiates between infections not directly related to the device, those associated with the pump itself, percutaneous site infection (PSI), pocket infections and finally sepsis. In the trials, the rates of infections are: PSI (12–32 %), pump pocket infections (2–9 %), and systemic infections (11–36 %) [101]. A recent review of 593 patients entered into the INTERMACS database has summarized the problem, and the findings suggest where improvements may be made. Bacterial pathogens dominate fungal organisms at a ratio of nearly 9:1. Infection presents most commonly in the blood (32 %) or driveline (21 %). There were nearly 2.5 cumulative infections per patient at 18 months, but most occurred within the 3-month perioperative period ($P < .0001$). Fungal infections are generally resistant to treatment and are associated with high mortality [102]. INTERMACS level 1, age older than 60 years, high blood urea nitrogen concentration, diabetes, obesity and need for biventricular support were predictors of infection. Specialists have described the problem of recurrent blood infections as "VADitis" and stress the life-long need for antibiotics. Prevention of device related infection remains a major focus for LVAD centers. General strategies include surgical best practice principles to prevent surgical site contamination. Antibiotic prophylaxis is routinely given before LVAD implantation. Additional strategies to minimize infection risk include tunneling the driveline contralateral to the pump pocket to lengthen the subcutaneous course, with the aim of creating a greater barrier for the passage of bacteria from driveline exit site to pump pocket. Clearly, small flexible drivelines that may be anchored to the skin and the elimination of pump pockets within the abdominal wall may both help to further lower infection incidence. Fully implantable systems utilizing advanced transcutaneous energy transfer systems will ultimately be employed for the patient's convenience and reduced risk of infection. Probably the single most important intervention is adequate pre-discharge patient education for wound care and trauma avoidance. Patients who do not clear their bacteremia after antibiotic administration are considered to have their device infected and the only effective treatment is device replacement or heart transplantation.

Aortic Insufficiency

The development of aortic insufficiency (AI) may impair pump function and has been associated with worse survival [103]. AI was seen more frequently in continuous flow than in pulsatile flow pumps. It is likely that the prevalence of this disorder increases over time. In a multivariate analysis, increases in aortic root size after LVAD were associated with the development of significant AI [104]. Transvalvular pressure is increased in magnitude and duration in continuous flow circulation and it has been postulated that these hemodynamic changes increase in stretch on the valve, pathological remodeling and commissural fusion [105]. With the development of AI, a closed circulatory loop is formed where a portion of LVAD output in the ascending aorta returns back into the device. In this situation, although pump flows are elevated, forward systemic flows are reduced. Serial echocardiographic follow up suggests that AI progresses over time [104]. The clinical spectrum of presentation of severe AI during LVAD support ranges from the asymptomatic patient with elevated LVAD flows to overt heart failure requiring more urgent intervention. It has been suggested that repair may be favorable due to shorter operative time and because bio-prosthetic valves appear to be at risk for degeneration. Recent reports describe a variety of percutaneous techniques to manage AI developing during continuous flow LVAD support, including occlusion devices and Transcatheter Aortic Valve Implantation.

Conclusion and Future Perspective

LVADs have changed the landscape for the treatment of HF and the technology will continue to develop in the foreseeable future. On the horizon are transcutaneously powered LVADs that are specifically engineered to reduce the risk of infections through the elimination of drivelines that exit the skin. Moreover, the risk of bleeding and thromboembolic phenomenon should be greatly reduced with further refinements in pump technologies. As the use of LVADs increases, physicians must be prepared to readily access and manage complications in the post-implantation period. It is speculated that better device selection combined with better patient selection, a multidisciplinary team approach and knowledgeable personnel will produce better outcomes, fewer complications and improved patient survival. Advances in the treatment of advanced HF in past decade have been tremendous and enthusiasm to develop newer therapeutic modalities and approaches continues to emerge.

References

1. Roger VL, Go AS, Lloyd-Jones DM, Adams RJ, Berry JD, Brown TM, et al. Heart disease and stroke statistics – 2011 update: a report from the American Heart Association. Circulation. 2011;123(4):e18–e209. Epub 2010/12/17.

2. McMurray JJ, Petrie MC, Murdoch DR, Davie AP. Clinical epidemiology of heart failure: public and private health burden. Eur Heart J. 1998;(19 Suppl P):P9–16. Epub 1999/01/14.
3. Mann DL. Left ventricular size and shape: determinants of mechanical signal transduction pathways. Heart Fail Rev. 2005;10(2):95–100. Epub 2005/11/01.
4. Backs J, Backs T, Neef S, Kreusser MM, Lehmann LH, Patrick DM, et al. The delta isoform of CaM kinase II is required for pathological cardiac hypertrophy and remodeling after pressure overload. Proc Natl Acad Sci U S A. 2009;106(7):2342–7. Epub 2009/01/31.
5. Libonati JR. Cardiac remodeling and function following exercise and angiotensin II receptor antagonism. Eur J Appl Physiol. 2012;112(8):3149–54. Epub 2011/12/07.
6. Olivetti G, Capasso JM, Sonnenblick EH, Anversa P. Side-to-side slippage of myocytes participates in ventricular wall remodeling acutely after myocardial infarction in rats. Circ Res. 1990;67(1):23–34. Epub 1990/07/01.
7. Chaanine AH, Gordon RE, Kohlbrenner E, Benard L, Jeong D, Hajjar RJ. Potential role of BNIP3 in cardiac remodeling, myocardial stiffness, and endoplasmic reticulum: mitochondrial calcium homeostasis in diastolic and systolic heart failure. Circ Heart Fail. 2013;6(3):572–83. Epub 2013/03/20.
8. Chaanine AH, Jeong D, Liang L, Chemaly ER, Fish K, Gordon RE, et al. JNK modulates FOXO3a for the expression of the mitochondrial death and mitophagy marker BNIP3 in pathological hypertrophy and in heart failure. Cell Death Dis. 2012;3:265. Epub 2012/02/03.
9. Narula J, Haider N, Virmani R, DiSalvo TG, Kolodgie FD, Hajjar RJ, et al. Apoptosis in myocytes in end-stage heart failure. N Engl J Med. 1996;335(16):1182–9. Epub 1996/10/17.
10. The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II): a randomised trial. Lancet. 1999;353(9146):9–13. Epub 1999/02/19.
11. Effect of metoprolol CR/XL in chronic heart failure: Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF). Lancet. 1999;353(9169):2001–7. Epub 1999/06/22.
12. Packer M, Coats AJ, Fowler MB, Katus HA, Krum H, Mohacsi P, et al. Effect of carvedilol on survival in severe chronic heart failure. N Engl J Med. 2001;344(22):1651–8. Epub 2001/06/02.
13. Poole-Wilson PA, Swedberg K, Cleland JG, Di Lenarda A, Hanrath P, Komajda M, et al. Comparison of carvedilol and metoprolol on clinical outcomes in patients with chronic heart failure in the Carvedilol Or Metoprolol European Trial (COMET): randomised controlled trial. Lancet. 2003;362(9377):7–13. Epub 2003/07/11.
14. Pitt B, Zannad F, Remme WJ, Cody R, Castaigne A, Perez A, et al. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators. N Engl J Med. 1999;341(10):709–17. Epub 1999/09/02.
15. Rywik TM. [Summary of the article: Zannad F, McMurray JJV, Krum H et al., for the EMPHASIS-HF Study Group. Eplerenone in patients with systolic heart failure and mild symptoms. N Engl J Med. 2011;364:11–21]. Kardiologia polska. 2011;69(6):631–2. Epub 2011/06/17. Badanie EMPHASIS – eplerenon w lagodnej, skurczowej niewydolnosci serca.
16. Cohn JN, Tognoni G. A randomized trial of the angiotensin-receptor blocker valsartan in chronic heart failure. N Engl J Med. 2001;345(23):1667–75. Epub 2002/01/05.
17. McMurray JJ, Ostergren J, Swedberg K, Granger CB, Held P, Michelson EL, et al. Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function taking angiotensin-converting-enzyme inhibitors: the CHARM-Added trial. Lancet. 2003;362(9386):767–71. Epub 2003/09/19.
18. Rose EA, Gelijns AC, Moskowitz AJ, Heitjan DF, Stevenson LW, Dembitsky W, et al. Long-term use of a left ventricular assist device for end-stage heart failure. N Engl J Med. 2001;345(20):1435–43. Epub 2002/01/17.
19. Rogers JG, Butler J, Lansman SL, Gass A, Portner PM, Pasque MK, et al. Chronic mechanical circulatory support for inotrope-dependent heart failure patients who are not transplant candidates: results of the INTrEPID Trial. J Am Coll Cardiol. 2007;50(8):741–7. Epub 2007/08/21.

20. Fowler MB. Carvedilol prospective randomized cumulative survival (COPERNICUS) trial: carvedilol in severe heart failure. Am J Cardiol. 2004;93(9A):35B–9B. Epub 2004/05/18.
21. Wilson SR, Givertz MM, Stewart GC, Mudge Jr GH. Ventricular assist devices: The challenges of outpatient management. J Am Coll Cardiol. 2009;54(18):1647–59. Epub 2009/10/20.
22. Prothero J, Burton AC. The physics of blood flow in capillaries. I. The nature of the motion. Biophys J. 1961;1:565–79. Epub 1961/09/01.
23. Kamdar F, Boyle A, Liao K, Colvin-adams M, Joyce L, John R. Effects of centrifugal, axial, and pulsatile left ventricular assist device support on end-organ function in heart failure patients. J Heart Lung Transplant. 2009;28(4):352–9. Epub 2009/04/01.
24. Saito S, Westaby S, Piggot D, Dudnikov S, Robson D, Catarino PA, et al. End-organ function during chronic nonpulsatile circulation. Ann Thorac Surg. 2002;74(4):1080–5. Epub 2002/10/29.
25. Burke DJ, Burke E, Parsaie F, Poirier V, Butler K, Thomas D, et al. The Heartmate II: design and development of a fully sealed axial flow left ventricular assist system. Artif Organs. 2001;25(5):380–5. Epub 2001/06/14.
26. Nguyen DQ, Thourani VH. Third-generation continuous flow left ventricular assist devices. Innovations (Philadelphia). 2010;5(4):250–8. Epub 2010/07/01.
27. Hoshi H, Shinshi T, Takatani S. Third-generation blood pumps with mechanical noncontact magnetic bearings. Artif Organs. 2006;30(5):324–38. Epub 2006/05/11.
28. Moazami N, Fukamachi K, Kobayashi M, Smedira NG, Hoercher KJ, Massiello A, et al. Axial and centrifugal continuous-flow rotary pumps: a translation from pump mechanics to clinical practice. J Heart Lung Transplant. 2013;32(1):1–11. Epub 2012/12/25.
29. Garbade J, Bittner HB, Barten MJ, Mohr FW. Current trends in implantable left ventricular assist devices. Cardiol Res Pract. 2011;2011:290561. Epub 2011/08/09.
30. Morshuis M, El-Banayosy A, Arusoglu L, Koerfer R, Hetzer R, Wieselthaler G, et al. European experience of DuraHeart magnetically levitated centrifugal left ventricular assist system. Eur J Cardiothorac Surg. 2009;35(6):1020–7. discussion 7-8. Epub 2009/02/24.
31. Aaronson KD, Slaughter MS, Miller LW, McGee EC, Cotts WG, Acker MA, et al. Use of an intrapericardial, continuous-flow, centrifugal pump in patients awaiting heart transplantation. Circulation. 2012;125(25):3191–200. Epub 2012/05/24.
32. Najjar SS, Slaughter MS, Pagani FD, Starling RC, McGee EC, Eckman P, et al. An analysis of pump thrombus events in patients in the HeartWare ADVANCE bridge to transplant and continued access protocol trial. J Heart Lung Transplant. 2014;33(1):23–34. Epub 2014/01/15.
33. Lindenfeld J, Feldman AM, Saxon L, Boehmer J, Carson P, Ghali JK, et al. Effects of cardiac resynchronization therapy with or without a defibrillator on survival and hospitalizations in patients with New York Heart Association class IV heart failure. Circulation. 2007;115(2):204–12. Epub 2006/12/28.
34. Strueber M, O'Driscoll G, Jansz P, Khaghani A, Levy WC, Wieselthaler GM. Multicenter evaluation of an intrapericardial left ventricular assist system. J Am Coll Cardiol. 2011;57(12):1375–82. Epub 2011/03/19.
35. Pagani FD, Miller LW, Russell SD, Aaronson KD, John R, Boyle AJ, et al. Extended mechanical circulatory support with a continuous-flow rotary left ventricular assist device. J Am Coll Cardiol. 2009;54(4):312–21. Epub 2009/07/18.
36. Birks EJ. Molecular changes after left ventricular assist device support for heart failure. Circ Res. 2013;113(6):777–91. Epub 2013/08/31.
37. Bruckner BA, Stetson SJ, Perez-Verdia A, Youker KA, Radovancevic B, Connelly JH, et al. Regression of fibrosis and hypertrophy in failing myocardium following mechanical circulatory support. J Heart Lung Transplant. 2001;20(4):457–64. Epub 2001/04/11.
38. Ambardekar AV, Walker JS, Walker LA, Cleveland Jr JC, Lowes BD, Buttrick PM. Incomplete recovery of myocyte contractile function despite improvement of myocardial architecture with left ventricular assist device support. Circ Heart Fail. 2011;4(4):425–32. Epub 2011/05/05.

39. Dipla K, Mattiello JA, Jeevanandam V, Houser SR, Margulies KB. Myocyte recovery after mechanical circulatory support in humans with end-stage heart failure. Circulation. 1998;97(23):2316–22. Epub 1998/06/25.
40. Bruckner BA, Razeghi P, Stetson S, Thompson L, Lafuente J, Entman M, et al. Degree of cardiac fibrosis and hypertrophy at time of implantation predicts myocardial improvement during left ventricular assist device support. J Heart Lung Transplant. 2004;23(1):36–42. Epub 2004/01/22.
41. Segura AM, Frazier OH, Demirozu Z, Buja LM. Histopathologic correlates of myocardial improvement in patients supported by a left ventricular assist device. Cardiovasc Pathol. 2011;20(3):139–45. Epub 2010/02/27.
42. Yamada Y, Saito S, Nishinaka T, Yamazaki K. Myocardial size and fibrosis changes during left ventricular assist device support. ASAIO J. 2012;58(4):402–6. Epub 2012/06/29.
43. Dandel M, Weng Y, Siniawski H, Potapov E, Drews T, Lehmkuhl HB, et al. Prediction of cardiac stability after weaning from left ventricular assist devices in patients with idiopathic dilated cardiomyopathy. Circulation. 2008;118(14 Suppl):S94–105. Epub 2008/10/10.
44. Birks EJ, Tansley PD, Hardy J, George RS, Bowles CT, Burke M, et al. Left ventricular assist device and drug therapy for the reversal of heart failure. N Engl J Med. 2006;355(18):1873–84. Epub 2006/11/03.
45. Mancini D, Lietz K. Selection of cardiac transplantation candidates in 2010. Circulation. 2010;122(2):173–83. Epub 2010/07/14.
46. Deng MC, Edwards LB, Hertz MI, Rowe AW, Keck BM, Kormos R, et al. Mechanical circulatory support device database of the International Society for Heart and Lung Transplantation: third annual report – 2005. J Heart Lung Transplant. 2005;24(9):1182–7. Epub 2005/09/07..
47. Lietz K, Long JW, Kfoury AG, Slaughter MS, Silver MA, Milano CA, et al. Outcomes of left ventricular assist device implantation as destination therapy in the post-REMATCH era: implications for patient selection. Circulation. 2007;116(5):497–505. Epub 2007/07/20.
48. Peura JL, Colvin-Adams M, Francis GS, Grady KL, Hoffman TM, Jessup M, et al. Recommendations for the use of mechanical circulatory support: device strategies and patient selection: a scientific statement from the American Heart Association. Circulation. 2012;126(22):2648–67. Epub 2012/10/31.
49. Slaughter MS, Pagani FD, Rogers JG, Miller LW, Sun B, Russell SD, et al. Clinical management of continuous-flow left ventricular assist devices in advanced heart failure. J Heart Lung Transplant. 2010;29(4 Suppl):S1–39. Epub 2010/02/26.
50. Wilson SR, Mudge Jr GH, Stewart GC, Givertz MM. Evaluation for a ventricular assist device: selecting the appropriate candidate. Circulation. 2009;119(16):2225–32. Epub 2009/04/29.
51. Oz MC, Goldstein DJ, Pepino P, Weinberg AD, Thompson SM, Catanese KA, et al. Screening scale predicts patients successfully receiving long-term implantable left ventricular assist devices. Circulation. 1995;92(9 Suppl):II169–73. Epub 1995/11/01.
52. Rao V, Oz MC, Flannery MA, Catanese KA, Argenziano M, Naka Y. Revised screening scale to predict survival after insertion of a left ventricular assist device. J Thorac Cardiovasc Surg. 2003;125(4):855–62. Epub 2003/04/17.
53. Cowger J, Sundareswaran K, Rogers JG, Park SJ, Pagani FD, Bhat G, et al. Predicting survival in patients receiving continuous flow left ventricular assist devices: the HeartMate II risk score. J Am Coll Cardiol. 2013;61(3):313–21. Epub 2012/12/26.
54. Stevenson LW, Pagani FD, Young JB, Jessup M, Miller L, Kormos RL, et al. J Heart Lung Transplant. 2009;28(6):535–41. Epub 2009/06/02.
55. Kirklin JK, Naftel DC, Kormos RL, Stevenson LW, Pagani FD, Miller MA, et al. INTERMACS profiles of advanced heart failure: the current picture. Second INTERMACS annual report: more than 1,000 primary left ventricular assist device implants. J Heart Lung Transplant. 2010;29(1):1–10. Epub 2010/02/04
56. Stevenson LW. Clinical use of inotropic therapy for heart failure: looking backward or forward? Part II: chronic inotropic therapy. Circulation. 2003;108(4):492–7. Epub 2003/07/30.
57. Taylor DO, Edwards LB, Boucek MM, Trulock EP, Aurora P, Christie J, et al. Registry of the International Society for Heart and Lung Transplantation: twenty-fourth official adult heart transplant report – 2007. J Heart Lung Transplant. 2007;26(8):769–81. Epub 2007/08/19.

58. Morgan JA, John R, Rao V, Weinberg AD, Lee BJ, Mazzeo PA, et al. Bridging to transplant with the HeartMate left ventricular assist device: The Columbia Presbyterian 12-year experience. J Thorac Cardiovasc Surg. 2004;127(5):1309–16. Epub 2004/04/30.
59. Aaronson KD, Eppinger MJ, Dyke DB, Wright S, Pagani FD. Left ventricular assist device therapy improves utilization of donor hearts. J Am Coll Cardiol. 2002;39(8):1247–54. Epub 2002/04/17.
60. Hong KN, Iribarne A, Yang J, Ramlawi B, Takayama H, Naka Y, et al. Do posttransplant outcomes differ in heart transplant recipients bridged with continuous and pulsatile flow left ventricular assist devices? Ann Thorac Surg. 2011;91(6):1899–906. Epub 2011/04/26.
61. Healy AH, Baird BC, Drakos SG, Stehlik J, Selzman CH. Impact of ventricular assist device complications on posttransplant survival: an analysis of the United network of organ sharing database. Ann Thorac Surg. 2013;95(3):870–5. Epub 2012/12/12.
62. John R, Pagani FD, Naka Y, Boyle A, Conte JV, Russell SD, et al. Post-cardiac transplant survival after support with a continuous-flow left ventricular assist device: impact of duration of left ventricular assist device support and other variables. J Thorac Cardiovasc Surg. 2010;140(1):174–81. Epub 2010/05/08.
63. Miller LW, Pagani FD, Russell SD, John R, Boyle AJ, Aaronson KD, et al. Use of a continuous-flow device in patients awaiting heart transplantation. N Engl J Med. 2007;357(9):885–96. Epub 2007/09/01.
64. Slaughter MS, Rogers JG, Milano CA, Russell SD, Conte JV, Feldman D, et al. Advanced heart failure treated with continuous-flow left ventricular assist device. N Engl J Med. 2009;361(23):2241–51. Epub 2009/11/19.
65. Kirklin JK, Naftel DC, Kormos RL, Stevenson LW, Pagani FD, Miller MA, et al. Third INTERMACS annual report: the evolution of destination therapy in the United States. J Heart Lung Transplant. 2011;30(2):115–23. Epub 2011/01/11.
66. Starling RC, Naka Y, Boyle AJ, Gonzalez-Stawinski G, John R, Jorde U, et al. Results of the post-U.S. Food and Drug Administration-approval study with a continuous flow left ventricular assist device as a bridge to heart transplantation: a prospective study using the INTERMACS (Interagency Registry for Mechanically Assisted Circulatory Support). J Am Coll Cardiol. 2011;57(19):1890–8. Epub 2011/05/07.
67. Kirklin JK, Naftel DC, Kormos RL, Stevenson LW, Pagani FD, Miller MA, et al. Fifth INTERMACS annual report: risk factor analysis from more than 6,000 mechanical circulatory support patients. J Heart Lung Transplant. 2013;32(2):141–56. Epub 2013/01/29.
68. Green CP, Porter CB, Bresnahan DR, Spertus JA. Development and evaluation of the Kansas City Cardiomyopathy Questionnaire: a new health status measure for heart failure. J Am Coll Cardiol. 2000;35(5):1245–55. Epub 2000/04/12.
69. Rector TS. A conceptual model of quality of life in relation to heart failure. J Card Fail. 2005;11(3):173–6. Epub 2005/04/07.
70. Maciver J, Ross HJ. Quality of life and left ventricular assist device support. Circulation. 2012;126(7):866–74. Epub 2012/08/15.
71. Abraham WT, Fisher WG, Smith AL, Delurgio DB, Leon AR, Loh E, et al. Cardiac resynchronization in chronic heart failure. N Engl J Med. 2002;346(24):1845–53. Epub 2002/06/14.
72. Taylor AL, Ziesche S, Yancy C, Carson P, D'Agostino Jr R, Ferdinand K, et al. Combination of isosorbide dinitrate and hydralazine in blacks with heart failure. N Engl J Med. 2004;351(20):2049–57. Epub 2004/11/10.
73. Kugler C, Malehsa D, Tegtbur U, Guetzlaff E, Meyer AL, Bara C, et al. Health-related quality of life and exercise tolerance in recipients of heart transplants and left ventricular assist devices: a prospective, comparative study. J Heart Lung Transplant. 2011;30(2):204–10. Epub 2010/10/29.
74. Pinney SP. Timing isn't everything: donor heart allocation in the present LVAD era. J Am Coll Cardiol. 2012;60(1):52–3. Epub 2012/05/01.
75. Dardas T, Mokadam NA, Pagani F, Aaronson K, Levy WC. Transplant registrants with implanted left ventricular assist devices have insufficient risk to justify elective organ procurement and transplantation network status 1 A time. J Am Coll Cardiol. 2012;60(1):36–43. Epub 2012/05/01.

76. Komoda T, Hetzer R, Lehmkuhl HB. Destiny of candidates for heart transplantation in the Eurotransplant heart allocation system. Eur J Cardiothorac Surg. 2008;34(2):301–6. discussion 6. Epub 2008/04/15.
77. Crow S, Chen D, Milano C, Thomas W, Joyce L, Piacentino 3rd V, et al. Acquired von Willebrand syndrome in continuous-flow ventricular assist device recipients. Ann Thorac Surg. 2010;90(4):1263–9. discussion 9. Epub 2010/09/28.
78. Geisen U, Heilmann C, Beyersdorf F, Benk C, Berchtold-Herz M, Schlensak C, et al. Non-surgical bleeding in patients with ventricular assist devices could be explained by acquired von Willebrand disease. Eur J Cardiothorac Surg. 2008;33(4):679–84. Epub 2008/02/20.
79. Meyer AL, Malehsa D, Bara C, Budde U, Slaughter MS, Haverich A, et al. Acquired von Willebrand syndrome in patients with an axial flow left ventricular assist device. Circ Heart Fail. 2010;3(6):675–81. Epub 2010/08/27.
80. Copeland H, Nolan PE, Covington D, Gustafson M, Smith R, Copeland JG. A method for anticoagulation of children on mechanical circulatory support. Artif Organs. 2011;35(11):1018–23. Epub 2011/11/22.
81. Pereira NL, Chen D, Kushwaha SS, Park SJ. Discontinuation of antithrombotic therapy for a year or more in patients with continuous-flow left ventricular assist devices. Interact Cardiovasc Thorac Surg. 2010;11(4):503–5. Epub 2010/07/20.
82. Saito S, Westaby S, Piggott D, Katsumata T, Dudnikov S, Robson D, et al. Reliable long-term non-pulsatile circulatory support without anticoagulation. Eur J Cardiothorac Surg. 2001;19(5):678–83. Epub 2001/05/10.
83. Boyle AJ, Russell SD, Teuteberg JJ, Slaughter MS, Moazami N, Pagani FD, et al. Low thromboembolism and pump thrombosis with the HeartMate II left ventricular assist device: analysis of outpatient anti-coagulation. J Heart Lung Transplant. 2009;28(9):881–7. Epub 2009/09/01.
84. Crow S, John R, Boyle A, Shumway S, Liao K, Colvin-Adams M, et al. Gastrointestinal bleeding rates in recipients of nonpulsatile and pulsatile left ventricular assist devices. J Thorac Cardiovasc Surg. 2009;137(1):208–15. Epub 2009/01/22.
85. Cannegieter SC, Rosendaal FR, Briet E. Thromboembolic and bleeding complications in patients with mechanical heart valve prostheses. Circulation. 1994;89(2):635–41. Epub 1994/02/01.
86. Aggarwal A, Pant R, Kumar S, Sharma P, Gallagher C, Tatooles AJ, et al. Incidence and management of gastrointestinal bleeding with continuous flow assist devices. Ann Thorac Surg. 2012;93(5):1534–40. Epub 2012/05/01.
87. Morgan JA, Paone G, Nemeh HW, Henry SE, Patel R, Vavra J, et al. Gastrointestinal bleeding with the HeartMate II left ventricular assist device. J Heart Lung Transplant. 2012;31(7):715–8. Epub 2012/03/20.
88. Zucker MJ, Sabnani I, Baran DA, Balasubramanian S, Camacho M. Cardiac transplantation and/or mechanical circulatory support device placement using heparin anti-coagulation in the presence of acute heparin-induced thrombocytopenia. J Heart Lung Transplant. 2010;29(1):53–60. Epub 2009/10/13.
89. Adzic A, Patel SR, Maybaum S. Impact of adverse events on ventricular assist device outcomes. Curr Heart Fail Rep. 2013;10(1):89–100. Epub 2013/01/15.
90. MacGowan GA, Schueler S. Right heart failure after left ventricular assist device implantation: early and late. Curr Opin Cardiol. 2012;27(3):296–300. Epub 2012/02/14.
91. Holman WL. Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS): what have we learned and what will we learn? Circulation. 2012;126(11):1401–6. Epub 2012/09/12.
92. Patlolla B, Beygui R, Haddad F. Right-ventricular failure following left ventricle assist device implantation. Curr Opin Cardiol. 2013;28(2):223–33. Epub 2013/01/23.
93. Kormos RL, Teuteberg JJ, Pagani FD, Russell SD, John R, Miller LW, et al. Right ventricular failure in patients with the HeartMate II continuous-flow left ventricular assist device: incidence, risk factors, and effect on outcomes. J Thorac Cardiovasc Surg. 2010;139(5):1316–24. Epub 2010/02/06.

94. Matthews JC, Koelling TM, Pagani FD, Aaronson KD. The right ventricular failure risk score a pre-operative tool for assessing the risk of right ventricular failure in left ventricular assist device candidates. J Am Coll Cardiol. 2008;51(22):2163–72. Epub 2008/05/31.
95. Fitzpatrick 3rd JR, Frederick JR, Hsu VM, Kozin ED, O'Hara ML, Howell E, et al. Risk score derived from pre-operative data analysis predicts the need for biventricular mechanical circulatory support. J Heart Lung Transplant. 2008;27(12):1286–92. Epub 2008/12/09.
96. Atluri P, Goldstone AB, Fairman AS, MacArthur JW, Shudo Y, Cohen JE, et al. Predicting right ventricular failure in the modern, continuous flow left ventricular assist device era. Ann Thorac Surg. 2013;96(3):857–63. discussion 63-4. Epub 2013/06/25.
97. Catena E, Milazzo F, Montorsi E, Bruschi G, Cannata A, Russo C, et al. Left ventricular support by axial flow pump: the echocardiographic approach to device malfunction. J Am Soc Echocardiogr. 2005;18(12):1422. Epub 2005/12/27.
98. Mishkin JD, Enriquez JR, Meyer DM, Bethea BT, Thibodeau JT, Patel PC, et al. Utilization of cardiac computed tomography angiography for the diagnosis of left ventricular assist device thrombosis. Circ Heart Fail. 2012;5(2):e27–9. Epub 2012/03/23.
99. Starling RC, Moazami N, Silvestry SC, Ewald G, Rogers JG, Milano CA, et al. Unexpected abrupt increase in left ventricular assist device thrombosis. N Engl J Med. 2013; Epub 2013/11/29.
100. Aggarwal A, Gupta A, Kumar S, Baumblatt JA, Pauwaa S, Gallagher C, et al. Are blood stream infections associated with an increased risk of hemorrhagic stroke in patients with a left ventricular assist device? ASAIO J. 2012;58(5):509–13. Epub 2012/07/24.
101. Holman WL, Kirklin JK, Naftel DC, Kormos RL, Desvign-Nickens P, Camacho MT, et al. Infection after implantation of pulsatile mechanical circulatory support devices. J Thorac Cardiovasc Surg. 2010;139(6):1632–6. e2. Epub 2010/04/07.
102. Nurozler F, Argenziano M, Oz MC, Naka Y. Fungal left ventricular assist device endocarditis. Ann Thorac Surg. 2001;71(2):614–8. Epub 2001/03/10.
103. Toda K, Fujita T, Domae K, Shimahara Y, Kobayashi J, Nakatani T. Late aortic insufficiency related to poor prognosis during left ventricular assist device support. Ann Thorac Surg. 2011;92(3):929–34. Epub 2011/08/30.
104. Cowger J, Pagani FD, Haft JW, Romano MA, Aaronson KD, Kolias TJ. The development of aortic insufficiency in left ventricular assist device-supported patients. Circ Heart Fail. 2010;3(6):668–74. Epub 2010/08/27.
105. Balachandran K, Sucosky P, Jo H, Yoganathan AP. Elevated cyclic stretch alters matrix remodeling in aortic valve cusps: implications for degenerative aortic valve disease. Am J Physiol Heart Circ Physiol. 2009;296(3):H756–64. Epub 2009/01/20.

Chapter 28
Medical Management of the Patient with Chronic Mechanical Circulatory Support

Sunu S. Thomas and Ulrich P. Jorde

Introduction

Continuous flow ventricular assist devices (CF-LVADs) have become a well-established therapeutic option for patients with end-stage heart disease. Whether as a bridge to transplant (BTT) or as destination therapy (DT) in those who are transplant ineligible, mechanical circulatory support has afforded both survival and quality of life benefits to patients with symptoms and hemodynamics refractory to medical therapy. Survival rates of 80 and 70 % at 1 and 2 years post-implant have led to a dramatic rise in both the number of devices in use and the centers implanting them. Indeed, more than 5300 devices have been implanted in the United States over the last 5 years [1].

Current CF-LVADs with Federal Drug Administration (FDA) approval are the *Thoratec HeartMate II* (Pleasanton, CA) and *Heartware HVAD* (Framinghman, MA) (Figs. 28.1 and 28.2). Both devices pump blood from the left ventricle through an inflow cannula and divert it towards the systemic circulation via an outflow graft anastamosed to the ascending aorta. Both share a similar design, with an external system controller serving as the patient-device interface which is linked to the pump via a percutaneous drive line. Both devices are dependent on rechargeable batteries for power. Differences arise in relative size, pump position and mechanism generating continuous flow (See Table 28.1). The HeartMate II weighing 342 g is surgically

S.S. Thomas, MD, MSc, FRCPC (✉)
Harvard Medical School, Heart Failure & Transplant Services, Massachusetts General Hospital, 55 Fruit Street, Bigelow 800, Boston, MA 02114, USA
e-mail: ssthomas@partners.org

U.P. Jorde, MD
Division of Cardiology, Montefiore Medical Center/Albert Einstein College of Medicine, 3400 Bainbridge Avenue, Medical Arts Pavilion, 7th Floor, Bronx, NY 10467, USA
e-mail: ujorde@montefiore.org

H. Eisen (ed.), *Heart Failure*, DOI 10.1007/978-1-4471-4219-5_28

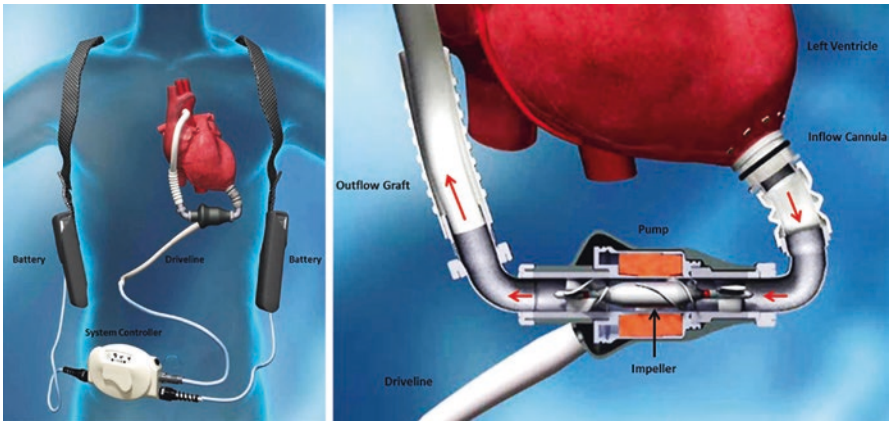


Fig. 28.1 Thoratec HeartMate II Left Ventricular Assist Device (*LVAD*). *Left*; LVAD system complete with external controller connected to the LVAD via a percutaneous drive line with power input from batteries suspended in a holster. The pump is located within the extraperitoneal space. *Right*; Impeller generated unidirectional axial flow *(arrows)* (Images courtesy of Thoratec (Pleasanton, CA))

Fig. 28.2 Heartware HVAD Left Ventricular Assist Device. *Left*; HVAD with system controller and battery packs affixed to patient belt. Note position of HVAD directly opposed to left ventricular apex within the intrapericardial space. *Right Upper*; HVAD components. *Right Lower*; Unidirectional centrifugal flow through the HVAD (Image courtesy of Heartware (Framingham, MA))

Table 28.1 Continuous flow left ventricular assist devices with United States Food and Drug Administration Approval [2–4]

	HeartMate II	HVAD
Manufacturer	Thoratec	Heartware
FDA approval	Bridge to transplant (2008)	Bridge to transplant (2012)
	Destination therapy (2010)	
Clinical trials	HeartMate II BTT trial [2]	ADVANCE BTT trial [4]
	HeartMate II DT trial [3]	
Size	342 g	160 g
Speed range	6000–15,000 rpm	1800–4000 rpm
Mechanism of flow	Axial	Centrifugal
Flow estimation	Less reliable	More reliable

placed within an extraperitoneal pocket. It provides axial flow with its impeller stabilized by inflow and outflow stators within the pump housing. The HVAD is a smaller device weighing approximately 160 g and can be surgically fitted into the intra-pericardial space. Unlike the HeartMate II, its impeller is freely suspended within the pump by the interaction of hydrodynamic and magnetic forces that generate centrifugal continuous flow.

The HeartMate II device has become the predominant CF-LVAD for patients with medically refractory heart failure [5, 6]. In 2008, it was approved by the US Food and Drug Administration (FDA) as a bridge to transplant strategy after pivotal clinical trial data demonstrated 6–12 month survival rates of 75 % and –68 %, respectively, in patients awaiting cardiac transplantation [2]. In 2010, it received FDA approval for destination therapy after the HeartMate II DT trial [3] demonstrated a 2 year survival rate of 58 % in patients with CF-LVADs, and superior outcomes with respect to disabling stroke, reoperation or device replacement as compared to the first generation pulsatile LVADs.

The Heartware HVAD received its FDA approval as a bridge to transplant strategy in 2012 following results of the ADVANCE trial [4]. In comparison to INTERMACS controls, consisting predominantly of HeartMate II LVADs, Heartware HVAD outcomes were non-inferior for the primary endpoint of 180 day survival, transplantation or device explantation for myocardial recovery. In addition, patients with Heartware HVADs had improved functional capacity and overall quality of life [4].

The continuously improving outcomes benefits afforded by LVADs have been somewhat offset by device-related complications. Reports from the INTERMACS registry indicate significant adverse event rates related to bleeding, infection and cardiac arrhythmias [1] that often lead to increased hospitalization and patient morbidity [7]. With pressures to improve patient survival, enhance quality of life and limit hospital readmission rates, optimizing LVAD outpatient medical management has become both a necessity and priority. This chapter will outline current approaches to the care of the ambulatory patient with continuous flow ventricular assist devices.

Goals of Outpatient Management

Prior to discharge, patients undergo extensive preparation for life outside of the hospital with a ventricular assist device [8]. A multidisciplinary team is involved to ensure patient safety and education. This medical team includes cardiac surgeons, heart failure cardiologists, nurse practitioners, physician assistants, physical and occupational therapists, nutritionists and pharmacists. Specific learning objectives include recognition of device alarms, percutaneous lead and abdominal wound care, and safe device operation including power cable and battery exchanges. Additional teaching will inform the patient of potential signs and symptoms of VAD-related complications, and reinforce compliance with medications and healthy heart lifestyles standard to their pre-device heart failure management. Only following an education program, and often requiring successful completion of an examination, are patients deemed safe for hospital discharge either to a home environment or rehabilitation center.

Ambulatory Clinical Assessment and Management

Regular outpatient follow-up ensures the longitudinal assessment of patient status, evaluation of appropriate device function, screening for VAD-related complications and optimization of medical therapy. Additional studies including the 6-min walk test, cardiopulmonary exercise testing, echocardiography and right-heart catheterization may provide further indices of functional capacity and overall myocardial function. Accordingly, the clinical assessment may be divided into a thorough examination of patient and device.

LVAD Focused Patient History

A clinical history will attempt to reveal signs and symptoms of volume overload, including fatigue, dyspnea, orthopnea, paroxysmal nocturnal dyspnea, pedal edema and worsening abdominal girth. Potential LVAD-related complications may be elicited from a history of fever, jaundice, discolored urine, transient neurological deficits, bleeding, defibrillator discharges or audible LVAD alarms. Additional history may focus on a review of medications and patient compliance, dietary discretion, quality of life and caregiver fatigue.

Physical Examination

Physical examination begins with a measurement of baseline and orthostatic vitals. A palpable pulse may not reliably be present in the CF-LVAD patient depending on the degree of mechanical unloading, aortic valve opening and intrinsic myocardial

contractility. As such, heart rate and rhythm are typically derived from a traditional electrocardiogram. Measurement of an auscultatory blood pressure using a sphygmomanometer may also prove difficult in the absence of pulsatility. In such patients, a Doppler probe may be used to signal a blood pressure reading. Once the brachial artery is localized using the Doppler, the blood pressure cuff is inflated until the signal is no longer audible. The blood pressure is recorded at which point the signal returns with cuff deflation. However, care must be taken in LVAD patients with a pulse as the Doppler recording may in fact represent a systolic blood pressure rather than the assumed mean [9].

Measurement of jugular venous distension, the presence of c-v waves or a Kussmaul's sign may be indicative of elevated right-sided filling pressures due to right ventricular dysfunction or frank volume overload.

Precordial auscultation should reveal a continuous LVAD hum with superimposed first (*S1*) and second (*S2*) heart sounds, the latter predominantly arising from pulmonic valve closure with potential contribution from the aortic valve depending upon the frequency and degree of its opening. Low frequency heart sounds including an S3 or S4 may prove challenging to auscultate over the LVAD hum. Systemic perfusion may be derived from the relative warmth of the peripheral extremities.

A respiratory exam including measurement of ambient oxygen saturation and auscultation of the chest for potential adventitious sounds may be followed with an examination of the abdomen for ascites, hepatomegaly or jaundice suggestive of liver congestion or hemolysis. A rectal exam may be necessary if a clinical history elicits concern for melena or frank blood per rectum. The key component of the abdominal exam is assessment of the percutaneous driveline, its position, securement and the healing status of its exit site. Discharge, purulence, or palpable tenderness along the driveline's intra-abdominal course should heighten the suspicion for an infection.

Neurological examination may yield potential deficits arising from a cerebral bleed or embolic event to which the LVAD patient is vulnerable. Assessment of body mass index (BMI) may serve as a marker of nutritional status and cardiac transplant eligibility.

LVAD Interrogation: Thoratec HeartMate II

LVAD parameters can be assessed once the patient connects their system controller to a power base unit (PBU). The initial PBU display provides a table of parameter readings logged in chronological order (See Fig. 28.3). Device alarms and temporal trends of LVAD flow, pulsatility index (PI) and pump power may provide important clues to device function and patient clinical status.

Power, the product of the voltage and current applied to the motor, is directly measured by the LVAD. Normal power for the HeartMate II LVAD may range from 5 to 7 Watts. Higher power readings may reflect greater demand from faster device

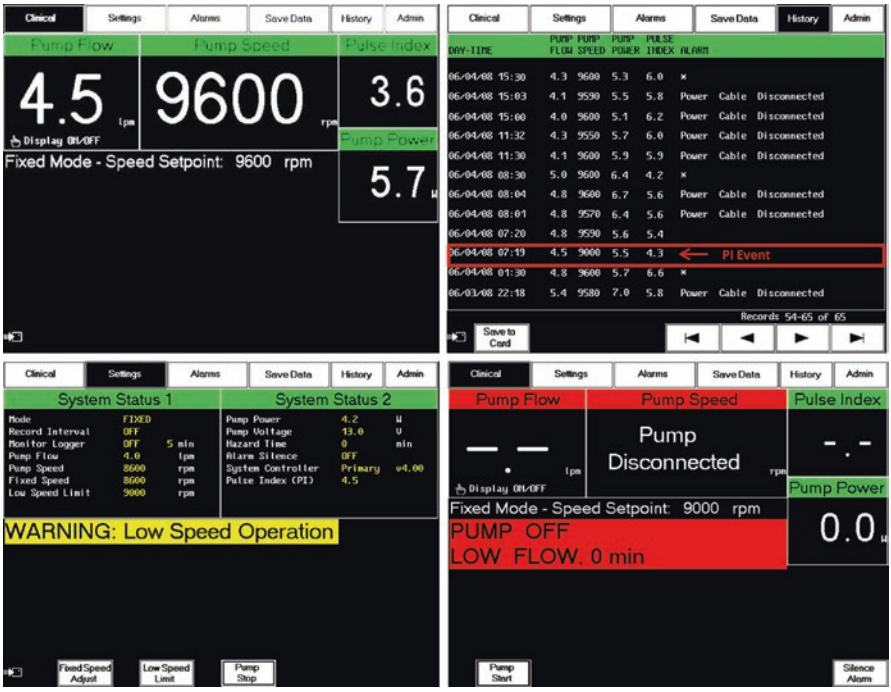


Fig. 28.3 HeartMate II Monitor Display Screens. *Upper left panel*; Power base unit (*PBU*) display demonstrating normal values for pump speed, flow, power and pulsatility index (*PI*). *Upper right panel*; PBU display detailing device speeds, power and pulsatility index over time. The highlighted PI event is notable for a speed drop from 9600 rpm to the low speed limit set at 9000 rpm. *Lower left panel*; Low speed alarm triggered if the device operates at a speed at least 200 rpm slower than the low speed limit. In this instance, the LVAD speed is 8600 rpm despite a low speed limit of 9000 rpm. *Lower right panel*; Red heart alarm display resulting from a pump stoppage, low flow (< 2.5 L/min) or disconnection of the percutaneous lead (Modified and courtesy of Thoratec (Pleasanton, CA))

speeds. However, sustained power spikes of greater than 10–12 Watts at baseline speed may suggest intermittent resistance to flow from a developing device thrombosis.

Flow is an estimated value derived from device speed and consumed power. As such, higher flow values may be confounded by conditions (i.e. device thrombosis) that result in increasing power requirements but not greater pump flow.

The PI displayed on the power module represents the average magnitude of each flow pulse over a 15 s interval of time. A low PI (<3.0) may arise from conditions related to poor left ventricular preload, including excessive unloading from accelerated device speeds, hypovolemia, functional mitral stenosis, severe pulmonary hypertension, right ventricular failure or cardiac tamponade. In contrast, higher PI values may reflect enhanced contractility indicative of myocardial recovery or alternatively, high left ventricular preload states resulting from volume overload or inadequate mechanical unloading due to slower device speeds.

A "PI event" refers to a sudden change in pump flow pulsatility of at least 45 % of the PI averaged over the preceding 15 s interval. PI events may be attributed to significant orthostasis exaggerated by hypovolemia or vasodilation, or arrhythmias leading to poor ventricular preload. They may also arise from "suction events" due to transient septal contact with the inflow cannula, or from acute proximal device occlusion. In response to a PI event and assuming a suction event, the HeartMate II will automatically slow down to a preset lower speed to improve preload conditions (See Fig. 28.4). Initial clinical management of a PI event entails optimization of ventricular preload conditions, clinical reassessment with slower device speeds and echocardiography to assess ventricular chamber size.

Red heart alarms indicate critically low pump flow and/or pump stoppage either representing mechanical failure of the pump itself or, more commonly, malfunction or disconnection of the percutaneous driveline and/or controller circuits. Such events should prompt a thorough evaluation of the device with inputs from the manufacturer and the LVAD care team including cardiac surgeons and heart failure specialists.

LVAD Interrogation: Heartware HVAD

The Heartware HVAD monitor also displays pump speed and power. Flow is reported with very good precision using software that takes the patient's current hematocrit into account. In addition, flow is presented as a pulsatility waveform. With the HVAD, pulsatility is measured as the difference between the peak and trough of the flow waveform. Optimal pump flow requires a waveform trough and calculated pulsatility to each be greater than 2 l per minute. The relationship between device speed, the magnitude and pattern of waveform pulsatility, and LVAD flow is depicted in Fig. 28.5. Highlighting the dynamic relationship between patient clinical status and device function. As demonstrated, faster device speeds result in higher LVAD flow and therefore, greater mechanical unloading. However, excessive LVAD speed may unduly unload the ventricle. This may lead to reduced pulsatility and smaller ventricular chamber sizes that are vulnerable to suction events and possible device occlusion with complete cessation of flow. As such, an understanding of HVAD waveform analysis can facilitate the optimization of device-based patient care. In addition, the HVAD monitor may display critical alarms and provide a differential diagnosis of their potential etiologies.

Investigations

Routine laboratory tests measured during an LVAD clinic visit typically consist of a measured hematocrit, electrolytes, creatinine and blood urea nitrogen (BUN). Anticoagulation targets may be adjusted according to device and patient-specific

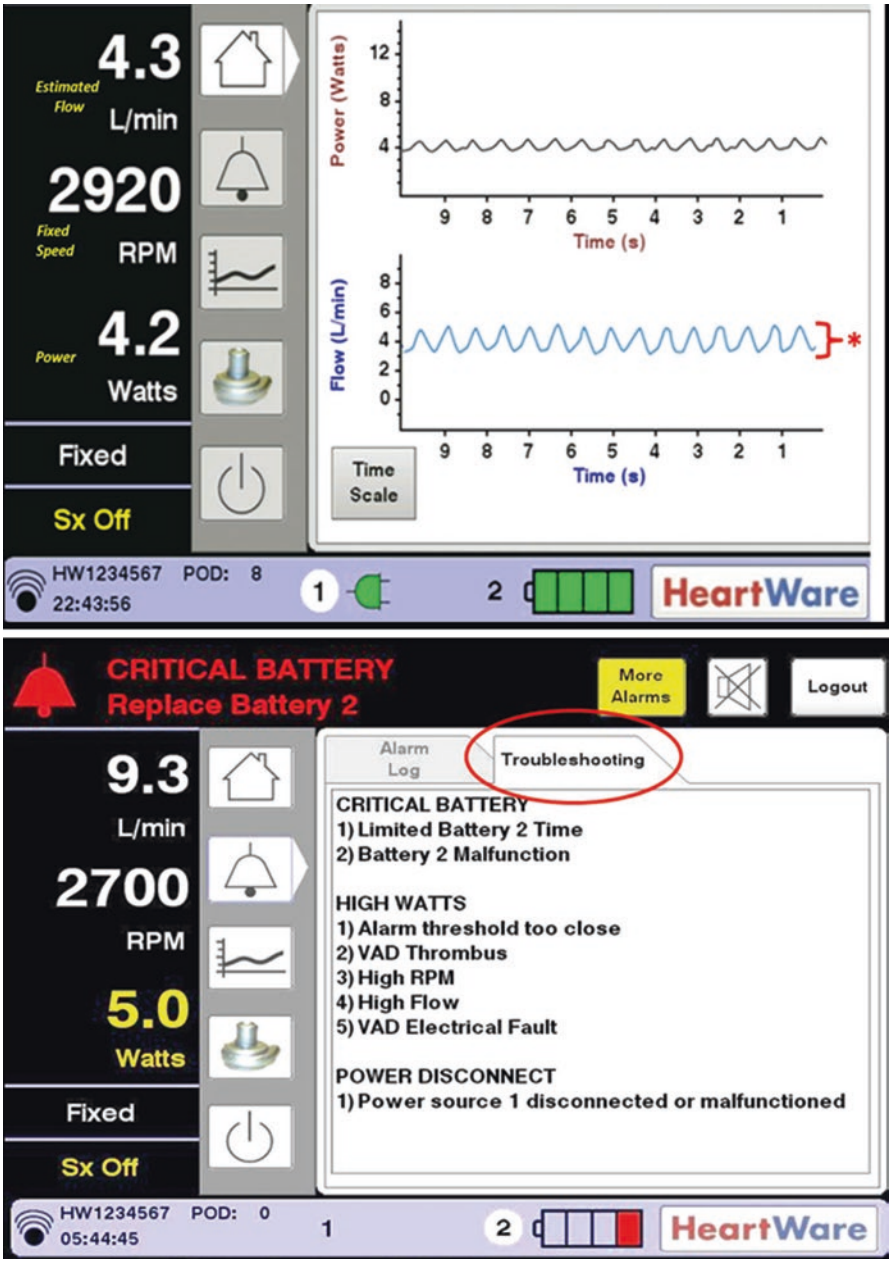


Fig. 28.4 Heartware HVAD monitor display screens. *Upper*; Normal HVAD Power Base Unit (*PBU*) display demonstrating fixed pump speed, estimated flow and device power. Normal flow waveforms with a minimum trough flow and its difference from peak greater than 2 L/min (*). *Lower*; HVAD PBU display screen demonstrating a red heart alarm due to a critical battery issue. The troubleshooting tab provides a differential diagnosis underscoring each of the three potential red heart alarm triggers (critical battery, high watts and power disconnect) (Image modified and courtesy of Heartware (Framingham, MA))

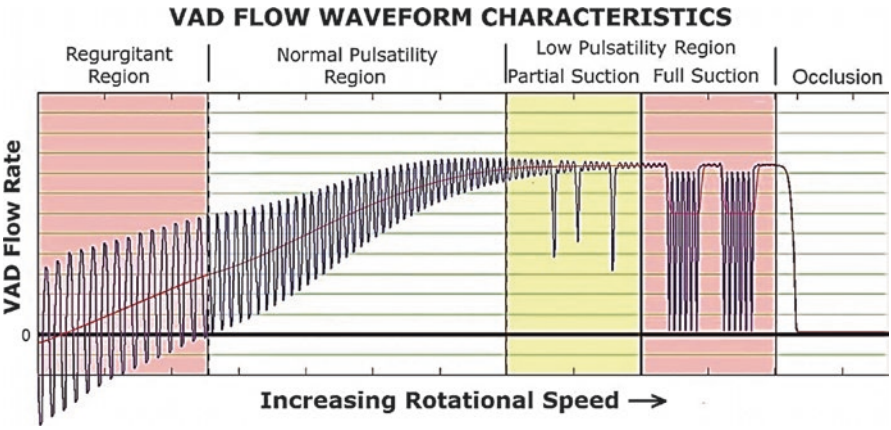


Fig. 28.5 Relationship between Heartware HVAD flow rate, device speed and pulsatility. Faster HVAD speeds result in higher LVAD flow rates and lower pulsatility from greater mechanical unloading. Partial and full suction events, characterized by both waveform inversion and their magnitude of deflection, can arise if speeds are increased beyond permissive ventricular loading conditions and may eventually lead to cessation of pump flow from device occlusion (Image courtesy of Heartware (Framingham, MA))

international normalized ratio (INR) goals. Serum lactate dehydrogenase (LDH) may be used as an important marker of hemolysis. Clinical suspicion for device thrombosis should also prompt testing for plasma free and urine hemoglobin, haptoglobin levels and reticulocyte counts [10]. Abnormal cardiac biomarker measures, such as brain natriuretic peptide (BNP) or troponin, may suggest myocardial strain from elevated filling pressures, inadequate mechanical unloading or infarction.

Chest and abdominal x-rays provide important clues related to LVAD inflow cannula position, outflow graft bend relief status and the integrity of system controller wires.

A transthoracic echocardiogram should be undertaken at routine intervals during follow-up or with any change in clinical status [11]. A baseline echocardiogram offers invaluable information related to cardiac structure and hemodynamics following LVAD implantation. Prior to discharge, a ramp echocardiogram is often performed to assess the change in left and right ventricular dimensions and severity of valvular regurgitation across a range of device speeds. Although a validated approach with prognostic evidence is lacking, there is general consensus that the optimal device speed refers to that which ensures the adequate decompression of the left ventricle while maintaining the interventricular septum in mid-position, minimizing mitral regurgitation and preserving right ventricular size and function. During subsequent clinical follow-up, echocardiographic comparisons of these indices or the presence of a device-related complication (e.g. thrombus, aortic insufficiency) may account for changes in clinical status, and suggest the need for further tailoring of medical therapy or adjustment of LVAD parameters.

Medical Therapy

Heart Failure

Volume overload may arise in the LVAD patient due to inadequate diuresis, medical or dietary non-compliance, right ventricular failure or ineffective mechanical unloading. Therapy entails counseling and optimization of diuretics and device parameters. There is general consensus that chronic heart failure management, including beta-blockers, angiotensin converting enzyme inhibitors or angiotensin blockers, and aldosterone antagonists be re-initiated following LVAD implantation [11]. Whether such therapies alter the natural history of the right or mechanically supported left ventricle in all LVAD patients remains to be clarified. However, there is evidence that amongst select individuals, namely younger patients with non-ischemic cardiomyopathies of short (< 3 months) duration, maximally tolerated neurohormonal blockade with adjunctive mechanical support may facilitate myocardial recovery [12]. Previous studies demonstrated recovery rates ranging from 1 to 13 % amongst LVAD patients supported with variable device types and medical therapies [13–15].

The Harefield protocol [12] was the first to mandate a two phase strategy in which patients with dilated non-ischemic cardiomyopathies follow a strict neurohormonal regimen of lisinopril 40 mg daily, carvediolol 25 mg three times daily, spironolactone 25 mg daily, digoxin 125 μg daily and losartan 100 mg daily to promote reverse ventricular remodeling following placement of a HeartMate II LVAD. Patients were maintained on this protocol until which time their left ventricular end diastolic dimension was less than 60 mm when measured at the lowest LVAD speed of 6000 rpm for 15 min. Subsequently, in the second phase of the protocol, patients were given clenbuterol, a sympathomimetic amine with β2 agonist properties, with the substitution of the non-selective beta-blocker, carvedilol, with the β1 antagonist, bisoprolol. It has been proposed that the addition of clenbuterol promotes physiologic myocardial hypertrophy. With this strategy, 63 % of patients underwent LVAD explantation after an average of 286 days of mechanical support with normalization of filling pressures, ejection fraction and an 83 % survival without recurrent heart failure at 1 and 3 years following device removal [16].

More recently, the Montefiore three-step cardiac recovery protocol, involving echocardiography, cardiopulmonary stress testing and right heart catheterization, demonstrated normalization of cardiac function in 24 % of LVAD patients with a device explantation rate of 14 % [17, 18]. Myocardial recovery did not require clenbuterol and was achieved using the combination of neurohormonal blockade and continuous flow mechanical support.

Blood Pressure Management

Current consensus recommends a mean blood pressure of less than 80 mmHg for patients with CF-LVADs [11]. Heart failure medications, such as beta blockers and renin-angiotensin-aldosterone system antagonists are the preferred first line agents to achieve a normotensive LVAD state [11]. Higher systemic pressures have anecdotally been associated with an increased propensity for intracranial bleeding. Pressure-dependent long term outcomes, particularly in DT LVAD patients, merit further investigation.

Antithrombotic Therapy

CF-LVADs require both anticoagulation and antiplatelet therapy to reduce the risk of device thrombosis and other thromboembolic events. Coumadin is initiated in the post-operative state once hemostasis has been achieved. INR targets vary according to LVAD device (2.0 ± 0.5 for HM II and 2.0–3.0 for Heartware) and their relative thrombotic risk [10]. This range bears clinical significance as an INR < 1.5 has been associated with an increased risk of thromboembolism in HeartMate II patients, whereas hemorrhagic event rates were reportedly higher with an INR > 2.5 [19]. In practice, however, this may vary according to institutional experience and individual patient history with respect to bleeding and thrombosis.

All LVAD patients should receive daily aspirin (81–325 mg). Some institutions may also add dipyridamole 75 mg three times daily to their antiplatelet regimen. Heartware HVAD patients should be assessed for aspirin resistance using Verifynow, a P2Y12 resistance assay. For aspirin non-responders, combination therapy with clopidogrel or dipyridamole may be necessary.

Adjuvant Medical Therapy

Particular patients may require specific medical therapies given their VAD-related complications, including anti-arrhythmic agents for ventricular arrhythmias, chronic suppressive antibiotic therapy for drive-line infections and pulmonary vasodilators for right ventricular dysfunction.

LVAD-Related Complications

Despite improved survival outcomes with device therapy, LVAD complications remain a significant source of patient morbidity and healthcare burden [20]. The following section will elaborate upon common complications related to CF-LVADs and their current management strategies.

The Hemostatic Conundrum: Bleeding and Thrombosis

Bleeding

In both clinical trials and registry data, bleeding constitutes the greatest complication burden to patients with CF-LVADs. Patients are at significant risk for bleeds ranging from epistaxis and gastrointestinal (GI) bleeding to fatal intracerebral hemorrhage. The incidence of hemorrhagic strokes in the HeartMate II BTT, DT and Heartware ADVANCE trials has ranged from 2 to 11 % with annual event per patient rates as high [2–4].

However, the vast majority of bleeding complications with CF-LVADs arise from GI bleeding. Some centers report an incidence of 19–23 % in their HeartMate II patient population with independent predictors consisting of thrombocytopenia, an elevated INR, hypertension and a prior history of GI bleeding source [21–23]. Thrombotic and bleeding complications amongst HeartMate II patients have respectively been reported to account for 9 and 29 % of hospital readmissions [7].

CF-LVAD patients predisposed to the development of arteriovenous malformations [23, 24] in a manner similar to Heyde's syndrome in which high shear stress across a stenotic aortic valve is associated with angiodysplasia within the GI tract, although it is uncertain whether new AVMs develop or existing AVMs bleed because of anticoagulation and the bleeding diathesis induced by CF-LVADs [25]. Specifically, continuous flow through the LVAD pump may lead to an acquired Type IIa von Willebrand syndrome through the loss of high molecular weight multimers of von Willebrand factor (vwf) [26–28]. Occurring as early as within 1 day following CF-LVAD implantation [27], the syndrome may lead to an age-dependent increase in mucosal bleeding [28]. Reversibility of the syndrome was evidenced by vwf restoration following device removal or cardiac transplantation [28, 29]. Yet, bleeding does not occur in all CF-LVAD patients despite ubiquitous vwf deficiency and further study is needed to prospectively identify those patients who may be free of thrombosis with minimal or no anticoagulation.

Management of a bleed typically begins with discontinuation of anticoagulation and antiplatelet therapies, blood transfusions when deemed necessary, initiation of proton-pump inhibitors and consultation with gastroenterology specialists. Investigations include fecal occult blood tests to confirm melena and imaging modalities such as upper GI endoscopy, colonoscopy, push enteroscopy, mesenteric angiography, tagged red blood cell scans or pill capsule endoscopy to localize and potentially treat a bleeding source [23, 30, 31]. However, non-focal GI bleeding may occur in a subset of patients despite diagnostic efforts creating a management dilemma. Studies have begun to explore novel therapies including the somatostatin analogue, octreotide; Factor VIII/von Willebrand factor replacement therapy using Humate P; and even adrenaline as a means of increasing pulsatility to address the presumed culprit of continuous flow [21, 32, 33].

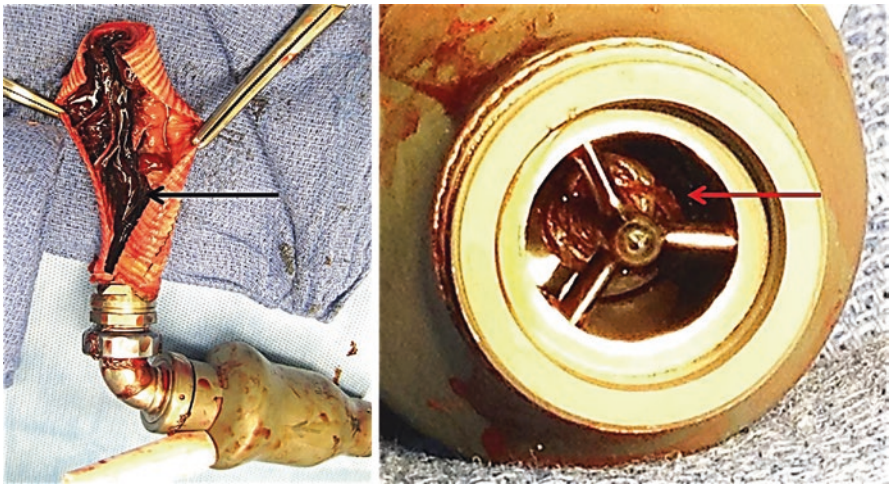


Fig. 28.6 VAD-Related Thrombosis. Clot within the outflow graft (*left*; *black arrow*). In situ device thrombus (*right*; *red arrow*) (Images courtesy of Dr. Hiroo Takayama, Division of Cardiothoracic Surgery, Columbia University Medical Center)

Device Thrombosis

Thrombus within the pump or the outflow graft increases the risk for systemic embolization and may lead to inadequate ventricular unloading or pump failure (See Fig. 28.6). The incidence is not trivial with an initially reported rate of occurrence of 2 [2] and 4 % [3] in the HeartMate BTT and DT trials. It is noteworthy that criteria for device thrombosis were quite rigid in the clinical trials. We believe that clinically relevant device thrombosis may occur in up to 10 % of patients and recent preliminary reports from the ADVANCE-CAP study [34] and the FDA report for Heartware HVAD approval support this contention.

Pump thrombosis may arise from multiple factors including inadequate anticoagulation, malposition of the inflow cannula, intrinsic hypercoagulability, ingestion of residual clot from the cardiac chambers or from imperfections of the impeller. Frequency of aortic valve opening and device flow have been proposed as plausible risk factors for pump thrombosis [35]. Closure of the aortic valve with faster speeds ensures that blood flows *in series* from the ventricle into the pump ensuring maximal flow through the device. On the other hand, aortic root washout may be suboptimal in this setting. In contrast, LVAD flow may be diminished when blood *flows in parallel* via both the pump and the left ventricular outflow tract when the aortic valve is permitted to open although this situation permits optimal root washout. Ultimately, such hypotheses will have to be prospectively investigated.

Device thrombosis may initially present with or without of signs and symptoms of worsening heart failure due to inadequate mechanical unloading. Clinical markers of hemolysis including jaundice or icterus, and laboratory

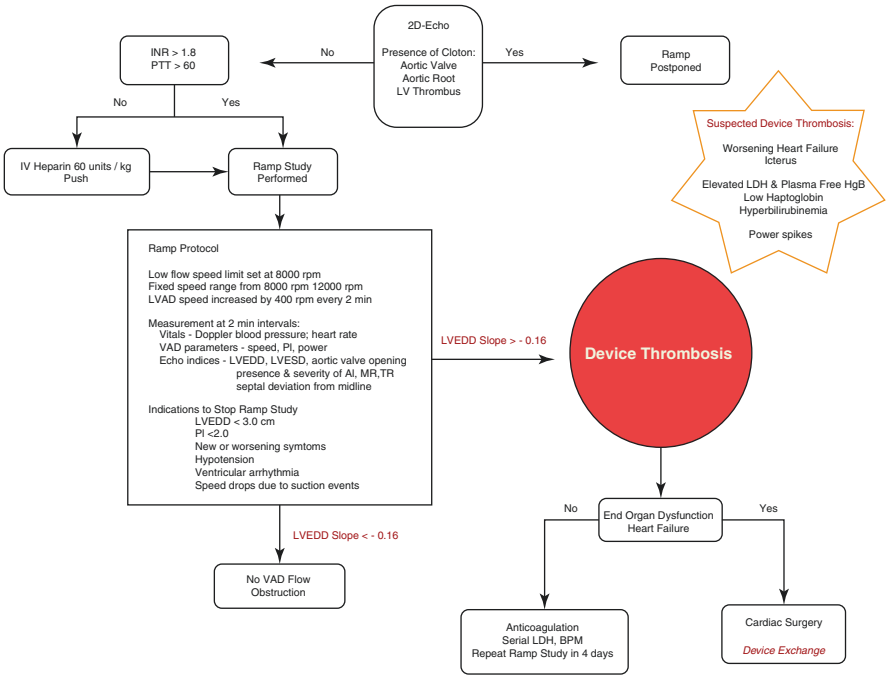


Fig. 28.7 Diagnostic algorithm for device thrombosis using the Columbia Ramp Protocol (Modified from Uriel et al. [36])

measures such as an elevated plasma free hemoglobin, low haptoglobin or the presence of hemoglobinuria are suggestive of red blood cell lysis due to obstruction-related non-laminar flow through the device. Moreover, a serum level of lactate dehydrogenase (LDH) greater than three times normal has been found to have a specificity of 90 and a 100 % sensitivity for a device thrombosis [36]. Interrogation of the system controller may further reveal episodes of sustained power spikes. Echocardiographic findings of an unloaded ventricle including increased myocardial contractility, ventricular dilatation, changes in Doppler flows or worsening mitral regurgitation may also suggest impairment of LVAD function [37]. In the presence of a high pre-test likelihood of device thrombosis, e.g. LDH greater than three times normal, the Columbia Ramp protocol can be used to quantify the relative change in left ventricular dimension with changing LVAD speeds (See Fig. 28.7). The slope derived from the linearization of this relationship may be used to noninvasively identify device thrombosis [36]. In this study, each patient with a positive ramp study and evidence of end-organ dysfunction, e.g. renal failure, proceeded to device exchange with subsequent intra-operative confirmation of pump thrombosis.

Management of Device Thrombosis

Initial management of an in situ pump thrombosis entails aggressive anticoagulation typically with intravenous heparin. The use of GPIIa/IIIb inhibitors [38] and intraventricular thrombolytics [39] have demonstrated modest success but have frequently been limited by potentially fatal hemorrhagic complications. Increasing LVAD speed may also be considered as a strategy to overcome a hemodynamically obstructive pump thrombosis. However, this carries the theoretical risk of systemic LVAD clot embolization. Ultimately, symptom severity and signs of end-organ damage indicative of poor systemic perfusion often requires reoperation for device exchange.

A subset of patients with HeartMate II LVADs implanted between February 2010 and April 2012 may be at risk for a bend relief disconnect [40, 41]. The bend relief refers to the polytetrafluoroethylene tubing that sheathes the proximal outflow graft at its insertion point with the pump. Detachment renders the underlying outflow graft susceptible to malformation, damage and potential obstruction from kinking or in situ thrombus formation. Patients may present with features of hemolysis and symptoms of heart failure due to outflow impairment. The incidence of full and partial disconnection has been reported to be as high as 11 and 23 % at Columbia University Medical Center for LVADs implanted during this period. Anterior-posterior abdominal x-rays facilitate the diagnosis and treatment may require surgical correction (See Fig. 28.8). However, design modifications following a US FDA Class 1R recall in April 2012 should obviate this complication for HeartMate II LVADs produced after this date.

Aortic Insufficiency

The de novo development of native valve aortic insufficiency (AI) has gained greater recognition as an acquired complication with long-term device use. Mild to moderate AI has been reported by several groups to have a prevalence of 25 % after 1 year of support [42–44]. In the presence of AI, blood initially pumped by the LVAD into the ascending aorta regurgitates back into the left ventricle rendering the device inefficient. Multiple risk factors have been associated with AI development including patient age, duration of LVAD support, as well as aortic root diameter. In addition, failure of the aortic valve to open during LVAD support has been associated with AI and its progression [43–45]. Leaflet stasis arising from aortic valve closure can predispose to commissural fusion and consequent malcoaptation leading to valvular incompetence [46]. However, consensus is lacking in regards to the ideal LVAD setting to ensure appropriate mechanical unloading and frequency of aortic valve opening as lower speeds required to accomplish this may be associated with a higher frequency of device thrombosis.

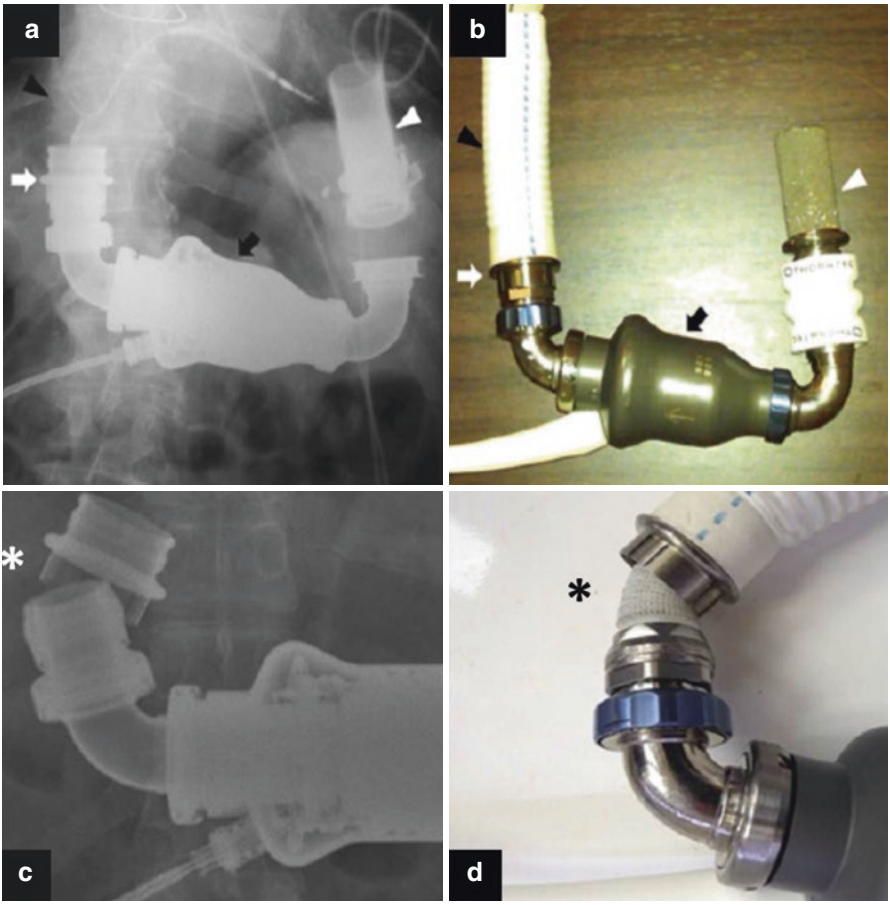


Fig. 28.8 HeartMate II bend relief disconnect. Normal bend relief position (*white arrow*) at its insertion point between the outflow graft (*black arrowhead*) and the LVAD pump (*black arrow*) as demonstrated by an abdominal x-ray (**a**) and photo (**b**). Inflow cannula marked by *white arrowhead*. Abdominal x-ray (**c**) and photo (**d**) of a full bend relief disconnection [40]

AI presentations may range in clinical severity from the asymptomatic to heart failure or frank cardiogenic shock [47]. Diagnosis and the quantification of AI severity typically require echocardiography. Right heart catheterization may provide additional hemodynamic data regarding the degree of decompensation and may facilitate LVAD speed adjustments and tailored medical therapies using inotropes, vasodilators and diuretics. Ultimately, however, definitive management may require invasive correction of the valve, particularly for destination therapy patients for whom cardiac transplantation is not an option. The surgical techniques typically employed for pre-existing AI during initial LVAD implantation may also be considered for de novo AI correction. These include central aortic valve repair using a "Park" stitch, or definitive left ventricular outflow tract closure by a pericardial disk

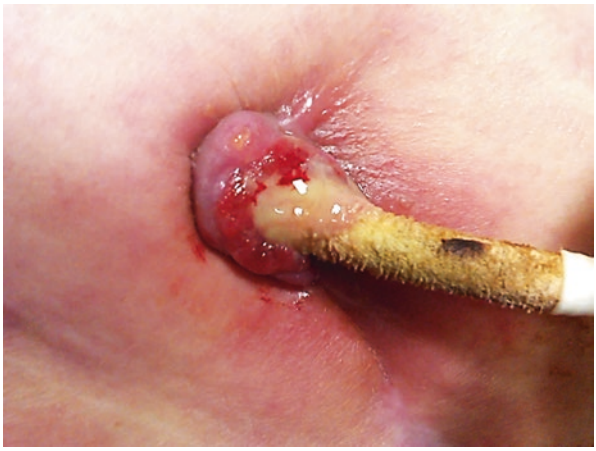


Fig. 28.9 HeartMate II percutaneous drive line infection (Image courtesy of Dr. Hiroo Takayama, Division of Cardiothoracic Surgery, Columbia University Medical Center)

or patch [48–52]. However, with the elimination of potential flow through the aortic valve, survival is dependent on native left ventricular ejection through a patent device. Alternatively, valve replacement with a bioprosthetic may be considered [53, 54]. More recently, case reports have described the percutaneous closure of the aortic valve using an Amplatzer septal occluder device [55, 56]. While such approaches are promising, further clinical study is warranted as outcomes have not consistently been favorable.

Infection

Infection in the CF-LVAD patient may present across a clinical spectrum ranging from the asymptomatic to fever, fatigue and generalized malaise. The percutaneous driveline is the predominant source of infection as its communication with the intra-abdominal cavity creates a critical portal of entry for pathogens [2–4] (See Fig. 28.9). In the HeartMate II BTT and Heartware ADVANCE trials, the respective incidence of a driveline infection was 14.0 and 12.1 % [2, 4]. Although driveline infections are not themselves a risk factor for death [57], they do contribute to broader patient morbidity including increasing risks for intracerebral hemorrhage and stroke, rehospitalization, long-term antibiotic therapy, and repeat surgery for device exchange [7, 58, 59]. For BTT LVAD patients, an active infection may negatively influence their transplant candidacy and potentially lead to poorer survival post-transplant [60].

Patient comorbidities including renal failure, prolonged hospitalization, obesity and diabetes predispose to a relative immunocompromised state and greater infection risk [61]. Prior to hospital discharge, the patient and their caregivers are instructed on appropriate driveline care using sterile technique and the importance of driveline immobilization. Although institutional practice may vary, drive line

Table 28.2 Diagnostic criteria for ventricular assist device-specific infection [64]

Major criteria
Positive peripheral blood cultures consistent with:
An indistinguishable organism recovered from ≥ 2 blood cultures taken ≥ 12 h apart with no other focus of infection, *or* All of 3 or a majority of ≥4 separate blood cultures (with the first and last set drawn ≥ least 1 h apart) with no other focus of infection
≥ 2 positive blood cultures drawn simultaneously from central and peripheral venous catheters
Echocardiogram positive for VAD-related IE with evidence of any or all of the following:
Intracardiac mass associated with the inflow cannula or in an area of turbulent flow Vegetation on implanted material Abscess New or partial dehiscence of outflow cannula
Minor criteria
Fever ≥ 38 °C
Vascular
Major arterial emboli, septic pulmonary infarcts Mycotic aneurysm Intracerebral, visceral or conjunctival hemorrhage Janeway's lesions
Immune-mediated
Glomerulonephritis, Osler's nodes, Roth spots
Positive blood culture that does not meet criteria as noted above Excluding single positive culture for coagulase-negative staphylococci or Stapylococcus lugdunensis

dressings are typically changed daily until which time the exit site has healed with adequate granulation tissue [62]. Depression was recently found in a multicenter trial to be a significant risk factor for LVAD infection raising psychosocial health and ability for self-care as important determinants of LVAD outcome [63].

Infection in the LVAD patient may be categorized as (1) VAD-specific; (2) VAD-related or (3) VAD-non- related [64]. ***VAD-specific infections*** refer to the primary involvement of device hardware including the driveline, pump components, the inflow cannula, outflow graft and the pump pocket. For the HeartMate II, the latter may be defined as the extraperitoneal cavity within which the pump resides. In contrast, the Heartware HVAD is surgically implanted within the intrapericardial space and does not require creation of a pocket. Diagnostic requirements for VAD-specific infections are summarized in Table 28.2 and are modelled after traditional Duke infective endocarditis criteria including positive blood cultures, echocardiography and suggestive clinical findings [65]. ***VAD-related infections*** are defined as those not directly involving the device but to which it is vulnerable. These include blood stream infections, infective endocarditis and mediastinitis. ***Non-VAD related infections*** refer to those that affect systems independent of the device and include urinary tract infections, pneumonia, cholecystitis and diarrhea from *Clostridium difficile*.

Clinical examination may reveal erythema or discharge at the driveline exit site. Tenderness along its intra-abdominal course can signify either an associated superficial tissue infection or a more concerning deeper source extending to the LVAD pocket and the device itself. Other sources, including urinary, skin, oral and respiratory infections may spread hematogenously to secondarily infect the LVAD.

Cultures from blood and driveline exit site swabs for bacterial and fungal infections are imperative for diagnosis and tailoring of antimicrobial therapy. Laboratory investigations may also include a complete blood count (CBC), measurement of erythrocyte sedimentation rates (ESR) and C-reactive protein (CRP). Palpable fluctuance and abdominal tenderness should prompt further imaging by ultrasonography or computed tomography of the abdomen and thorax to assess for deeper tissue involvement, fluid collections and possible pocket infection.

Most driveline infections arise from the proliferation of Gram-positive bacteria. Staphylococcus epidermidis, Staphylococcus aureus, Enterococcus spp., Escherichia coli, Enterobacter faecalis, Klebsiella pneumonia and Pseudomonas aeruginosa are known to colonize the driveline and eventually lead to infection. Of known microbial offenders, Candida infections portend the highest mortality in LVAD patients.

If a driveline infection has extended to the adjacent tissue, surgical debridement and/or or the use of a vacuum assisted closure device should be employed [61]. However, infections that migrate into the LVAD pocket render the device equally infected. The decision to intervene surgically is often dictated by virulence of pathogen, patient clinical status, surgical risk and transplant candidacy [66, 67]. For patients with DT LVADs, management may involve long-term suppressive antibiotic therapy with possible consideration for pump exchange depending on morbidity and likelihood for re-infection with a new device. In contrast, bridge to transplant LVAD patients may remain on antibiotic therapy with the benefit of a higher priority on the transplant waiting list due to a device complication [68], provided that their acuity and extent of infection have not deemed them transplant ineligible.

Ventricular Arrhythmia

Ventricular tachyarrhythmias (VT) may be acutely tolerated by patients with LVADs with case reports of survival even after 12 h of ventricular fibrillation [69–71]. On the other hand, right ventricular failure leading to impairment in LVAD output and the formation of an intra-cardiac thrombus are potential consequences of sustained VT [72–74]. The VT burden amongst HeartMate II patients has been reported to be greatest within the early post-operative period ranging in incidence from 13 to 39 % [2, 75, 76]. The true incidence of late ventricular arrhythmias, however, may be underestimated owing to inconsistent defibrillator use and non-standard device settings for the monitoring of arrhythmic events.

Patients may be asymptomatic with VT, with detection arising only upon defibrillator interrogation. Symptoms may include fatigue, dyspnea, weakness, nausea,

edema, dizziness, syncope and chest pain, and correlate with arrhythmia duration and its impact on ventricular function [72].

Predictors for VT include a history of pre-LVAD ventricular arrhythmia [72, 77], older age [78], lower rates of β-blocker treatment [79], and the use of the device as destination therapy [78] highlighting the relative contribution of patient comorbidity to their VT predisposition. Ischemic and non-ischemic cardiomyopathies have both been associated with VT across multiple studies amongst both pulsatile and continuous flow devices [80–82]. The myocardium itself may be arrhythmogenic resulting from progression of an underlying cardiomyopathy or from a history of structural heart disease already predisposed to arrhythmia such as sarcoidosis or hypertrophic cardiomyopathy. LVAD surgery may contribute to a VT focus, particularly from the apical scar around the inflow cannula [80, 83]. In addition, VT may result from "suction" events that occur when the left ventricle is excessively decompressed either by aggressive device speeds or inadequate LV preload. The septum is drawn towards the inflow cannula by the negative pressure generated by such conditions and its contact with the inflow cannula serves as the arrhythmic precipitant [76, 84]. Suction events are typically transient with obligate speed reduction programmed into the LVAD for patient safety. However, without correction of baseline speed, suction-induced VT may progress from intermittent septal contact to a frank mechanical obstruction of the inflow cannula by the septal myocardium [85]. With the exception of hemodynamically destabilizing suction events, VAD-related VT is otherwise not acutely decompensating. Management is typically less emergent and mainly driven by signs and symptoms of right heart failure and low output. However, if VT is hemodynamically destabilizing, the LVAD patient may be externally defibrillated with electrical shocks. Anti-arrhythmic therapy, including intravenous amiodarone, lidocaine or procainamide, may have limited effectiveness against VT in the LVAD setting [72]. Reversible causes merit correction including QTc prolongation by electrolyte imbalance or offending medications. For patients with recurrent or incessant ventricular arrhythmias, invasive electrophysiology studies and ablation strategies may be of therapeutic benefit [83, 86, 87].

VT prophylaxis may begin with beta-blocker therapy for both the recognition of its absence as a predictor of arrhythmic events in LVAD patients and for its benefit in left ventricular remodeling and possible myocardial recovery [16, 18]. Continuation of amiodarone or other anti-arrhythmic agents may be considered in patients with a pre-existing history of their use. The use of implantable cardioverter-defibrillators (ICD) for primary and secondary prevention against sudden cardiac death has been controversial. Current guidelines recommend defibrillator implantation in all patients undergoing LVAD placement or reactivation of their anti-arrhythmic therapies in those with pre-existing ICDs [11]. The challenge lies in the relative paucity of contemporary data to justify such recommendations. Studies demonstrating survival benefits amongst LVAD patients with ICDs included those supported with earlier generation pulsatile devices [77, 79]. However, in a study with CF-LVADs, no deaths occurred from malignant ventricular arrhythmias amongst 44 Heartmate II and 17 Heartware patients over a mean prospective follow-up of 365 days [82]. Defibrillators were implanted in each of the study partici-

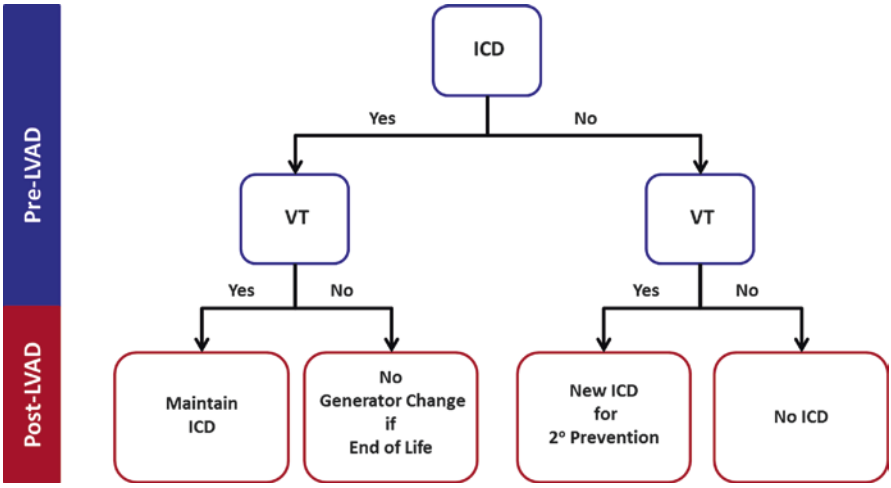


Fig. 28.10 Defibrillator therapy algorithm following ventricular assist device implantation (Modified from Garan et al. [89])

pants which enabled the detection of a 34 % rate of appropriate ICD therapy for episodes of ventricular fibrillation and mono- and polymorphic VT. Similarly, retrospective findings involving 23 HeartMate II patients failed to demonstrate ventricular arrhythmia-related death [76]. Absent definitive clinical trials examining this issue, some advocate that all LVAD patients receive ICDs due to the anticipated VT burden following implantation and its impact on right ventricular function [76, 82, 88]. Our decision to implant a primary prevention ICD relies on a patient's history of preoperative VT (Fig. 28.10). This is based on the fact that VT in LVAD patients does not usually result in sudden death, as well as our prospective study of 95 HeartMate II patients revealing only a 4 % incidence of (hemodynamically stable) VT in those patients without preimplant ventricular arrhythmias [89].

Conclusion

Continuous flow left ventricular assist devices have provided an unprecedented mortality benefit to patients with end-stage heart disease. Early clinical trials that established their use as bridge to transplant and destination therapies reported survival rates of 68 % at 1 year [2] and 58 % [3] at 2 years following device implantation, respectively. Recent INTERMACS reports have consistently attested to 1–2 year actuarial survival of greater than 80 and 70 % [1, 5] approximating outcomes typically reserved for the current gold standard for heart replacement therapy, cardiac transplantation [90]. While improvements in patient selection, surgical expertise and medical care have evolved with our collective experience, LVAD-related complications burden both patient and the healthcare system. Their recognition and

study promise to improve both clinic outcomes and our understanding of device and heart failure physiology. In turn, such advancements will undoubtedly broaden the application of mechanical circulatory support therapies to a greater number of patients in need and eliminate the need for cardiac transplantation in many.

References

1. Kirklin JK, Naftel DC, Kormos RL, Stevenson LW, Pagani FD, Miller MA, et al. Fifth INTERMACS annual report: risk factor analysis from more than 6,000 mechanical circulatory support patients. J Heart Lung Transplant. 2013;32(2):141–56.
2. Miller LW, Pagani FD, Russell SD, John R, Boyle AJ, Aaronson KD, et al. Use of a continuous-flow device in patients awaiting heart transplantation. N Engl J Med. 2007;357(9):885–96.
3. Slaughter MS, Rogers JG, Milano CA, Russell SD, Conte JV, Feldman D, et al. Advanced heart failure treated with continuous-flow left ventricular assist device. N Engl J Med. 2009;361(23):2241–51.
4. Aaronson KD, Slaughter MS, Miller LW, McGee EC, Cotts WG, Acker MA, et al. Use of an intrapericardial, continuous-flow, centrifugal pump in patients awaiting heart transplantation. Circulation. 2012;125(25):3191–200.
5. Kirklin JK, Naftel DC, Kormos RL, Stevenson LW, Pagani FD, Miller MA, et al. The fourth INTERMACS annual report: 4,000 implants and counting. J Heart Lung Transplant. 2012;31(2):117–26.
6. Stewart GC, Givertz MM. Mechanical circulatory support for advanced heart failure: patients and technology in evolution. Circulation. 2012;125(10):1304–15.
7. Hasin T, Marmor Y, Kremers W, Topilsky Y, Severson CJ, Schirger JA, et al. Readmissions after implantation of axial flow left ventricular assist device. J Am Coll Cardiol. 2013;61(2):153–63.
8. MacIver J, Ross HJ, Delgado DH, Cusimano RJ, Yau TM, Rodger M, et al. Community support of patients with a left ventricular assist device: The Toronto General Hospital experience. Can J Cardiol. 2009;25(11):e377–81.
9. Lanier G, Orlanes K, Demmer RT, Hayashi Y, Murphy J, Flannery M, et al. Validity and reliability of a novel slow cuff-deflation system for non-invasive blood pressure monitoring in patients with continuous-flow left ventricular assist device (CF-LVAD). Circulation. 2012;126:A16567.
10. Slaughter MS, Pagani FD, Rogers JG, Miller LW, Sun B, Russell SD, et al. Clinical management of continuous-flow left ventricular assist devices in advanced heart failure. J Heart Lung Transplant. 2010;29(4 Suppl):S1–39.
11. Feldman D, Pamboukian SV, Teuteberg JJ, Birks E, Lietz K, Moore SA, et al. The 2013 International Society for Heart and Lung Transplantation Guidelines for mechanical circulatory support: Executive summary. J Heart Lung Transplant. 2013;32(2):157–87.
12. Birks EJ, Tansley PD, Hardy J, George RS, Bowles CT, Burke M, et al. Left ventricular assist device and drug therapy for the reversal of heart failure. N Engl J Med. 2006;355(18):1873–84.
13. Mancini DM, Beniaminovitz A, Levin H, Catanese K, Flannery M, DiTullio M, et al. Low incidence of myocardial recovery after left ventricular assist device implantation in patients with chronic heart failure. Circulation. 1998;98(22):2383–9.
14. Dandel M, Weng Y, Siniawski H, Potapov E, Lehmkuhl HB, Hetzer R. Long-term results in patients with idiopathic dilated cardiomyopathy after weaning from left ventricular assist devices. Circulation. 2005;112(9 Suppl):I37–45.
15. Maybaum S, Mancini D, Xydas S, Starling RC, Aaronson K, Pagani FD, et al. Cardiac improvement during mechanical circulatory support: a prospective multicenter study of the LVAD Working Group. Circulation. 2007;115(19):2497–505.

16. Birks EJ, George RS, Hedger M, Bahrami T, Wilton P, Bowles CT, et al. Reversal of severe heart failure with a continuous-flow left ventricular assist device and pharmacological therapy: a prospective study. Circulation. 2011;123(4):381–90.
17. Formica P, Murthy S, Edwards P, Goldstein D, Maybaum S. A structured 3-step approach to evaluate cardiac recovery with continuous flow circulatory support. J Heart Lung Transplant. 2010;29(12):1440–2.
18. Patel SR, Saeed O, Murthy S, Bhatia V, Shin JJ, Wang D, et al. Combining neurohormonal blockade with continuous-flow left ventricular assist device support for myocardial recovery: a single-arm prospective study. J Heart Lung Transplant. 2013;32(3):305–12.
19. Boyle AJ, Russell SD, Teuteberg JJ, Slaughter MS, Moazami N, Pagani FD, et al. Low thromboembolism and pump thrombosis with the HeartMate II left ventricular assist device: analysis of outpatient anti-coagulation. J Heart Lung Transplant. 2009;28(9):881–7.
20. Miller LW, Guglin M, Rogers J. Cost of ventricular assist devices: can we afford the progress? Circulation. 2013;127(6):743–8.
21. Aggarwal A, Pant R, Kumar S, Sharma P, Gallagher C, Tatooles AJ, et al. Incidence and management of gastrointestinal bleeding with continuous flow assist devices. Ann Thorac Surg. 2012;93(5):1534–40.
22. Morgan JA, Paone G, Nemeh HW, Henry SE, Patel R, Vavra J, et al. Gastrointestinal bleeding with the HeartMate II left ventricular assist device. J Heart Lung Transplant. 2012;31(7):715–8.
23. Demirozu ZT, Radovancevic R, Hochman LF, Gregoric ID, Letsou GV, Kar B, et al. Arteriovenous malformation and gastrointestinal bleeding in patients with the HeartMate II left ventricular assist device. J Heart Lung Transplant. 2011;30(8):849–53.
24. Huang RJ, Wong RJ, Draper KV, Winter TA. De novo arteriovenous malformations following implantation of the HeartMate II left ventricular assist device. Endoscopy. 2012;44(Suppl 2 UCTN):E441.
25. Heyde E. Gastrointestinal bleeding in aortic stenosis. N Engl J Med. 1958;259:196.
26. Crow S, Chen D, Milano C, Thomas W, Joyce L, Piacentino 3rd V, et al. Acquired von Willebrand syndrome in continuous-flow ventricular assist device recipients. Ann Thorac Surg. 2010;90(4):1263–9 ; discussion 9.
27. Heilmann C, Geisen U, Beyersdorf F, Nakamura L, Trummer G, Berchtold-Herz M, et al. Acquired Von Willebrand syndrome is an early-onset problem in ventricular assist device patients. Eur J Cardiothorac Surg. 2011;40(6):1328–33 ; discussion 233.
28. Uriel N, Pak SW, Jorde UP, Jude B, Susen S, Vincentelli A, et al. Acquired von Willebrand syndrome after continuous-flow mechanical device support contributes to a high prevalence of bleeding during long-term support and at the time of transplantation. J Am Coll Cardiol. 2010;56(15):1207–13.
29. Meyer AL, Malehsa D, Bara C, Budde U, Slaughter MS, Haverich A, et al. Acquired von Willebrand syndrome in patients with an axial flow left ventricular assist device. Circ Heart Fail. 2010;3(6):675–81.
30. Decker GA, Miller ED, Pasha SF, Harrison ME, Leighton JA. Deep enteroscopy in patients with left ventricular assist devices: practical and technical considerations. Endoscopy. 2010;42(Suppl 2):E194.
31. Bechtel JF, Wellhoner P, Charitos EI, Bucsky B, Morshuis M, Sievers HH. Localizing an occult gastrointestinal bleeding by wireless PillCam SB capsule videoendoscopy in a patient with the HeartMate II left ventricular assist device. J Thorac Cardiovasc Surg. 2010;139(4):e73–4.
32. Cushing M, Kawaguchi K, Friedman KD, Mark T. Factor VIII/von Willebrand factor concentrate therapy for ventricular assist device-associated acquired von Willebrand disease. Transfusion. 2012;52(7):1535–41.
33. Hayes HM, Dembo LG, Larbalestier R, O'Driscoll G. Management options to treat gastrointestinal bleeding in patients supported on rotary left ventricular assist devices: a single-center experience. Artif Organs. 2010;34(9):703–6.
34. Slaughter MS, Aaronson KD, Boyce S, Miller LW, McGee EC, Cotts WG, et al. HVAD BTT pivotal trial and continued access program (ADVANCE): interim report of the expanded study. J Heart Lung Transplant. 2011;30(4):S84–5.

35. Eckman PM, John R. Bleeding and thrombosis in patients with continuous-flow ventricular assist devices. Circulation. 2012;125(24):3038–47.
36. Uriel N, Morrison KA, Garan AR, Kato TS, Yuzefpolskaya M, Latif F, et al. Development of a novel echocardiography ramp test for speed optimization and diagnosis of device thrombosis in continuous-flow left ventricular assist devices: the Columbia ramp study. J Am Coll Cardiol. 2012;60(18):1764–75.
37. Paluszkiewicz L, Gursoy D, Spiliopoulos S, Dogan G, Daliakopoulos S, Tenderich M, et al. HeartMate II ventricular assist device thrombosis-an echocardiographic approach to diagnosis: can Doppler evaluation of flow be useful? J Am Soc Echocardiogr. 2011;24(3):350 e1–4.
38. Al-Quthami AH, Jumean M, Kociol R, Pham DT, Kiernan M, DeNofrio D, et al. Eptifibatide for the treatment of HeartMate II left ventricular assist device thrombosis. Circ Heart Fail. 2012;5(4):e68–70.
39. Kiernan MS, Pham DT, DeNofrio D, Kapur NK. Management of HeartWare left ventricular assist device thrombosis using intracavitary thrombolytics. J Thorac Cardiovasc Surg. 2011;142(3):712–4.
40. Yuzefpolskaya M, Uriel N, Chow DS, Restaino SW, Mancini DM, Flanenery M, et al. Prevalence and timing of bend relief disconnection in patients supported by the late version HeartMate II left ventricular assist device. J Heart Lung Transplant. 2013;32(3):320–5.
41. Agarwal R, Adatya S, Uriel N, Jorde UP. Clinical impact, diagnosis, and management of a disconnected outflow graft bend relief in a patient supported by the HeartMate II left ventricular assist system. J Heart Lung Transplant. 2012;31(11):1238–9.
42. Toda K, Fujita T, Domae K, Shimahara Y, Kobayashi J, Nakatani T. Late aortic insufficiency related to poor prognosis during left ventricular assist device support. Ann Thorac Surg. 2011;92(3):929–34.
43. Pak SW, Uriel N, Takayama H, Cappleman S, Song R, Colombo PC, et al. Prevalence of de novo aortic insufficiency during long-term support with left ventricular assist devices. J Heart Lung Transplant. 2010;29(10):1172–6.
44. Cowger J, Pagani FD, Haft JW, Romano MA, Aaronson KD, Kolias TJ. The development of aortic insufficiency in left ventricular assist device-supported patients. Circ Heart Fail. 2010;3(6):668–74.
45. Hatano M, Kinugawa K, Shiga T, Kato N, Endo M, Hisagi M, et al. Less frequent opening of the aortic valve and a continuous flow pump are risk factors for postoperative onset of aortic insufficiency in patients with a left ventricular assist device. Circ J. 2011;75(5):1147–55.
46. Mudd JO, Cuda JD, Halushka M, Soderlund KA, Conte JV, Russell SD. Fusion of aortic valve commissures in patients supported by a continuous axial flow left ventricular assist device. J Heart Lung Transplant. 2008;27(12):1269–74.
47. Russo MJ, Freed BH, Jeevanandam V, Hashmi M, Paul JD, Anderson A, et al. Percutaneous transcatheter closure of the aortic valve to treat cardiogenic shock in a left ventricular assist device patient with severe aortic insufficiency. Ann Thorac Surg. 2012;94(3):985–8.
48. McKellar SH, Deo S, Daly RC, Durham 3rd LA, Joyce LD, Stulak JM, et al. Durability of central aortic valve closure in patients with continuous flow left ventricular assist devices. J Thorac Cardiovasc Surg. 2014;147(1):344–8.
49. Adamson RM, Dembitsky WP, Baradarian S, Chammas J, May-Newman K, Chillcott S, et al. Aortic valve closure associated with HeartMate left ventricular device support: technical considerations and long-term results. J Heart Lung Transplant. 2011;30(5):576–82.
50. Rao V, Slater JP, Edwards NM, Naka Y, Oz MC. Surgical management of valvular disease in patients requiring left ventricular assist device support. Ann Thorac Surg. 2001;71(5): 1448–53.
51. Cohn WE, Demirozu ZT, Frazier OH. Surgical closure of left ventricular outflow tract after left ventricular assist device implantation in patients with aortic valve pathology. J Heart Lung Transplant. 2011;30(1):59–63.
52. Goda A, Takayama H, Pak SW, Uriel N, Mancini D, Naka Y, et al. Aortic valve procedures at the time of ventricular assist device placement. Ann Thorac Surg. 2011;91(3):750–4.

53. Feldman CM, Silver MA, Sobieski MA, Slaughter MS. Management of aortic insufficiency with continuous flow left ventricular assist devices: bioprosthetic valve replacement. J Heart Lung Transplant. 2006;25(12):1410–2.
54. Dranishnikov N, Stepanenko A, Potapov EV, Dandel M, Siniawski H, Mladenow A, et al. Simultaneous aortic valve replacement in left ventricular assist device recipients: single-center experience. Int J Artif Organs. 2012;35(7):489–94.
55. Grohmann J, Blanke P, Benk C, Schlensak C. Trans-catheter closure of the native aortic valve with an Amplatzer Occluder to treat progressive aortic regurgitation after implantation of a left-ventricular assist device. Eur J Cardiothorac Surg. 2011;39(6):e181–3.
56. Freed BH, Paul JD, Bhave NM, Russo MJ, Jeevanandam V, Lang RM, et al. Percutaneous transcatheter closure of the native aortic valve to treat de novo aortic insufficiency after implantation of a left ventricular assist device. JACC Cardiovasc Intervent. 2012;5(3):358–9.
57. Topkara VK, Kondareddy S, Malik F, Wang IW, Mann DL, Ewald GA, et al. Infectious complications in patients with left ventricular assist device: etiology and outcomes in the continuous-flow era. Ann Thorac Surg. 2010;90(4):1270–7 . P.
58. Aggarwal A, Gupta A, Kumar S, Baumblatt JA, Pauwaa S, Gallagher C, et al. Are blood stream infections associated with an increased risk of hemorrhagic stroke in patients with a left ventricular assist device? ASAIO J. 2012;58(5):509–13.
59. Kato TS, Schulze PC, Yang J, Chan E, Shahzad K, Takayama H, et al. Pre-operative and post-operative risk factors associated with neurologic complications in patients with advanced heart failure supported by a left ventricular assist device. J Heart Lung Transplant. 2012;31(1):1–8.
60. Healy AH, Baird BC, Drakos SG, Stehlik J, Selzman CH. Impact of ventricular assist device complications on posttransplant survival: an analysis of the United network of organ sharing database. Ann Thorac Surg. 2013;95(3):870–5.
61. Pereda D, Conte JV. Left ventricular assist device driveline infections. Cardiol Clin. 2011;29(4):515–27.
62. Cannon A, Elliott T, Ballew C, Cavey J, O'Shea G, Franzwa J, et al. Variability in infection control measures for the percutaneous lead among programs implanting long-term ventricular assist devices in the United States. Prog Transplant. 2012;22(4):351–9.
63. Gordon RJ, Weinberg AD, Pagani FD, Slaughter MS, Pappas PS, Naka Y, et al. Prospective, multicenter study of ventricular assist device infections. Circulation. 2013;127(6):691–702.
64. Hannan MM, Husain S, Mattner F, Danziger-Isakov L, Drew RJ, Corey GR, et al. Working formulation for the standardization of definitions of infections in patients using ventricular assist devices. J Heart Lung Transplant. 2011;30(4):375–84.
65. Li JS, Sexton DJ, Mick N, Nettles R, Fowler Jr VG, Ryan T, et al. Proposed modifications to the Duke criteria for the diagnosis of infective endocarditis. Clin Infect Dis. 2000;30(4):633–8.
66. Stulak JM, Cowger J, Haft JW, Romano MA, Aaronson KD, Pagani FD. Device exchanege after primary left ventricular assist device implantation: indications and outcomes. Ann Thorac Surg. 2013;95(4):1262–7.
67. Moazami N, Milano CA, John R, Sun B, Adamson RM, Pagani FD, et al. Pump replacement for left ventricular assist device failure can be done safely and is associated with low mortality. Ann Thorac Surg. 2013;95(2):500–5.
68. Uriel N, Jorde UP, Woo Pak S, Jiang J, Clerkin K, Takayama H, et al. Impact of long term left ventricular assist device therapy on donor allocation in cardiac transplantation. J Heart Lung Transplant. 2013;32(2):188–95.
69. Sims DB, Rosner G, Uriel N, Gonzalez-Costello J, Ehlert FA, Jorde UP. Twelve hours of sustained ventricular fibrillation supported by a continuous-flow left ventricular assist device. Pacing Clin Electrophysiol. 2012;35(5):e144–8.
70. Boilson BA, Durham LA, Park SJ. Ventricular fibrillation in an ambulatory patient supported by a left ventricular assist device: highlighting the ICD controversy. ASAIO J. 2012;58(2):170–3.
71. Busch MC, Haap M, Kristen A, Haas CS. Asymptomatic sustained ventricular fibrillation in a patient with left ventricular assist device. Ann Emerg Med. 2011;57(1):25–8.

72. Raasch H, Jensen BC, Chang PP, Mounsey JP, Gehi AK, Chung EH, et al. Epidemiology, management, and outcomes of sustained ventricular arrhythmias after continuous-flow left ventricular assist device implantation. Am Heart J. 2012;164(3):373–8.
73. Shirazi JT, Lopshire JC, Gradus-Pizlo I, Hadi MA, Wozniak TC, Malik AS. Ventricular arrhythmias in patients with implanted ventricular assist devices: a contemporary review. Europace (European Pacing, Arrhythmias, and Cardiac Electrophysiology : J Working Groups on Cardiac Pacing, Arrhythmias, and Cardiac Cellular Electrophysiology of the Eur Soc Cardiol). 2013;15(1):11–7.
74. Oz MC, Rose EA, Slater J, Kuiper JJ, Catanese KA, Levin HR. Malignant ventricular arrhythmias are well tolerated in patients receiving long-term left ventricular assist devices. J Am Coll Cardiol. 1994;24(7):1688–91.
75. Pagani FD, Miller LW, Russell SD, Aaronson KD, John R, Boyle AJ, et al. Extended mechanical circulatory support with a continuous-flow rotary left ventricular assist device. J Am Coll Cardiol. 2009;54(4):312–21.
76. Andersen M, Videbaek R, Boesgaard S, Sander K, Hansen PB, Gustafsson F. Incidence of ventricular arrhythmias in patients on long-term support with a continuous-flow assist device (HeartMate II). J Heart Lung Transplant. 2009;28(7):733–5.
77. Cantillon DJ, Tarakji KG, Kumbhani DJ, Smedira NG, Starling RC, Wilkoff BL. Improved survival among ventricular assist device recipients with a concomitant implantable cardioverter-defibrillator. Heart Rhythm. 2010;7(4):466–71.
78. Ambardekar AV, Allen LA, Lindenfeld J, Lowery CM, Cannon AP, Cleveland Jr JC, et al. Implantable cardioverter-defibrillator shocks in patients with a left ventricular assist device. J Heart Lung Transplant. 2010;29(7):771–6.
79. Refaat M, Chemaly E, Lebeche D, Gwathmey JK, Hajjar RJ. Ventricular arrhythmias after left ventricular assist device implantation. Pacing Clin Electrophysiol. 2008;31(10):1246–52.
80. Ziv O, Dizon J, Thosani A, Naka Y, Magnano AR, Garan H. Effects of left ventricular assist device therapy on ventricular arrhythmias. J Am Coll Cardiol. 2005;45(9):1428–34.
81. Bedi M, Kormos R, Winowich S, McNamara DM, Mathier MA, Murali S. Ventricular arrhythmias during left ventricular assist device support. Am J Cardiol. 2007;99(8):1151–3.
82. Oswald H, Schultz-Wildelau C, Gardiwal A, Lusebrink U, Konig T, Meyer A, et al. Implantable defibrillator therapy for ventricular tachyarrhythmia in left ventricular assist device patients. Eur J Heart Fail. 2010;12(6):593–9.
83. Cantillon DJ, Bianco C, Wazni OM, Kanj M, Smedira NG, Wilkoff BL, et al. Electrophysiologic characteristics and catheter ablation of ventricular tachyarrhythmias among patients with heart failure on ventricular assist device support. Heart Rhythm. 2012;9(6):859–64.
84. Vollkron M, Voitl P, Ta J, Wieselthaler G, Schima H. Suction events during left ventricular support and ventricular arrhythmias. J Heart Lung Transplant. 2007;26(8):819–25.
85. Badiwala MV, Ross HJ, Rao V. An unusual complication of support with a continuous-flow cardiac assist device. N Engl J Med. 2007;357(9):936–7.
86. Osaki S, Alberte C, Murray MA, Brahmbhatt RD, Johnson MR, Edwards NM, et al. Successful radiofrequency ablation therapy for intractable ventricular tachycardia with a ventricular assist device. J Heart Lung Transplant. 2008;27(3):353–6.
87. Mulloy DP, Bhamidipati CM, Stone ML, Ailawadi G, Bergin JD, Mahapatra S, et al. Cryoablation during left ventricular assist device implantation reduces postoperative ventricular tachyarrhythmias. J Thorac Cardiovasc Surg. 2013;145(5):1207–13.
88. Cowger J, Romano MA, Stulak J, Pagani FD, Aaronson KD. Left ventricular assist device management in patients chronically supported for advanced heart failure. Curr Opin Cardiol. 2011;26(2):149–54.
89. Garan AR, Morrison K, Letarte L, Vazquez J, Dano D, Colombo P, et al. Ventricular arrhythmias in patients following continuous flow left ventricular assist device implantation. Circulation. 2012;126:A19448. J Am Coll Cardiol. 2013;61(25):2542–50.
90. Colvin-Adams M, Smith JM, Heubner BM, Skeans MA, Edwards LB, Waller C, et al. OPTN/SRTR 2011 Annual Data Report: heart. Am J Transplant. 2013;13(Suppl 1):119–48.

Chapter 29
The Total Artificial Heart

Keyur B. Shah, Anit K. Mankad, Daniel G. Tang, and Vigneshwar Kasirajan

Introduction

The National Health Institute (NHI) established the Artificial Heart Program in 1964 to promote development of a device to *replace* the dying heart. More than four decades later, the twenty first century has brought with it the dawn of the mechanical circulatory support age for the treatment of advanced heart failure. However, recent progress is highlighted by technological advances and improved clinical outcomes of left ventricular *assist* devices (LVAD), while heart *replacement* technologies have exhibited a more modest evolution.

None the less, the total artificial heart (TAH) is an effective means for treating advanced heart failure in patients dying of biventricular heart failure. Furthermore, the device represents a lifesaving alternative for patients with severe shock and anatomical contraindications to LVAD therapy. This chapter reviews the development, technical considerations and patient selection for the TAH.

History

The notion of an artificial heart has long captured the imagination. As early as 1812, M. Le Gallois, a French physician in the midst of the Industrial Revolution, noted: "… if the place of the heart could be … artificially formed … then life might be

K.B. Shah, MD (✉) • A.K. Mankad, MD
Pauley Heart Center, Division of Cardiology, Virginia Commonwealth University, Medical College of Virginia, 1200 East Broad Street, P.O. Box 980204, Richmond, VA 23298, USA
e-mail: keyur.shah@vcuhealth.org; anit.mankad@va.gov

D.G. Tang, MD • V. Kasirajan, MD
Division of Cardiothoracic Surgery, Virginia Commonwealth University, Medical College of Virginia, 1200 East Broad Street, Richmond, VA 23298, USA
e-mail: daniel.tang@vcuhealth.org; vigneshwar.kasirajan@vcuhealth.org

H. Eisen (ed.), *Heart Failure*, DOI 10.1007/978-1-4471-4219-5_29

indefinitely maintained …" [1]. A century later in 1929, O.S. Gibbs reported one of the earliest uses of an extracorporeal artificial heart to completely support circulation in an animal model [2]. The use of left heart bypass in 1952 by Forrest Dodrill to perform a mitral commissurotomy and cardiopulmonary bypass in 1953 by John Gibbon to close an atrial septal defect marked the beginning of modern cardiac surgery [3, 4]. In 1957, Willem Kolff and Tetsuzo Akutsu developed a pneumatically driven orthotopic total artificial heart that was successfully implanted and supported a dog for 90 min [5]. The investigators and their trainees would go on to pioneer artificial heart research programs at multiple centers and their efforts would eventually culminate in human implantation.

In 1964, the NHI established the U.S. Artificial Heart Program, paralleling the ambitions of the U.S. Space Program. The initial goal of the program was to develop a fully implantable atomic powered artificial heart for clinical use within 10 years. Near this time, the 1st human heart transplant was performed in South Africa with intense media fanfare; however poor survival would soon dampen enthusiasm. A similar experience would later be repeated with the artificial heart.

In 1969, Denton Cooley and Domingo Liotta implanted the first human artificial heart in a 47 year old man with severe ischemic cardiomyopathy who was undergoing remodeling ventriculoplasty. An experimental pneumatic artificial heart designed by Liotta was implanted after the patient was unable to come off cardiopulmonary bypass. The artificial heart successfully provided hemodynamic support, but the patient quickly developed hemolysis and progressive renal failure. A donor heart was found and he underwent transplantation after 64 h of support; unfortunately, the patient died 32 h later from sepsis [6, 7]. The ground breaking event was filled with controversy as Cooley and Liotta were criticized for performing an experimental procedure without appropriate prior institutional or federal approval. The patient's family unsuccessfully sued (and appealed up to the U.S. Supreme Court) alleging negligence, lack of informed consent, and improper experimentation [8]. Cooley resigned from the Baylor College of Medicine and Liotta was suspended and would subsequently return to Argentina. Claims of intellectual theft culminated in one of the most infamous professional feuds between Cooley and Michael DeBakey [9].

Another decade would pass before further human attempts with a TAH. In 1981, Cooley implanted another pneumatic artificial heart (designed by Akutsu) as a bridge to transplant for a 36 year old man with cardiac arrest shortly following coronary bypass surgery. His postoperative course was notable for renal failure and severe hypoxia attributed to left pulmonary venous obstruction, requiring veno-venous extracorporeal membrane oxygenation. He underwent transplantation after 55 h of TAH support, however the patient died 1 week later from overwhelming sepsis [10].

In 1982, with both federal and institutional approval, William DeVries performed the well-publicized permanent implant of the Jarvik-7 TAH as destination therapy into Dr. Barney Clark [11]. Dr. Clark was not a candidate for transplantation and he survived for 112 days tethered to the device's large pneumatic console driver. His postoperative course was difficult. He developed recurrent respiratory failure

requiring tracheostomy, fracture of the prosthetic mitral valve strut requiring replacement of the artificial left ventricle, fevers, stroke, seizures, delirium, intermittent renal failure, and bleeding related to anticoagulation. He ultimately succumbed to pseudomembranous colitis. On numerous occasions, Dr. Clark stated that he volunteered for the experiment for the benefit of science; however, he also similarly asked numerous times to be allowed to die. The public spectacle of his story provoked discussions of the ethics of extreme human experimentation.

DeVries went on to perform three more implants as permanent or destination therapy. Survival ranged from 10 to 620 days and the clinical outcomes were marred by significant complications. The high cost of therapy with limited survival and poor quality of life tempered enthusiasm. Eventually, no further implants as destination therapy were allowed and focus shifted to the development of partial circulatory support with ventricular assist devices.

Nonetheless, experience with artificial hearts as a bridge to transplant continued to accumulate at a handful of centers. In 1985, Copeland performed the first successful bridge to transplantation with the Jarvik-7 TAH [12]. The device was eventually renamed the CardioWest TAH (Syncardia, Tuscon, AZ) with minor design changes to become the contemporary TAH approved for a bridge to transplantation in 2004.

Human trials of another TAH for destination therapy began in 2001. The Abiomed AbioCor Implantable Replacement Heart (IRH) (AbioMed, Danvers, MA) is fully implantable utilizing a transcutaneous energy transfer (TET) coil to recharge the batteries and an electrically driven hydraulic pump to actuate the ventricles. Results of the first seven patients implanted were reported in 2004 and revealed significant complications [13]. One died intraoperatively from bleeding and another died several hours postoperatively from a presumed aprotinin reaction. The remaining five had difficult postoperative courses with only two patients surviving to discharge. Ultimately 14 patients were implanted with the longest surviving 512 days. The device received FDA approval for destination therapy in 2006, but manufacturer has so far elected not to market the device.

Device Design

The CardioWest TAH descends from the Jarvik-7 which was developed at the University of Utah. Initially known as the Jarvik TAH with a 100 mL fill volume, its first human implantation was performed in 1982. The Jarvik TAH attached to atrial cuffs, replacing the entire ventricular myocardium and all four valves. In 1984, the Jarvik-7 was introduced with a fill volume of 70 mL for each ventricle. This device was then FDA-approved for investigational use with a new drive line coated with Dacron velour in 1993 as the CardioWest TAH.

The CardioWest TAH consists of two separate pulsatile, polyurethane-lined blood pumps that together weigh 160 g and displaces 400 mL of volume. Each pump has a pneumatic driver that pulls a 4-layer polyurethane diaphragm down to allow blood to

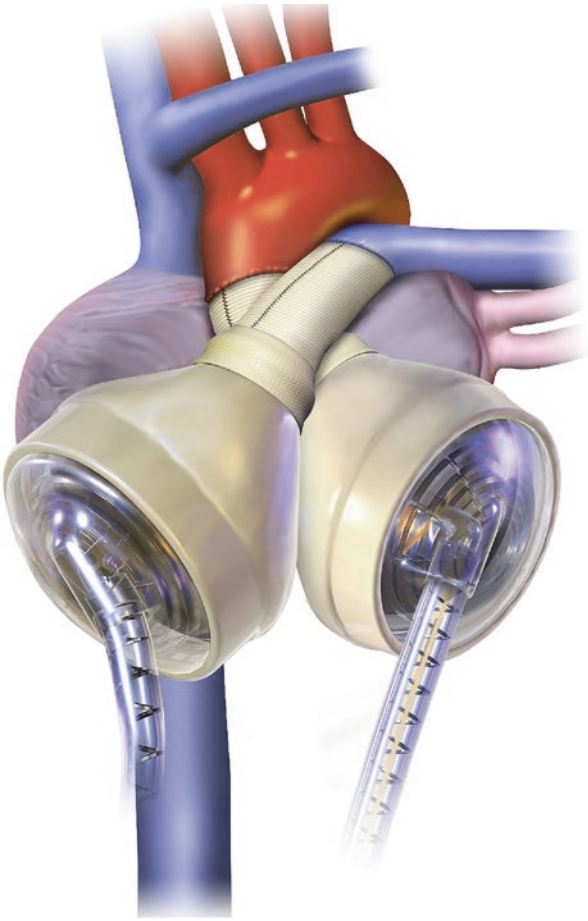


Fig. 29.1 The CardioWest Total Artificial Heart (*TAH*). The TAH consists of two pneumatically driven pulsatile pumps that replace the ventricle and four heart valves. The device is connected to the atrial cuffs and great vessels (Reprinted with permission from Syncardia Systems Inc.)

enter the ventricle, and then a precisely calibrated pulse of air is used to push the blood out of the ventricle (Fig. 29.1). There are two Bjork-Shiley tilting-disc valves for each ventricular unit (placed in the inflow and outflow ports), that ensure unidirectional flow through the device. The settings (heart rate and drive pressure) are optimized by the operator to achieve partial fill of each ventricle (minimizing stasis and risk of thrombus formation) with complete ejection of the blood that is contained. This pump is capable of generating up to 9.5 L/min of flow through each ventricle. Upon implantation, the patient is tethered to an external drive console weighing 400 pounds that contains pistons to support the drive pressure and controls the heart rate and systolic duration (Fig. 29.2a). Development of the portable Excor driver in Europe and the Freedom driver (CE Mark approved in Europe and under clinical trial in the U.S.) have enabled discharge of TAH patients (Fig. 29.2b). The ability to discharge patients from a hospital environment has been the main limiting factor in more widespread use of this technology. Successful discharge using a portable driver may allow the use of the TAH as a destination device in selected patients.

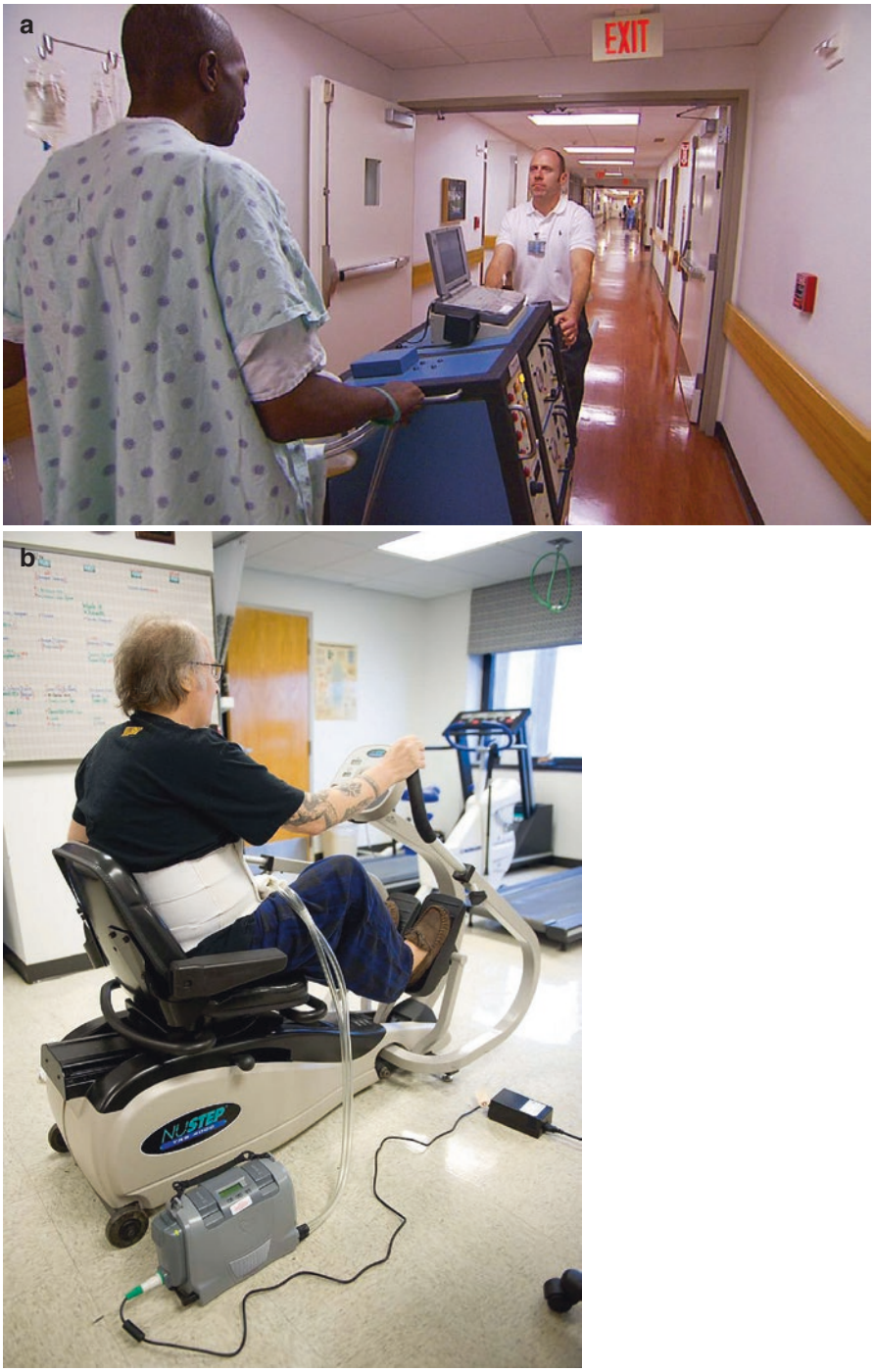


Fig. 29.2 The pneumatic drivers for the CardioWest Total Artificial Heart (*TAH*). Patients after device implantation are connected to the 400 lb. in hospital drive (**a**). The portable Freedom Driver (**b**) is under clinic investigation and will allow for discharge to home with the CardioWest TAH (Images provided by Joe Kuttenkuler, Virginia Commonwealth University)

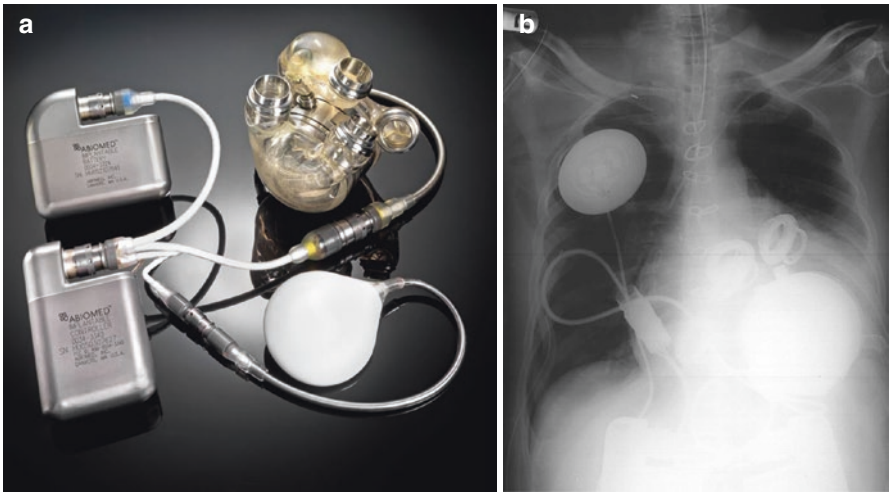


Fig. 29.3 The fully implantable AbioCor Implantable Replacement Heart (*IRH*). The device is shown in panel (**a**) with all of the implantable internal components include the AbioCor thoracic unit, lithium ion battery, controller, and TET coil. The chest x-ray (**b**) shows the components of the device in a patient (Reprinted with permission from Abiomed)

The AbioCor IRH replaces the ventricles of the heart, and has a unique charging mechanism allowing it to be free of a percutaneous driveline [14]. The AbioCor IRH has four internal components and four external components. The internal components include the AbioCor thoracic unit, lithium ion battery, controller, and TET coil (Fig. 29.3). The thoracic unit consists of an energy converter, two pumping chambers (left and right ventricles) and four 24 mm tri-leaflet valves, along with a hydraulic pumping system. The energy converter is situated between the chambers and contains a centrifugal pump driven by a brushless direct current motor. The centrifugal pump pressurizes low-viscosity hydraulic fluid, which utilizes a 2-position switching valve to alternate pumping of the right and left chambers. Displacing fluid to one ventricle creates negative pressure in the other ventricle resulting in alternating left and right ventricular pumping. The rate of the switching valve can be set between 75 and 150 beats per minute and results in flows of 4–8 liters per minute. Blood contacting surfaces are made of polyetherurethane. The internal controller transmits device performance data to a bedside console by radiofrequency transmission, including hydraulic pressure waveforms and battery status. Implementing a process of inductive coupling, internal TET coil accepts high frequency power transmitted through the skin from an external TET coil (secured over the internal TET coil with adhesive dressings). The external components include the external TET coil, portable TET module (ambulatory use), bedside console, and batteries.

The AbioCor IRH was first approved by the Food and Drug Administration (FDA) in September of 2006 as a Humanitarian Use Device. However, this pump is currently no longer being manufactured, thus the remainder of the chapter will focus on the CardioWest TAH.

Clinical Trials

Much of the contemporary published experience with the CardioWest TAH comes from the 10-year North American pivotal study and single center experiences from high volume European hospitals (data summarized in Table 29.1). There are no randomized, controlled trials that compare the TAH to other forms of biventricular support or replacement.

In 1990, use of the Jarvik-7 was banned in the United States, until 1993 when the FDA approved the device for investigational use at five U.S. centers. Dr. Jack Copeland and colleagues published their 10-year experience evaluating the safety and efficacy of the now renamed CardioWest TAH as a bridge to heart transplantation [19]. The study included 95 patients of which 81 met the standard inclusion criteria of the protocol. The survival analysis of this protocol group was the basis for eventual FDA approval of the device in the United States. Fourteen of the patients were excluded from the core analysis because they failed to meet the protocol inclusion criteria or received the device on a compassionate use exception (absent documentation for meeting inclusion criteria [4], rescue from LVAD [3], dialysis [2], not transplant candidate [2], co-existing medical condition likely to prevent survival [2] or failing cardiac allograft [1]).

The investigators established that the device restored end-organ function and hemodynamic stability, thus effectively bridging dying patients to heart transplantation at an impressive rate of 79 %, the highest reported rate for any device at the time of publication. Additionally, patients experienced a post-transplant survival comparable to published registry data (1-year 86 %, 5-year 64 %). The device had very low failure rates (1 case of diaphragm rupture) and most of the device- related complications were related to fitting complications (2 deaths) and catheter entrapment from upper extremity central venous lines (3 deaths).

Unlike in the United States, European utilization of the Jarvik-7/CardioWest TAH has been uninterrupted since the 1980's. Reports from France and Germany describe outcomes from a wide spectrum of patients of high severity of illness including a higher prevalence of preoperative cardiac arrest, hemodialysis, and mechanical ventilation. Leprince published the French experience in 127 patients over 15 years [15]. Most deaths were related to multi-organ failure and occurred within 2 weeks (12 ± 9 days) of device implantation. A German series by El-Banayosy et al. reported on 42 patients implanted with the TAH who were extremely sick, many who would have been excluded criteria for the U.S. trial. The

Table 29.1 Summary of major clinical studies with the CardioWest total artificial heart [15–18]

	Copeland et al. [17]		Leprince et al. [15] (127 pts);	El-Banayosy et al. [16] (42 patients)	Roussel et al. [18] (42 patients)
	Protocol (N = 81)	Exception (N = 14)			
Preoperative characteristics					
Age (years, mean ± SD)	51 ± 10	NR	38 ± 13	51 ± 13	46 ± 10
Male gender (%)	86 %	NR	85 %	88 %	95 %
IABP (%)	36 %	NR	NR	67 %	33 %
Multiple/Inotropes Pressors (%)	100 %	NR	NR	100 %	NR
Mechanical ventilation (%)	42 %	NR	NR	74 %	14 %
Pre-operative dialysis (%)	0 %	NR	NR	52 %	7 %
Pre-operative cardiac arrest (%)	37 %	NR	NR	45 %	14 %
Failure to wean from CPB (%)	19 %	NR	NR	26 %	NR
Survival to transplant (%)	79 %	50 %	< 1993 = 43 %; 1993–1997 = 55 %; 1997–2001 = 74 %	26 % transplanted;22 % alive on device	72 %
Days on device (Mean ± SD)	79 ± 84	NR	NR	86 ± 89	101 ± 86
Device malfunction					
Ruptured diaphragm (%)	1 %		1 %	2 %	0 %
Catheter entrapment (%)	3 %		NR	2 %	2 %
Fit complication (%)	5 %		NR	19 %	5 %
Complications					
Any bleeding (%)	44 %		26 %	21 %	NR
Bleeding requiring re-operation (%)	21 %		NR	19 %	52 %
Pump/mediastinal infection (%)	5 %	NR	3 %	5 %	5 %
Driveline infection (%)	21 %	NR	NR	7 %	14 %
Any infection (%)	77 %		NR	NR	83 %
Any neurological Event (%)	27 %		0.016 event/ month	9.6 %	
Stroke (%)	12 %	NR	0 %	NR	8 %
Hemodialysis (%)	27 %			15 % in those with normal baseline	64 %

Table 29.1 (continued)

	Copeland et al. [17]		Leprince et al. [15] (127 pts);	El-Banayosy et al. [16] (42 patients)	Roussel et al. [18] (42 patients)
	Protocol (N = 81)	Exception (N = 14)			
Outcomes					
Survival to transplant (%)	79 %	50 %	< 1993 = 43 %; 1993–1997 = 55 %; 1997–2001 = 74 %	26 % transplanted; 22 % alive on device	72 %
Post-transplant 1-Yr Survival (%)	86 %	NR	NR	NR	90 %

CPB cardiopulmonary bypass, *IABP* intraaortic balloon pump, *NR* not reported, *Yr* year

study reported a 52 % mortality rate on the TAH, with most patients dying from irreversible pre-implantation end organ failure [16]. The findings of the German study highlight the limitations of the pump in the setting of chronically or severely compromised liver and kidney function.

Patient Selection

The current application of the TAH is to bridge patients dying from bi-ventricular failure to heart transplantation. The inclusion criteria for the U.S. clinical trial included (1) heart transplant eligibility, (2) New York Heart Association class IV symptoms, (3) adequate thoracic cavity size, and (4) hemodynamic compromise (Cardiac index ≤2.0 liters/min/m^2 *with* systemic hypotension or high central venous pressure [>18 mmHg] *or* requirement of multiple vasoactive medication/IABP/CPB) [19]. Real world application of the device has extended to a number of indications where LVAD therapy is not ideal: including patients with myocardial wall rupture, extensive intracavitary thrombus formation, cardiac allograft failure, refractory arrhythmias, mechanical valves, complex congenital heart disease, restrictive cardiomyopathy, hypertrophic cardiomyopathy, proximal aortic disease, failed LVAD therapy and acute fulminant cardiogenic shock.

Right ventricular failure in patients who have LVADs portends a poor outcome [20]. However, identifying patients with right ventricular dysfunction that would benefit from biventricular support/replacement rather than an LVAD for bridge to heart transplantation remains clinically challenging. While a myriad of risk measures for right ventricular failure have been identified, congruency of these measures in the real world patient is often absent. Table 29.2 lists a sampling of the various echocardiographic, hemodynamic, clinical and laboratory measures that have been proposed [20–24]. Furthermore, selecting type of biventricular therapy can be clinically challenging. In retrospective reports, outcomes with biventricular assist devices (bi-VADs) have been generally sub-optimal compared to the TAH,

Table 29.2 Summary of various clinical parameters shown to predict right ventricular failure after left ventricular assist device placement [20–24]

	No RVF	RVF	P	Study
Hemodynamic parameters				
RVSWI (mmHg •mL•m^{-2})	368 ± 245	151 ± 75 (RVAD)	0.01	Fukamachi et al. [24]
	556 ± 298	391 ± 226 (RVAD) 541 ± 344 (inotropes > 14d) 560 ± 335 (Late RVF)	0.04	Kormos et al. [20]
	463 ± 180	330 ± 160 (RVAD, inhaled NO, inotropes>14d)	0.002	Kato et al. [23]
Cardiac output (L/min)	3.5 ± 0.9	2.8 ± 0.5 (RVAD)	0.02	Fukamachi et al. [24]
Cardiac index (L/min/m2)	2.5 (IQR 1.2–4.3)	2.1 (IQR 1.5–3.1) (RVAD, inhaled NO, hypotension)	0.04	Potapov et al. [21]
Pulmonary artery systolic pressure (mmHg)	38 ± 11	31 ± 5 (RVAD)	0.015	Fukamachi et al. [24]
	52 ± 11	62 ± 11 (inotropes>14d)	0.03	Puwanant et al. [22]
Central venous pressure (mmHg)	12 ± 6.4	16 ± 6 (RVAD) 15 ± 7 (inotropes > 14d) 13 ± 8 (late RVF)	0.01	Kormos et al. [20]
Echocardiographic parameters				
TAPSE (mm)	15 ± 6	8 ± 4 (inotropes>14d)	<0.01	Puwanant et al. [22]
RV systolic pressure (mmHg)	46 ± 11	60 ± 14 (inotropes>14d)	0.02	Puwanant et al. [22]
LVEDd (mm)	75 (IQR 53–102)	68 (IQR 64–75) (RVAD, inhaled NO, hypotension)	0.03	Potapov et al. [21]
	73 ± 13	63 ± 10 (RVAD, inhaled NO, inotropes>14d)	<0.001	Kato et al. [23]
LA/LVEDd	0.8 ± 0.2	0.7 ± 0.1 (RVAD, inhaled NO, inotropes>14d)	0.004	Kato et al. [23]
Laboratory parameters				
AST (mg/dL)	74 ± 201	236 ± 557 (RVAD) 78 ± 236 (inotropes > 14d) 89 ± 164 (late RVF)	0.02	Kormos et al. [20]
	146 ± 189	637 ± 1519 (RVAD)	0.006	Fukamachi et al. [24]

Table 29.2 (continued)

	No RVF	RVF	P	Study
Albumin (mg/dL)	3.4 ± 0.6	3.7 ± 0.6 (RVAD, inhaled NO, inotropes>14d)	0.028	Kato et al. [23]
Total Bilirubin (mg/dL)	1.6 ± 0.8	2.1 ± 1.6 (RVAD, inhaled NO, inotropes>14d)	0.018	Kato et al. [23]
BUN(mg/dL)	30 ± 17	36 ± 17 (RVAD) 32 ± 14 (inotropes>14d) 33 ± 20 (late RVF)	0.05	Kormos et al. [20]
INR	1.4 (IQR 1.1–5.0)	1.64 (IQR 1.2–3.0) (RVAD, inhaled NO, hypotension)	0.046	Potapov et al. [21]
NT-proBNP (pg/mL)	4699 (IQR 925–10,433)	13,026 (IQR 8800–17,566) (RVAD, inhaled NO, hypotension)	0.046	Potapov et al. [21]
C-reactive Protein	1.8 (IQR 0.3–20)	4.3 (IQR 1.3–30) (RVAD, inhaled NO, hypotension)	0.02	Potapov et al. [21]
Clinical characteristics				
Ventilator support	21 (5 %)	11(37 %) (RVAD) 5 (14 %) (inotropes>14d) 3 (9 %) (late RVF)	<0.001	Kormos et al. [20]
Myocarditis	0	3 (27 %) (RVAD)	<0.001	Fukamachi et al. [24]
Body Surface Area (m^2)	2 ± 0.2	1.7 ± 0.2 (RVAD)	<0.001	Fukamachi et al. [24]

AST Aspartate Aminotransferase, *BUN* Blood Urea Nitrogen, *LA/LVEDd* Left Atrial diameter divided by Left Ventricular End Diastolic diameter, *LVEDd* Left Ventricular End Diastolic diameter, *NO* Nitric Oxide, *RV* Right Ventricular, *RVAD* Right Ventricular Assist Device, *RVSWI* Right Ventricular Stroke Work Index, *RVF* Right Ventricular Failure, *TAPSE* Tricuspid Annular Plane Systolic Excursion, *TR* Tricuspid regurgitation Grade: Grade I, regurgitation jet reaches middle part of the right atrium; Grade II, regurgitation jet reaches roof of the right atrium; Grade III, regurgitation jet into caval veins; and Grade IV, pulsation of the hepatic and jugular veins

however comparative prospective data are lacking [25, 26]. In general, patients requiring biventricular support with potential for myocardial recovery should be considered for bi-VADs; while those with refractory shock or expected to require prolonged support may benefit from the TAH.

Anatomical limitations may preclude candidacy for the CardioWest TAH, as the device can compress venous return in undersized patients. In clinical study, a body-surface area of 1.7–2.5 m^2 or anterior-posterior distance (from the anterior vertebral body to the inner table of the sternum at the 10th thoracic vertebrate) greater than 10 cm on computed tomographic imaging were required for device placement [19].

While thoracic diameter has been used as a guideline for sizing, the size of the cardiac silhouette may be an important determinant for appropriate fitting of the TAH. El-Banayosy et al. reported numerous fit problems and difficulty with chest closure especially in patients with acute post-myocardial infarction cardiogenic shock, where the ventricle had not yet dilated as occurs in a chronic cardiomyopathy [16]. However, successful implantation is feasible in smaller patients who have an enlarged cardiac silhouette allowing for adequate space for the device after ventriculectomy. Furthermore, in smaller patients, displacement of the left TAH pump in the leftward direction can be considered to prevent compressive effects. Utilizing this strategy, Leprince and colleagues have reported successful implantation of the device in smaller patients with excellent clinical outcomes and rare fit complication [27]. Development of a smaller, 50 cc CardioWest TAH is ongoing and could allow for implantation of the device into children and smaller adults.

Clinical risk factors for the TAH differ from accepted risk factors for LVAD implantation and robust data for selecting patients are absent. In a post-hoc analysis of the patient included and eligible for the Pivotal U.S. Study, only a history of smoking identified risk of death on device in a multivariate analysis, while hemodynamic parameters and measures of end organ function were not predictors [28]. In European studies and the U.S. post-market experience, patients with the TAH implanted for allograft failure had less favorable outcomes [15, 16, 29]. As a general consideration, patients with irreversible end-organ damage (kidney, liver), markedly elevated pulmonary vascular resistance and unalterable contraindications to heart transplantation (U.S. only) should be excluded from candidacy.

Operative Techniques and Considerations

The device is implanted through a standard median sternotomy. Similar to implant techniques for LVADs, the left diaphragm is taken down and a small preperitoneal space is made. Once the patient is on cardiopulmonary bypass, the left and right ventricle are excised leaving a 1 cm rim of muscle below the mitral and tricuspid annulus. The incisions are carried through the right and left ventricular outflow tract and the aorta and pulmonary artery are transected just above the aortic and pulmonic valves. The mitral and tricuspid valve leaflets are excised leaving the annular rim. The cuffs of the atrial quick-connects and the grafts to the great arteries are then trimmed and sewn to their respective orifices. To minimize risk of thrombotic complications and kinking, the surgeon should make efforts to minimize the synthetic material used to form the atrial quick-connects and the length of the aortic and pulmonary graft.

The pericardium is lined with thin sheets of polytetrafluoroethylene (PTFE) to facilitate subsequent sternal re-entry for transplantation [30]. The drivelines are passed through the abdominal wall and the artificial ventricles are connected to their respective orifices. Inflammatory contracture of the pericardium about the device can limit the space available for a donor allograft. In addition to reducing device

induced inflammation with the PTFE, a standard breast prosthesis is placed where the apex of the heart would sit and generally filled with 200 ml of saline. The system is deaired and the aortic clamp is then removed. The artificial heart settings are steadily increased and the patient is taken off of cardiopulmonary bypass.

Early bleeding after TAH implant is frequent with high rates of surgical re-exploration in published reports (Table 29.1). Some institutions perform delayed sternal closure leaving the chest open often for several days until postoperative bleeding is stable. During chest closure, the right and left atrial venous return are subject to compression by the device and can result in abrupt drops in the fill volume and cardiac output. While intraoperative transesophageal echocardiography cannot visualize the pump clearly, it provides valuable information on right and left atrial venous inflow. Compression is more common with the right pump (both the cava and right-sided pulmonary veins) and can generally be treated with displacement of the device leftward and inferiorly.

Management Considerations

Pump Optimization

The optimal settings for the CardioWest ventricles maintains full ejection of each ventricle while only partially filling thus allowing for accommodation for fluxes in venous return. The driver console has a computer display showing the airflow waveforms for each pump in systole and diastole, stroke volume as estimated by displaced air in the driveline and cardiac output. The user can manipulate various parameters to modulate pump performance including ejection rate, vacuum pressure to augment filling, ejection pressure and percentage of each pump cycle spent in systole.

Changes in the displayed parameters may signal a physiological change or a device-related problem. Decreases in fill volumes and pump output should raise concern for hypovolemia. Early after device implantation, decreased pump output should prompt urgent evaluation for bleeding, atrial tamponade or compression of venous return. If the pumps are persistently full-filling despite optimization of ejection parameters, one should evaluate for venous congestion and consider diuresis. Clinicians should also investigate for an air leak or kink in the drivelines for any abrupt change in parameters, especially in late onset after device implantation.

Anticoagulation

Although anticoagulation therapy and monitoring vary from center to center, the incidence of thromboembolic complication with the CardioWest TAH is low. Once the chest is closed and there is minimal chest tube drainage, patients receive heparin or bivalirudin along with antiplatelet therapy with aspirin

(81 mg daily), and dipyridamole (50 mg thrice daily) [31, 32]. Once patients are ambulatory and tolerating a diet, warfarin is started to achieve an international normalized ratio (INR) between 2 and 3. Many centers implement a multitargeted monitoring approach to guide anticoagulation [31, 33, 34]. Antiplatelet agents are titrated by optical aggregometry to 20–40 % normal function and thromboelastography is used to guide anticoagulation early after device implantation.

Renal Failure and Natriuretic Peptides

The incidence of dialysis dependent acute renal failure after implantation of the TAH is high, and it is unclear if these finding are attributable to the pre-implantation condition of the patient or factors specific to the device itself. The reported incidence of renal failure, as defined as serum creatinine concentration $\geq$ 5 mg/dL or need for dialysis, ranged from 19 to 64 % in previous studies [17, 18]. Even after selecting for healthier patients with normal kidney function prior to surgery, El-Banayosy et al. still observed a 15 % rate of renal replacement therapy after implanting the TAH [16].

We and others have noted that exogenous perioperative replacement with low dose nesiritide may improve renal function as measured by urine output and glomerular filtration rate, and that patients can be gradually weaned from the nesiritide once they are clinically euvolemic [35, 36]. After ventriculectomy, the circulating concentrations of B-type natriuretic peptide (BNP) decrease to normal within hours of surgery and loss of intrinsic production of BNP may increase the risk of renal failure following TAH implantation. The abrupt removal of BNP may adversely impact renal function by altering renal hemodynamics and neurohormonal balance. The impact of nesiritide use on longer term outcomes is not defined.

Anemia

Severe anemia is prevalent during TAH support and reverses after heart transplantation. The etiology is not clear but appears to be multifactorial and includes low grade hemolysis from the four mechanical valves and ineffective erythropoeisis secondary to inflammation [37]. Despite the anemia, patients supported with the device exhibit reasonable exercise tolerance and minimal symptoms even with hemoglobin concentrations as low 6–8 g/dL. While overt hemolysis requiring blood transfusion was common in the early experience with the TAH, these issues improved by decreasing the $\Delta p/\Delta t$ of air delivery from the driver [38]. Blood transfusions are avoided to prevent sensitization unless patients are symptomatic or there are other concerns of limited end organ perfusion.

Exercise and Rehabilitation

Physical therapy and rehabilitation are feasible and encourage early after implantation of the TAH. In a study by Kohli and colleagues, patients were participating in physical therapy safely in the first week and ambulating on a treadmill by the third week after implantation [39]. Bearing in mind the device parameters and output are rather fixed and do not change in response to activity, patients in the study were observed to have a flat blood pressure response to moderate levels of activity. Prior to therapy, it is reasonable to augment device ejection rate to accommodate increased oxygen demands.

Future Direction and Devices

While already approved for use Europe, the Freedom driver used with the CardioWest TAH is being studied for home discharge in the United States. If the portable driver is approved, patients who were once tethered to the hospital awaiting heart transplantation may now be discharged home. Furthermore, home discharge of patients will allow once again evaluation of the TAH for destination therapy.

Considering the durability and clinical success with axial flow LVADs, development of a continuous flow TAH is under investigation. Frazier et al. developed a technique in which two HeartMate II LVADs (Thoratic Corporation; Pleasonton, California) supplanted excised ventricles by replacing the inflow and outflow grafts with titanium adapters [40]. The condition included two controllers for the two separate pumps. They were able to demonstrate changes in the pump flow during exercise on a treadmill, indicating that these non-pulsatile pumps could accommodate changes in venous return based on inflow pressure. The authors also reported a human implantation in a patient with severe systemic amyloid who achieved cardiovascular stability, but succumbed to hepatic failure from amyloid after 5 weeks [41].

The Cleveland Clinic Continuous Flow Total Artificial Heart (CFTAH; Cleveland, Ohio) has a single DC motor and rotating assembly affixed to two centrifugal pumps, the speed of which can be modulated to maintain pulsatility (Fig. 29.4) [24]. The remarkable passive self-regulating design allows a single magnet to be displaced either to the right or left depending on elevations in the left or right atrial pressure, respectively. Hence, with physiological elevations in left atrial pressure, there is a free axial shift of the magnet to the right reducing the right pump aperture size and flow to maintain a steady state. An automatic speed control mode is used to reduce pump flow in the setting of elevated systemic vascular resistance thereby blunting the effect of high systemic blood pressures on the function of the TAH. This device is currently undergoing in vivo studies, bench testing and fit studies in humans [42–44].

French investigators are implementing bioprosthetic material to design a TAH with reduced the need for anticoagulation. The Carmat TAH (CARMAT; Paris, France) is an implantable, electro-hydraulically driven, pulsatile flow device with

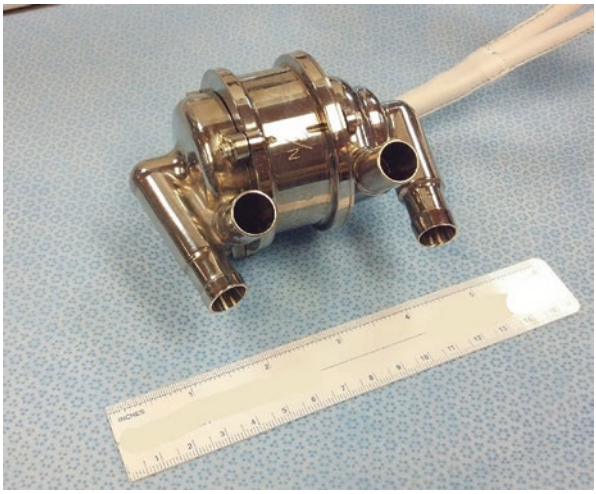


Fig. 29.4 The cleveland clinic continuous flow total artificial heart. The device consists of two centrifugal pumps and is currently under laboratory investigation (Image provided courtesy of Leonard Golding, MD, Cleveland Clinic)

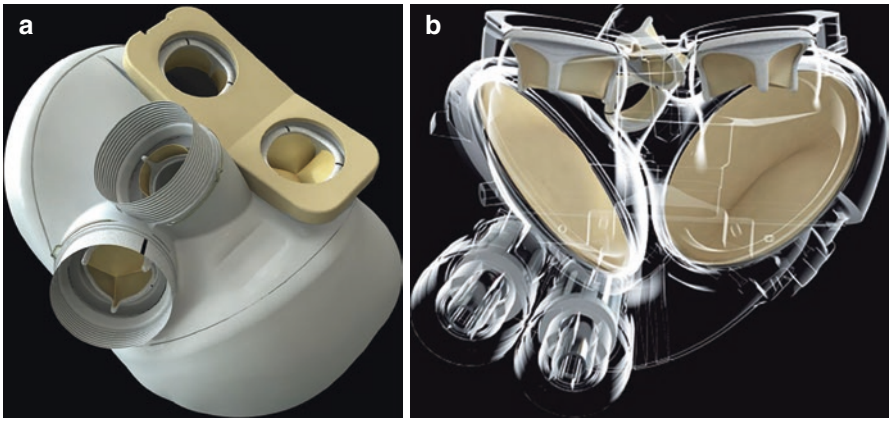


Fig. 29.5 The Carmat total artificial heart. The exterior (**a**) and inner workings (**b**) of the TAH revealing a electro-hydraulically driven, pulsatile flow device with four bioprosthetic valves (Image reprinted with permission from CARMAT)

four bioprosthetic valves [45]. Its' blood-pumping surfaces consist of processed pericardial tissue and expanded polytetrafluorethylene (ePTFE), potentially allowing for the reduction of anticoagulation. The Carmat TAH contains two ventricles, each with a blood compartment and a liquid compartment, separated by a pulsatile hybrid membrane (Fig. 29.5). The membrane has a polyurethane layer at the liquid-contacting surface and bovine pericardial tissue on the blood-contacting surface. The fixed surface of the blood compartment is covered with ePTFE. Electro-hydraulic pumps create a systolic and a diastolic phase by moving the silicone fluid and deploying the hybrid membrane. The stroke volume (30–65 ml) and the beat rate (35–150 bpm) of the prosthesis adapt automatically in response to changes in

preload detected by baroreceptors located in the device. The resulting pulsatile blood flow ranges from 2 to 9 L/min with a flow adjustment on the right side to correct for the bronchial shunt. The prosthesis is partially surrounded by a flexible compliance bag. This device is currently in the preclinical phase of bench testing.

Total heart replacement with a mechanical heart has proven to be an effective therapy to salvage the sickest patients dying of heart failure. As device technology becomes more portable, durable and bio-integrated, the artificial heart will challenge heart transplantation as the definitive therapy for end-stage heart failure.

References

1. LeGallois J. Experiments on the principles of life. Paris: D'Hautel; 1812.
2. Gibbs OS. An Artificial Heart. J Pharmacol Exp Ther. 1930;38(2):197–215.
3. Dodrill FD, Hill E, Gerisch RA. Temporary mechanical substitute for the left ventricle in man. J Am Med Assoc. 1952;150(7):642–4.
4. Gibbon JH Jr. Application of a mechanical heart and lung apparatus to cardiac surgery. Minn Med. 1954;37(3):171–185; passim.
5. Nosé Y. The birth of the artificial heart programs in the world: a special tribute to Tetsuo Akutsu and Valerÿ Shumakov. Artif Organs. 2008;32(9):667–83.
6. Cooley DA, Liotta D, Hallman GL, Bloodwell RD, Leachman RD, Milam JD. Orthotopic cardiac prosthesis for two-staged cardiac replacement. Am J Cardiol. 1969;24(5):723–30.
7. Cooley DA. The total artificial heart. Nat Med. 2003;9(1):108–11.
8. Curran WJ. Law-medicine notes. The first mechanical heart transplant: informed consent and experimentation. N Engl J Med. 1974;291(19):1015–6.
9. Cooley DA. Feuds: social and medical. Tex Heart Inst J. 2010;37(6):649–51.
10. Cooley DA, Akutsu T, Norman JC, Serrato MA, Frazier OH. Total artificial heart in two-staged cardiac transplantation. Cardiovasc Dis. 1981;8(3):305–19.
11. DeVries WC, Anderson JL, Joyce LD, Anderson FL, Hammond EH, Jarvik RK, et al. Clinical use of the total artificial heart. N Engl J Med. 1984;310(5):273–8.
12. Copeland JG, Levinson MM, Smith R, Icenogle TB, Vaughn C, Cheng K, et al. The total artificial heart as a bridge to transplantation. A report of two cases. JAMA. 1986;256(21): 2991–5.
13. Dowling RD, Gray Jr LA, Etoch SW, Laks H, Marelli D, Samuels L, et al. Initial experience with the AbioCor implantable replacement heart system. J Thorac Cardiovasc Surg. 2004;127(1):131–41.
14. Dowling RD, Gray Jr LA, Etoch SW, Laks H, Marelli D, Samuels L, et al. The AbioCor implantable replacement heart. Ann Thorac Surg. 2003;75(6 Suppl):S93–9.
15. Leprince P, Bonnet N, Rama A, Léger P, Bors V, Levasseur JP, et al. Bridge to transplantation with the Jarvik-7 (CardioWest) total artificial heart: a single-center 15-year experience. J Heart Lung Transplant. 2003;22(12):1296–303.
16. El-Banayosy A, Arusoglu L, Morshuis M, Kizner L, Tenderich G, Sarnowski P, et al. CardioWest total artificial heart: bad Oeynhausen experience. Ann Thorac Surg. 2005;80(2): 548–52.
17. Copeland JG, Smith RG, Arabia FA, Nolan PE, McClellan D, Tsau PH, et al. Total artificial heart bridge to transplantation: a 9-year experience with 62 patients. J Heart Lung Transplant. 2004;23(7):823–31.
18. Roussel JC, Sénage T, Baron O, Périgaud C, Habash O, Rigal JC, et al. CardioWest (Jarvik) total artificial heart: a single-center experience with 42 patients. Ann Thorac Surg. 2009;87(1): 124–30.

19. Copeland JG, Smith RG, Arabia FA, Nolan PE, Sethi GK, Tsau PH, et al. Cardiac replacement with a total artificial heart as a bridge to transplantation. N Engl J Med. 2004;351(9):859–67.
20. Kormos RL, Teuteberg JJ, Pagani FD, Russell SD, John R, Miller LW, et al. Right ventricular failure in patients with the HeartMate II continuous-flow left ventricular assist device: incidence, risk factors, and effect on outcomes. J Thorac Cardiovasc Surg. 2010;139(5):1316–24.
21. Potapov EV, Stepanenko A, Dandel M, Kukucka M, Lehmkuhl HB, Weng Y, et al. Tricuspid incompetence and geometry of the right ventricle as predictors of right ventricular function after implantation of a left ventricular assist device. J Heart Lung Transplant. 2008; 27(12):1275–81.
22. Puwanant S, Hamilton KK, Klodell CT, Hill JA, Schofield RS, Cleeton TS, et al. Tricuspid annular motion as a predictor of severe right ventricular failure after left ventricular assist device implantation. J Heart Lung Transplant. 2008;27(10):1102–7.
23. Kato TS, Farr M, Schulze PC, Maurer M, Shahzad K, Iwata S, et al. Usefulness of two-dimensional echocardiographic parameters of the left side of the heart to predict right ventricular failure after left ventricular assist device implantation. Am J Cardiol. 2012;109(2): 246–51.
24. Fukamachi K, Horvath DJ, Massiello AL, Fumoto H, Horai T, Rao S, et al. An innovative, sensorless, pulsatile, continuous-flow total artificial heart: device design and initial in vitro study. J Heart Lung Transplant. 2010;29(1):13–20.
25. Kirklin JK, Naftel DC, Kormos RL, Stevenson LW, Pagani FD, Miller MA, et al. The fourth INTERMACS annual report: 4,000 implants and counting. J Heart Lung Transplant. 2012;31(2):117–26.
26. Kirsch M, Mazzucotelli J-P, Roussel J-C, Bouchot O, N'loga J, Leprince P, et al. Survival after biventricular mechanical circulatory support: does the type of device matter? J Heart Lung Transplant. 2012;31(5):501–8.
27. Leprince P, Bonnet N, Varnous S, Rama A, Léger P, Ouattara A, et al. Patients with a body surface area less than 1.7 m2 have a good outcome with the CardioWest Total Artificial Heart. J Heart Lung Transplant. 2005;24(10):1501–5.
28. Copeland JG, Smith RG, Bose RK, Tsau PH, Nolan PE, Slepian MJ. Risk factor analysis for bridge to transplantation with the CardioWest Total Artificial Heart. Ann Thorac Surg. 2008;85(5):1639–44.
29. Quader MA, Tang D, Katlaps G, Shah KB, Kasirajan V. Total artificial heart for patients with allograft failure. J Thorac Cardiovasc Surg. 2013;145(2):e21–3.
30. Copeland JG, Arabia FA, Smith RG, Covington D. Synthetic membrane neo-pericardium facilitates total artificial heart explantation. J Heart Lung Transplant. 2001;20(6):654–6.
31. Ensor CR, Cahoon WD, Crouch MA, Katlaps GJ, Hess ML, Cooke RH, et al. Antithrombotic therapy for the CardioWest temporary total artificial heart. Tex Heart Inst J. 2010;37(2): 149–58.
32. Crouch MA, Kasirajan V, Cahoon W, Katlaps GJ, Gunnerson KJ. Successful use and dosing of bivalirudin after temporary total artificial heart implantation: a case series. Pharmacotherapy. 2008;28(11):1413–20.
33. Glauber M, Szefner J, Senni M, Gamba A, Mamprin F, Fiocchi R, et al. Reduction of haemorrhagic complications during mechanically assisted circulation with the use of a multi-system anticoagulation protocol. Int J Artif Organs. 1995;18(10):649–55.
34. Szefner J. Control and treatment of hemostasis in cardiovascular surgery. The experience of La Pitié Hospital with patients on total artificial heart. Int J Artif Organs. 1995;18(10):633–48.
35. Shah KB, Tang DG, Kasirajan V, Gunnerson KJ, Hess ML, Sica DA. Impact of low-dose B-type natriuretic peptide infusion on urine output after total artificial heart implantation. J Heart Lung Transplant. 2012;31(6):670–2.
36. Delgado R, Wadia Y, Kar B, Ethridge W, Zewail A, Pool T, et al. Role of B-type natriuretic peptide and effect of nesiritide after total cardiac replacement with the AbioCor total artificial heart. J Heart Lung Transplant. 2005;24(8):1166–70.

37. Mankad AK, Tang DG, Clark WB, Flattery M, Harton S, Katlaps GJ, et al. Persistent anemia after implantation of the total artificial heart. J Card Fail. 2012;18(6):433–8.
38. Levinson MM, Copeland JG, Smith RG, Cork RC, DeVries WC, Mays JB, et al. Indexes of hemolysis in human recipients of the Jarvik-7 total artificial heart: a cooperative report of fifteen patients. J Heart Transplant. 1986;5(3):236–48.
39. Kohli HS, Canada J, Arena R, Tang DG, Peberdy MA, Harton S, et al. Exercise blood pressure response during assisted circulatory support: comparison of the total artifical heart with a left ventricular assist device during rehabilitation. J Heart Lung Transplant. 2011;30(11): 1207–13.
40. Frazier OH, Cohn WE, Tuzun E, Winkler JA, Gregoric ID. Continuous-flow total artificial heart supports long-term survival of a calf. Tex Heart Inst J. 2009;36(6):568–74.
41. Frazier OH, Cohn WE. Continuous-flow total heart replacement device implanted in a 55-year-old man with end-stage heart failure and severe amyloidosis. Tex Heart Inst J. 2012;39(4):542–6.
42. Fumoto H, Horvath DJ, Rao S, Massiello AL, Horai T, Takaseya T, et al. In vivo acute performance of the Cleveland Clinic self-regulating, continuous-flow total artificial heart. J Heart Lung Transplant. 2010;29(1):21–6.
43. Kobayashi M, Horvath DJ, Mielke N, Shiose A, Kuban B, Goodin M, et al. Progress on the design and development of the continuous-flow total artificial heart. Artif Organs. 2012;36(8):705–13.
44. Shiose A, Nowak K, Horvath DJ, Massiello AL, Golding LAR, Fukamachi K. Speed modulation of the continuous-flow total artificial heart to simulate a physiologic arterial pressure waveform. ASAIO J. 2010;56(5):403–9.
45. Jansen P, Van Oeveren W, Capel A, Carpentier A. In vitro haemocompatibility of a novel bioprosthetic total artificial heart. Eur J Cardiothorac Surg. 2012;41(6):e166–72.

Chapter 30
Physiology of Stem Cells

Jos Domen and Kimberly Gandy

Stem Cells: History

Mammalian life, at conception, starts with a single zygote that has the ability to form all of the cells of the body (as well as extra-embryonic tissues). This cell by definition is a pluripotent stem cell, that is, it is capable of assuming all possible cell fates. It has long been recognized that certain tissues, such as blood, skin and gut epithelium, have a high turnover throughout life, and need to be replenished continuously from progenitor or stem cells. The need for stem cells in adults is less well understood, and only recently, has stem cell potential been identified in mature tissues that do not have rapid turnover.

A leading impetus in the search for stem cells was the aftermath of the atomic bomb explosions in World War II. It became clear that exposure to radiation could kill the ability of the body to generate new blood cells, and at somewhat higher doses, could destroy the ability of the intestinal tract to regenerate. Both conditions result in death. Mouse experiments confirmed the lethal consequences of irradiation and demonstrated that the ability to generate blood cells could be preserved if just one limb was shielded from radiation [1]. This was followed by the equally critical observation that transfer of non-irradiated bone marrow cells could restore the ability to generate blood cells [2]. It was then determined that irradiation followed by bone marrow transfer resulted in the appearance of colonies of myeloid and erythroid cells in the spleen and that all of the cells in a colony were derived from one

J. Domen, PhD (✉)
Section of Cardiac Surgery, Children's Mercy Hospital and Clinics and University of Missouri, Room 3730-08, 2401 Gilham Road, Kansas City, MO 64108, USA
e-mail: adomen@cmh.edu

K. Gandy, MD, PhD
Department of Biomedical and Health Informatics, University of Missouri, 4451 Francis Street, Kansas City, KS 66103, USA
e-mail: kgandy@playithealth.com

H. Eisen (ed.), *Heart Failure*, DOI 10.1007/978-1-4471-4219-5_30

cell [3]. Hematopoietic Stem Cells are the small subset of spleen colony-forming cells that can give rise to both secondary colonies, as well as lymphoid offspring [4, 5]. Specific labeling methods and reconstitution assays developed since [6, 7] have greatly improved our ability to study these cells.

Not only has a great deal been learned about these hematopoietic stem cells in the last 50 years, but they have also found widespread application in the clinic. Mimicking the original observation that bone marrow could rescue the hematopoietic system in an otherwise lethally irradiated recipient, bone marrow transplantation has become standard of care to treat cancer patients that undergo high dose chemo and/or radiation therapy, or that suffer from hematopoietic malignancies. Worldwide, more than 50,000 people receive bone marrow transplantations each year [8]. Approximately 21,000 are allogeneic, the rest are autologous transplants. Increasingly, mobilized peripheral blood or umbilical cord blood is used as the source.

Stem cells in most other systems are less well characterized, and in many cases, have only been recognized fairly recently as being present in adults. Clinical use is limited, at best, to trials.

Stem Cells: Definition

Stem cells are defined as cells that have, at the individual cell level, the ability to both self-renew (make more copies of themselves) and differentiate into one, many or all cell fates of the body (Fig. 30.1). Stem cells are typically rare and are often quiescent.

Self-renewal in its strictest sense implies unlimited proliferative capacity, since the daughters are identical to the parent cell. This is impossible to verify experimentally, at least without unlimited funding and time. A more practical definition would be the ability to function and produce cells beyond the normal lifespan of the organ-

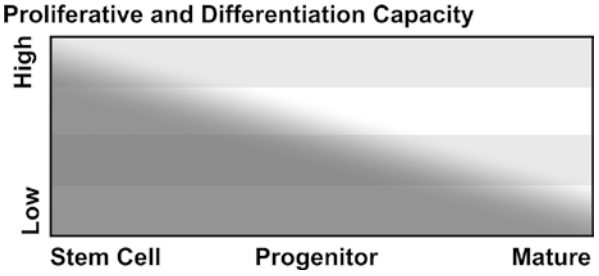


Fig. 30.1 Stem and progenitor cells defined by proliferative and differentiation capacity. This figure depicts the reduction in proliferative potential and differentiation potential during cell maturation. It should be kept in mind that these differences are not absolute. Some mature cells, e.g. lymphocytes, can proliferate extensively, and some mature cells retain the potential to differentiate further. B cell class switching would be an example

ism. E.g. murine hematopoietic stem cells can be transplanted serially, and repopulate new hosts, at least five times [9–11]. While this is not unlimited, it clearly suffices for the animal, even if the need for cells is higher than normal, such as following (repeated) serious injury and blood loss. In addition, it is important to note that the proliferative limitations encountered may well be a result of the experimental conditions (repeated transplantation into an irradiated environment) and do not necessarily represent the true limitations inherent to the stem cells themselves.

Cells that come much closer to demonstrating unlimited proliferative capacity are cells that can be maintained in culture, such as embryonic stem cells. Many of the murine ES cell lines have been in culture now for over 20 years, and have been used and expanded extensively by many different laboratories, without losing the ability to act as pluripotent stem cells with the capacity to regenerate a mouse.

The differentiation capacity is the main distinguishing feature between different types of stem cells. Pluripotent stem cells such as embryonic stem cells and iPS cells have the ability to generate all the different cells in the body (and can generate the organism as a whole). These cells represent germ line stem cells, the cells that allow life to pass from one generation to the next. Other types of stem cells in the adult body (sometimes referred to as "adult stem cells") are more restricted; they can differentiate into many (multipotent) or a few (oligopotent) cell lineages within the germ layer from which they are derived. Mesenchymal stem cells and hematopoietic stem cells, for instance, can make subsets of mature mesoderm cells. The ability of stem cells to produce cells derived from other germ layers was hotly debated a decade ago, a debate that was referred to as the stem cell plasticity debate. It was claimed, for instance, that blood cells could differentiate into brain cells, or liver cells [12, 13]. More extensive analysis revealed, however, that much of this apparent plasticity was due to experimental artifacts, such as cell fusion. Plasticity or transdifferentiation--differentiation into a lineage that is not part of the normal repertoire of the stem cell, seems to happen rarely, if at all, under normal conditions [14–16]. Interestingly, what has surfaced since this debate is the ability to reprogram cells, even regular somatic cells without stem cell ability, into pluripotent stem cells (the so-called iPS cells) with the ability to produce cells from endodermal, mesodermal and ectodermal origin [17–21].

Once stem cells commit to differentiation, and leave the stem cell pool, they typically go through an intermediate stage often referred to as progenitors (Fig. 30.2). In some systems other names are used for these cells: In skin, for instance, they are called transit-amplifying cells. Practically, the difference between stem and progenitor cells can be hard to make. Progenitor cells may still have the potential to generate several different types of mature cells. Progenitor cells often have extensive proliferative capacity, and much of the expansion needed to amplify the offspring of the rare stem cells into the many mature cells needed in tissues such as skin, blood and gut epithelium, occurs at the progenitor level. However, progenitor cells do not self-renew. With every cell division they move closer to the mature state. New cells from any given progenitor cell are only generated for a relatively brief period of time, whereas stem cells may produce new cells throughout life. However, the distinction between newly generated and older pre-existing cells can be hard to make when the mature cells are long-lived.

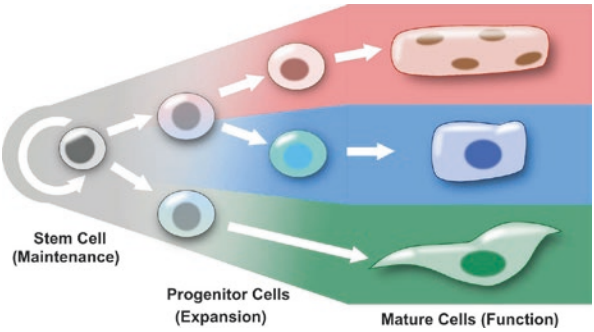


Fig. 30.2 Classical stem cell differentiation pattern. This would apply to hematopoietic cell differentiation, but also to other types of cells, e.g. skin [22]. Maintenance of stem cells is assured by stem cell self-renewal. Much of the proliferation needed to obtain the required number of mature cells occurs at the progenitor level. Progenitors can initially be oligopotent (more than one cell fate possible) or can be committed to a single outcome. Full commitment of progenitors to a new more restricted stage can take several days. Mature cells, depending on type, may retain the capacity for extensive proliferation (e.g. lymphocytes) or may not be able to divide at all (red blood cells, muscle cells)

Diagrams, such as the tree shown in Fig. 30.2 often depict progenitors as very distinct entities, with differentiation steps taking them from more primitive to less primitive, more restricted, progenitors, eventually resulting in mature cells. These entities are based on purification methods such as Fluorescence Activated Cell Sorting (FACS) or assays such as colony assays. The ability to purify, study and use progenitors with specific potential is very useful and informative. The cells themselves, however, can be thought of as being on a continuum, gradually shifting from one phenotype to the next, gradually restricting their differentiation potential.

Stem Cells: Niche and Regulation

Obviously, in view of their proliferative potential, stem cells need extensive regulation. While some stem cells, such as neuronal stem cells, are mostly quiescent and generate few offspring under normal conditions, other stem cells have to continuously generate large numbers of mature cells. For example, in the hematopoietic system more than 10^{11} mature cells need to be produced every day [23–25]. To control this expansion, and prevent it from escaping control, stem cells typically need specific signals to maintain their stem cell potential. In the absence of these signals the cells either differentiate along a default pathway, or undergo apoptosis. Yet it is also essential that the stem cell numbers are maintained. Loss of e.g. colon or hematopoietic stem cells would result in death in days to weeks. Stem cell homeostasis (Fig. 30.3) requires that under steady state conditions, following stem cell division, on average one of the daughter cells remains a stem cell, while the other cell either commits to differentiation, or undergoes apoptosis. The place where

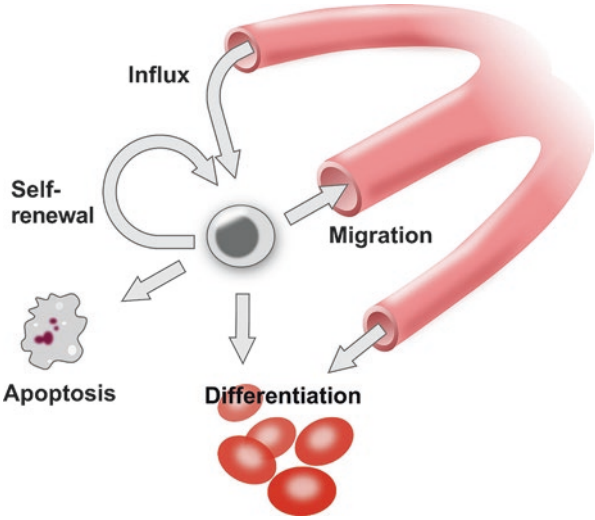


Fig. 30.3 Stem cell homeostasis. A stem cell pool size is regulated at different levels. Symmetrical self-renewing divisions (both daughters remain stem cells) are the main mechanism for expansion, while differentiation and apoptosis are the main exits from the stem cell pool. Migration, resulting in either resettlement in a stem cell niche, or in exit from the stem cell pool through differentiation or apoptosis, can complicate this process

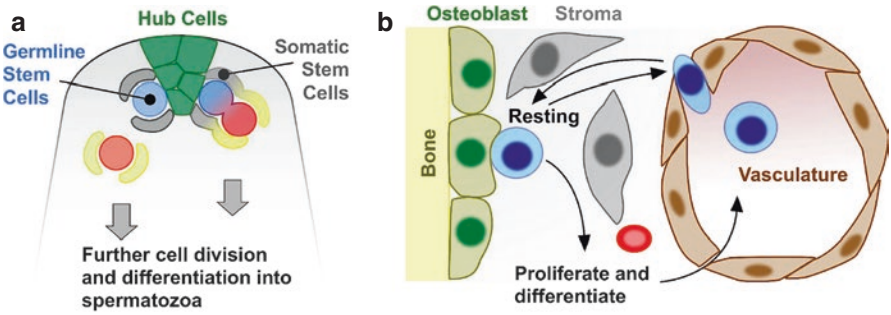


Fig. 30.4 The concept of the stem cell niche. Shown are two examples of stem cell niches, the Drosophila spermatogonium, and the mammalian hematopoietic stem cell. (**a**) In this niche concept the germ and somatic cells in the apical tip of the testis that are in direct contact with the hub cells remain stem cells. Once this contact is lost, through oriented cell division, the cells start their differentiation toward spermatozoa, which takes many steps and several more cell division. (**b**) In the hematopoietic system the organization is more flexible in that HSC have the ability to move from their resting niches near the bone to the vasculature, and back. Both environments differ significantly, e.g. in O_2 levels. Most differentiation (including the accompanying proliferation) also takes place in the bone marrow. The resulting mature cells enter the blood to leave the bone marrow

stem cells receive these signals is often referred to as the stem cell niche (Fig. 30.4). This can be a very defined, physical environment. Figure 30.4 shows two examples of stem cell niches. In the *Drosophila* spermatogonium the location of the stem cells that produce the spermatozoa is exactly defined. They are at the tip of the gonad, in direct contact with other cells known as hub-cells. These hub cells provide the signals necessary for the stem cells to remain stem cells. Once the stem cells divide the cell division is oriented such that one daughter cell remains in contact with the hub

cells, and the other daughter loses contact. The daughter cell that has lost contact commits to differentiation, resulting in an obligatory asymmetric cell division. A similar asymmetric division occurs for the accompanying cyst cells that surround the germ cell throughout the differentiation process. The critical signal, through the Jak/Stat pathway, provided by the hub cells is called Unpaired (Upd), which is a ligand for the receptor Domeless (Dome) and the associated Jak kinase Hopscotch (Hop). Upon binding of Upd the receptor is phosphorylated by Hop, followed by Stat binding, phosphorylation, dimerization, and translocation to the nucleus. Mutants in which the cyst cells overexpress the ligand Upd never form functional sperm. Instead the spermatogonium fills up with stem cells. Mutants without functional Stat do not maintain stem cells, but have a single early wave of spermatogenesis [26, 27].

In the mammalian bone marrow the location of the hematopoietic stem cells has been less clear. One reason is that bone marrow is typically studied as a cell suspension by flow cytometry and colony- or reconstitution assays after it has been removed from the marrow spaces, rather than by histology in situ. Also, regulation is more complex in that hematopoietic stem cells can leave their niches in the bone marrow and travel through the vasculature to new locations such as spleen and liver. They do so in a regulated fashion several times during development [28], but retain the ability to migrate in adult life as a response to various stimuli [29, 30], with CXCR4/SDF-1α signaling as a central component. Clinically, this is used to harvest them: Rather than harvest bone marrow directly hematopoietic stem cells are harvested as Mobilized Peripheral Blood (MPB) by leukapheresis after treatment of the donor with the growth factor G-CSF and the chemotherapeutic cyclophosphamide. Nevertheless, much has been learned in recent years about the important cells in the niche, and the signals governing stem cell behavior. An in-depth discussion is outside of the scope of this more general chapter, and many reviews can be used as starting points to further probe the literature, see e.g. [31–36]. A variety of cells have been reported to be part of this niche, including osteoblasts [37–39], sinusoidal endothelium [40], CXCL12 expressing reticular cells [41], adipocytes [42] and mesenchymal stem cells [43]. A number of regulators have been postulated to be involved in stem cell maintenance in this niche. These include Wnt proteins [44–47], the Notch pathway [48–50], insulin-like growth factor (IGF-2) and angiopoietin-like proteins [51–53]. Important regulators of cell cycle progression include the $p16^{Ink4a}$–CDk4/6Rb and $p19^{Arf}$-P53-$P21^{Cip1}$ pathways [54, 55]. Another important factor for stem cells is the ability to maintain telomere length during successive cell divisions. To accomplish this stem cells express telomerase. Loss of telomerase can limit stem cell self-renewal during serial transplantation [56] and aging [57]. It has recently been reported that telomerase activity is regulated by Wnt/β-catenin in stem cells [58]. Despite all of the progress that has been made in characterizing the regulation of hematopoietic stem cells no clear conditions have been defined yet that allow for robust expansion of these cells outside of the body [59], something that would be extremely useful in broadening their therapeutic potential. This indicates that our understanding of HSC self-renewal, and the molecular players involved, is still lacking.

Other types of stem cells, in particular Embryonic Stem cells, are capable of extensive expansion outside of the body using defined conditions without reduction of their pluripotency, their ability to differentiate into all tissues of the body. Much has been learned about the factors governing unlimited self-renewal and developmental potential [55, 60–62]. Central components include the transcription factors Oct4, Sox2 and Nanog. These transcription factors, which interact physically, form a finely tuned network, disturbance of which can lead to loss of pluripotency. Additional proteins, like the zinc-finger DNA binding protein Ronin, are also involved and can prevent differentiation [63]. In addition there is regulation at the epigenetic level, with Polycomp complexes playing an important role [62]. Ultimately demonstrating the importance of these pathways has been the ability to use forced expression of several of these proteins to convert somatic cells into pluripotent stem cells [61] (**See iPSC section below**.)

Overall, these examples illustrate that niches are important and specific, and their presence can limit and regulate stem cell presence. This regulation is especially critical for cells that continuously produce large numbers of mature cells. Loss of control of expansion would quickly result in a proliferative disease, or even cancer.

Stem Cells: Clinical Use

The specifics of the use of stem cells in the heart are discussed elsewhere in this book. This section will be limited to a more general overview of the current and potential use of stem cells in medicine. As mentioned earlier, hematopoietic stem cell transplantation is currently in widespread use, albeit that this involves transfer of stem cell containing cell preparations, and not highly purified HSC. This is an important distinction, as the main indication for use is the treatment of malignancies. Autologous transplants in which patients receive their own cells, harvested prior to intensive chemotherapy, thus carry a risk of reseeding the patient with cancer cells that contaminate the graft. Small-scale studies with highly purified autologous hematopoietic stem cells indicate that high level purification indeed improves outcome [64, 65]. Allogeneic transplants, in which the patient receives cells from a different individual, do not carry this risk, but, specific for hematopoietic transplants, may result in adaptive immune cells in the graft reacting against the host body. This is known as graft-versus host disease, and is a potentially lethal complication of allogeneic hematopoietic cell transplantation [66–68].

Hematopoietic stem cells have the potential, and are starting to be used for many other therapies [69], including the treatment of autoimmune diseases [70], the treatment of inherited metabolic diseases [71] and the induction of tolerance for solid organ transplantation [69, 72–74].

Skin is another tissue that is transplanted in routine clinical use, and that depends for functioning on the transplanted stem cells [75–77]. Skin, like blood, is continuously regenerated from stem cells. Old cells slough off and are discarded. Autologous

transplants, in which skin is harvested at one place of the body and transplanted to another, e.g. to cover a burn, results in lasting engraftment. Allogeneic skin transplants, typically harvested from a deceased donor, are used as temporary cover, as they will be rejected by the immune system.

Other types of stem cells, especially mesenchymal stem cells, are being tested in clinical trials [78–80], including trials addressing cardiac failures [81–83], but are not yet in routine use. Mesenchymal stem cells can be harvested relatively easily from various sources, including bone marrow and adipose tissue, expanded in culture and can differentiate into many tissues, including bone, adipose, myogenic and hepatic cells [84]. In addition, mesenchymal stem cells can modulate immune responses [78, 80]. Neuronal stem cells are also being tested in initial clinical trials, e.g. [85–87]. Other cells, including ES cells [88, 89] and iPS cells [21, 90–93], are being developed for eventual clinical use.

Stem Cells and Cancer

Stem cells, through their ability to persist for long periods of time while cycling, even if slowly, are prime candidates to collect the mutations necessary to allow escape from their normal controls and become transformed. Like normal, non-transformed, stem cells cancer stem cells may remain dependent on a stem cell niche for some of their regulatory (pro-mitogenic) signals [35, 94], even though they may have lost other parts of the normal regulatory circuitry, like essential tumor suppressor genes that should prevent these cells from proliferating [55, 95].

Interestingly, it has been recognized recently that cancers themselves tend to be organized in cancer stem cells, which may only make up a small part of the tumor and the bulk of the tumor cells which are derived from these stem cells, analogous to differentiated cells in normal tissues [96–101]. In this model the cancer stem cells are both necessary to maintain the tumor, and sufficient, if not eradicated completely, to regrow the tumor (relapse) after treatment.

Induced Pluripotent Stem Cells (IPSC)

One of the most exciting developments in stem cell biology in the last decade has been the discovery that a stem cell phenotype, even that of pluripotent stem cells, can be induced in somatic cells following transduction with a limited set of genes. In the initial landmark studies mouse fibroblasts, transduced with *Oct4, Sox2, Klf4* and *c-Myc*, were reprogrammed into cells very similar to Embryonic Stem cells [19]. These results were rapidly confirmed with human cells, and a slightly different gene combination (*Oct4, Sox2, Nanog* and *Lin28*) [18, 20]. Many different types of

cells are open to reprogramming, including fibroblasts (above), keratinocytes [102], neural stem cells, hepatocytes and gastric epithelial cells [103], adipocytes and hematopoietic cells [104].

IPS cells have a number of obvious advantages over ES cells. Unlike ES cells, their origin is not ethically controversial. Furthermore, the ability to generate pluripotent cells from any donor holds great promises for the development of specific disease models. However, it remains to be established how closely iPS cells resemble ES cells, and the presence, at least in the initial experiments, of the oncogene *c-Myc* in the transformation mix gives pause when contemplating clinical use [61]. The optimal gene combination for induction of iPS cells remains a subject of interest [61], complicated by the more recent observations that show that it is possible to reprogram cells to a different fate without passing through the pluripotent intermediate stage [105, 106]. It is possible, e.g. to reprogram fibroblasts directly into neurons [107] or cardiomyocytes [108]. While in early stages, this clearly further increases the possibilities for creating genetically matched tissues for research and therapy.

Stem Cells and the Heart

When discussing stem cells in the context of the heart in general, or heart failure in particular, there are several different points of view that can be considered. Stem cells play a role in generating the structures of the heart [109]. Heart specification starts with the so-called first heart field, which will initially form a tube with endocardial layer on the inside, and a myocardial layer on the outside. Through differential growth and folding this will eventually result in a multi-chambered heart, with cells from the first heart field forming the left side of the heart, while cells from a second heart field mostly form the right side and outflow tract [110, 111]. To some extent, progenitors remain present once the heart is formed and provide a certain level of regenerative potential. There may be other stem cells as well that can be used to ameliorate the function of damaged heart tissue [112–114]. In addition to endogenous heart cells [115], there are other somatic stem cells (like mesenchymal stem cells) [116] and pluripotent stem cells (ES cells or iPS cells) [21, 110]. The therapeutic use of stem cells for cardiac repair is discussed in more detail elsewhere in this book.

Interestingly, while regeneration of functional myocardial tissue is limited in heart failure following myocardial infarct or other damage, cardiac progenitor cells are present in the myocardium, e.g. [117–119]. It may be possible to use these cells to improve function in failing hearts. In addition to the presence of cardiac progenitors, it has recently also been shown that at least some existing cardiomyocytes retain the potential to divide and replace cells [120]. This potential of cardiomyocyte proliferation can be greatly stimulated with exogenous administration of select micro RNA's (miRNA's) [121].

Conclusion

Stem cells play an essential role, during development and continuing in adult life. While much has been learned about the biology of stem cells in different organs and organisms, much more remains to be learned. The clinical promise is enormous, and current use barely scratches the surface. To develop this promise into eventual clinical reality it will be essential to follow the winding path, despite its frequent switchbacks, carefully. As tempting as shortcuts can be, in systems as complex as those discussed here, a methodical approach is the only reliable method of distinguishing what does and does not work when translated to the clinic. The biggest danger in attempting and failing at shortcuts to the clinic is establishing as common knowledge that something "does not work" before it has been tested. This can prevent promising avenues from being explored and developed.

References

1. Jacobsen LO, Marks EK, Robson MJ, Gaston EO, Zirkle RE. Effect of spleen protection on mortality following x-irradiation. J Lab Clin Med. 1949;34:1538.
2. Lorenz E, Uphoff D, Reid TR, Shelton E. Modification of irradiation injury in mice and guinea pigs by bone marrow injections. J Natl Cancer Inst. 1951;12:197–201.
3. Becker AJ, Mc CE, Till JE. Cytological demonstration of the clonal nature of spleen colonies derived from transplanted mouse marrow cells. Nature. 1963;197:452–4.
4. Siminovitch L, McCulloch EA, Till JE. The distribution of colony-forming cells among spleen colonies. J Cell Physiol. 1963;62:327–36.
5. Wu AM, Till JE, Siminovitch L, McCulloch EA. Cytological evidence for a relationship between normal hemotopoietic colony-forming cells and cells of the lymphoid system. J Exp Med. 1968;127(3):455–64.
6. Spooncer E, Lord BI, Dexter TM. Defective ability to self-renew in vitro of highly purified primitive haematopoietic cells. Nature. 1985;316(6023):62–4.
7. Spangrude GJ, Heimfeld S, Weissman IL. Purification and characterization of mouse hematopoietic stem cells. Science. 1988;241(4861):58–62.
8. Gratwohl A, Baldomero H, Aljurf M, Pasquini MC, Bouzas LF, Yoshimi A, et al. Hematopoietic stem cell transplantation: a global perspective. JAMA. 2010;303(16): 1617–24.
9. Harrison DE, Astle CM. Loss of stem cell repopulating ability upon transplantation. Effects of donor age, cell number, and transplantation procedure. J Exp Med. 1982;156(6): 1767–79.
10. Pawliuk R, Eaves C, Humphries RK. Evidence of both ontogeny and transplant dose-regulated expansion of hematopoietic stem cells in vivo. Blood. 1996;88(8):2852–8.
11. Iscove NN, Nawa K. Hematopoietic stem cells expand during serial transplantation in vivo without apparent exhaustion. Curr Biol. 1997;7(10):805–8.
12. Lagasse E, Connors H, Al-Dhalimy M, Reitsma M, Dohse M, Osborne L, et al. Purified hematopoietic stem cells can differentiate into hepatocytes in vivo. Nat Med. 2000;6(11):1229–34.
13. Mezey. E, Chandross KJ, Harta G, Maki RA, McKercher SR. Turning blood into brain: cells bearing neuronal antigens generated in vivo from bone marrow. Science. 2000;290(5497): 1779–82.
14. Wagers AJ, Weissman IL. Plasticity of adult stem cells. Cell. 2004;116(5):639–48.

15. Camargo FD, Chambers SM, Goodell MA. Stem cell plasticity: from transdifferentiation to macrophage fusion. Cell Prolif. 2004;37(1):55–65.
16. Raff M. Adult stem cell plasticity: fact or artifact? Annu Rev Cell Dev Biol. 2003;19:1–22.
17. Ho PJ, Yen ML, Yet SF, Yen BL. Current applications of human pluripotent stem cells: possibilities and challenges. Cell Transplant. 2012;21(5):801–14.
18. Takahashi K, Tanabe K, Ohnuki M, Narita M, Ichisaka T, Tomoda K, et al. Induction of pluripotent stem cells from adult human fibroblasts by defined factors. Cell. 2007;131(5):861–72.
19. Takahashi K, Yamanaka S. Induction of pluripotent stem cells from mouse embryonic and adult fibroblast cultures by defined factors. Cell. 2006;126(4):663–76.
20. Yu J, Vodyanik MA, Smuga-Otto K, Antosiewicz-Bourget J, Frane JL, Tian S, et al. Induced pluripotent stem cell lines derived from human somatic cells. Science. 2007;318(5858):1917–20.
21. Zwi-Dantsis L, Gepstein L. Induced pluripotent stem cells for cardiac repair. Cell Mol Life Sci. 2012;69(19):3285–99.
22. Benitah SA, Frye M. Stem cells in ectodermal development. J Mol Med (Berl). 2012;90(7):783–90.
23. Domen J, Wagers AJ, Weissman IL. Bone marrow (hematopoietic stem cells). Regen Med. 2006;2006:13–34. Available from: http://stemcells.nih.gov/info/scireport/2006report.htm.
24. Lensch MW. An evolving model of hematopoietic stem cell functional identity. Stem Cell Rev. 2012;8(2):551–60.
25. Takizawa H, Manz MG. In vivo divisional tracking of hematopoietic stem cells. Ann N Y Acad Sci. 2012;1266:40–6.
26. Hombria JC, Brown S. The fertile field of Drosophila Jak/STAT signalling. Curr Biol. 2002;12(16):R569–75.
27. Resende LP, Jones DL. Local signaling within stem cell niches: insights from Drosophila. Curr Opin Cell Biol. 2012;24(2):225–31.
28. Christensen JL, Wright DE, Wagers AJ, Weissman IL. Circulation and chemotaxis of fetal hematopoietic stem cells. PLoS Biol. 2004;2(3):E75.
29. Hoggatt J, Pelus LM. Mobilization of hematopoietic stem cells from the bone marrow niche to the blood compartment. Stem Cell Res Ther. 2011;2(2):13.
30. Greenbaum AM, Link DC. Mechanisms of G-CSF-mediated hematopoietic stem and progenitor mobilization. Leukemia. 2011;25(2):211–7.
31. Shiozawa Y, Havens AM, Pienta KJ, Taichman RS. The bone marrow niche: habitat to hematopoietic and mesenchymal stem cells, and unwitting host to molecular parasites. Leukemia. 2008;22(5):941–50.
32. Garrett RW, Emerson SG. Bone and blood vessels: the hard and the soft of hematopoietic stem cell niches. Cell Stem Cell. 2009;4(6):503–6.
33. Lilly AJ, Johnson WE, Bunce CM. The haematopoietic stem cell niche: new insights into the mechanisms regulating haematopoietic stem cell behaviour. Stem Cells Int. 2011;2011:274564.
34. Mercier FE, Ragu C, Scadden DT. The bone marrow at the crossroads of blood and immunity. Nat Rev Immunol. 2012;12(1):49–60.
35. Tieu KS, Tieu RS, Martinez-Agosto JA, Sehl ME. Stem cell niche dynamics: from homeostasis to carcinogenesis. Stem Cells Int. 2012;2012:367567.
36. Shiozawa Y, Taichman RS. Getting blood from bone: an emerging understanding of the role that osteoblasts play in regulating hematopoietic stem cells within their niche. Exp Hematol. 2012;40(9):685–94.
37. Arai F, Hirao A, Ohmura M, Sato H, Matsuoka S, Takubo K, et al. Tie2/angiopoietin-1 signaling regulates hematopoietic stem cell quiescence in the bone marrow niche. Cell. 2004;118(2):149–61.
38. Calvi LM, Adams GB, Weibrecht KW, Weber JM, Olson DP, Knight MC, et al. Osteoblastic cells regulate the haematopoietic stem cell niche. Nature. 2003;425(6960):841–6.
39. Zhang J, Niu C, Ye L, Huang H, He X, Tong WG, et al. Identification of the haematopoietic stem cell niche and control of the niche size. Nature. 2003;425(6960):836–41.

40. Ding L, Saunders TL, Enikolopov G, Morrison SJ. Endothelial and perivascular cells maintain haematopoietic stem cells. Nature. 2012;481(7382):457–62.
41. Sugiyama T, Kohara H, Noda M, Nagasawa T. Maintenance of the hematopoietic stem cell pool by CXCL12-CXCR4 chemokine signaling in bone marrow stromal cell niches. Immunity. 2006;25(6):977–88.
42. Naveiras O, Nardi V, Wenzel PL, Hauschka PV, Fahey F, Daley GQ. Bone-marrow adipocytes as negative regulators of the haematopoietic microenvironment. Nature. 2009;460(7252):259–63.
43. Mendez-Ferrer S, Michurina TV, Ferraro F, Mazloom AR, Macarthur BD, Lira SA, et al. Mesenchymal and haematopoietic stem cells form a unique bone marrow niche. Nature. 2010;466(7308):829–34.
44. Reya T, Duncan AW, Ailles L, Domen J, Scherer DC, Willert K, et al. A role for Wnt signalling in self-renewal of haematopoietic stem cells. Nature. 2003;423(6938):409–14.
45. Willert K, Brown JD, Danenberg E, Duncan AW, Weissman IL, Reya T, et al. Wnt proteins are lipid-modified and can act as stem cell growth factors. Nature. 2003;423(6938):448–52.
46. Murdoch B, Chadwick K, Martin M, Shojaei F, Shah KV, Gallacher L, et al. Wnt-5 A augments repopulating capacity and primitive hematopoietic development of human blood stem cells in vivo. Proc Natl Acad Sci U S A. 2003;100(6):3422–7.
47. Luis TC, Naber BA, Roozen PP, Brugman MH, de Haas EF, Ghazvini M, et al. Canonical wnt signaling regulates hematopoiesis in a dosage-dependent fashion. Cell Stem Cell. 2011;9(4):345–56.
48. Varnum-Finney B, Xu L, Brashem-Stein C, Nourigat C, Flowers D, Bakkour S, et al. Pluripotent, cytokine-dependent, hematopoietic stem cells are immortalized by constitutive Notch1 signaling. Nat Med. 2000;6(11):1278–81.
49. Varnum-Finney B, Brashem-Stein C, Bernstein ID. Combined effects of Notch signaling and cytokines induce a multiple log increase in precursors with lymphoid and myeloid reconstituting ability. Blood. 2003;101(5):1784–9.
50. Delaney C, Heimfeld S, Brashem-Stein C, Voorhies H, Manger RL, Bernstein ID. Notch-mediated expansion of human cord blood progenitor cells capable of rapid myeloid reconstitution. Nat Med. 2010;16(2):232–6.
51. Zhang CC, Lodish HF. Insulin-like growth factor 2 expressed in a novel fetal liver cell population is a growth factor for hematopoietic stem cells. Blood. 2004;103(7):2513–21.
52. Huynh H, Iizuka S, Kaba M, Kirak O, Zheng J, Lodish HF, et al. Insulin-like growth factor-binding protein 2 secreted by a tumorigenic cell line supports ex vivo expansion of mouse hematopoietic stem cells. Stem Cells. 2008;26(6):1628–35.
53. Zhang CC, Kaba M, Iizuka S, Huynh H, Lodish HF. Angiopoietin-like 5 and IGFBP2 stimulate ex vivo expansion of human cord blood hematopoietic stem cells as assayed by NOD/SCID transplantation. Blood. 2008;111(7):3415–23.
54. Sherr CJ. Principles of tumor suppression. Cell. 2004;116(2):235–46.
55. He S, Nakada D, Morrison SJ. Mechanisms of stem cell self-renewal. Annu Rev Cell Dev Biol. 2009;25:377–406.
56. Allsopp RC, Morin GB, DePinho R, Harley CB, Weissman IL. Telomerase is required to slow telomere shortening and extend replicative lifespan of HSCs during serial transplantation. Blood. 2003;102(2):517–20.
57. Rossi DJ, Bryder D, Seita J, Nussenzweig A, Hoeijmakers J, Weissman IL. Deficiencies in DNA damage repair limit the function of haematopoietic stem cells with age. Nature. 2007;447(7145):725–9.
58. Hoffmeyer K, Raggioli A, Rudloff S, Anton R, Hierholzer A, Del Valle I, et al. Wnt/beta-catenin signaling regulates telomerase in stem cells and cancer cells. Science. 2012;336(6088):1549–54.
59. Walasek MA, van Os R, de Haan G. Hematopoietic stem cell expansion: challenges and opportunities. Ann N Y Acad Sci. 2012;1266:138–50.
60. Jaenisch R, Young R. Stem cells, the molecular circuitry of pluripotency and nuclear reprogramming. Cell. 2008;132(4):567–82.

61. De Los Angeles A, Loh YH, Tesar PJ, Daley GQ. Accessing naive human pluripotency. Curr Opin Genet Dev. 2012;22(3):272–82.
62. Li M, Liu GH, Izpisua Belmonte JC. Navigating the epigenetic landscape of pluripotent stem cells. Nat Rev Mol Cell Biol. 2012;13(8):524–35.
63. Dejosez M, Krumenacker JS, Zitur LJ, Passeri M, Chu LF, Songyang Z, et al. Ronin is essential for embryogenesis and the pluripotency of mouse embryonic stem cells. Cell. 2008;133(7):1162–74.
64. Negrin RS, Atkinson K, Leemhuis T, Hanania E, Juttner C, Tierney K, et al. Transplantation of highly purified CD34+Thy-1+ hematopoietic stem cells in patients with metastatic breast cancer. Biol Blood Marrow Transplant. 2000;6(3):262–71.
65. Muller AM, Kohrt HE, Cha S, Laport G, Klein J, Guardino AE, et al. Long-term outcome of patients with metastatic breast cancer treated with high-dose chemotherapy and transplantation of purified autologous hematopoietic stem cells. Biol Blood Marrow Transplant. 2012;18(1):125–33.
66. Harris AC, Ferrara JL, Levine JE. Advances in predicting acute GVHD. Br J Haematol. 2013;160(3):288–302 . Published online 2012 Dec 4. doi:10.1111/bjh.12142.
67. Harris AC, Levine JE, Ferrara JL. Have we made progress in the treatment of GVHD? Best Pract Res Clin Haematol. 2012;25(4):473–8.
68. Petersdorf EW. Genetics of graft-versus-host disease: The major histocompatibility complex. Blood Rev. 2013;27(1):1–12. doi:10.1016/j.blre.2012.10.001 . Epub 2012 Nov 20.
69. Domen J, Gandy K, Dalal J. Emerging uses for pediatric hematopoietic stem cells. Pediatr Res. 2012;71(4–2):411–7.
70. Sullivan KM, Muraro P, Tyndall A. Hematopoietic cell transplantation for autoimmune disease: updates from Europe and the United States. Biol Blood Marrow Transplant. 2010;16(1 Suppl):S48–56.
71. Prasad VK, Kurtzberg J. Cord blood and bone marrow transplantation in inherited metabolic diseases: scientific basis, current status and future directions. Br J Haematol. 2010;148(3):356–72.
72. Strober S. Protective conditioning against GVHD and graft rejection after combined organ and hematopoietic cell transplantation. Blood Cells Mol Dis. 2008;40(1):48–54.
73. Strober S, Spitzer TR, Lowsky R, Sykes M. Translational studies in hematopoietic cell transplantation: Treatment of hematologic malignancies as a stepping stone to tolerance induction. Semin Immunol. 2011;23(4):273–81.
74. Sachs DH, Sykes M, Kawai T, Cosimi AB. Immuno-intervention for the induction of transplantation tolerance through mixed chimerism. Semin Immunol. 2011;23(3):165–73.
75. Ghadially R. 25 years of epidermal stem cell research. J Invest Dermatol. 2012;132(3 Pt 2):797–810.
76. Goldstein J, Horsley V. Home sweet home: skin stem cell niches. Cell Mol Life Sci. 2012;69(15):2573–82.
77. Yan X, Owens DM. The skin: a home to multiple classes of epithelial progenitor cells. Stem Cell Rev. 2008;4(2):113–8.
78. Dalal J, Gandy K, Domen J. Role of mesenchymal stem cell therapy in Crohn's disease. Pediatr Res. 2012;71(4–2):445–51.
79. Harrop JS, Hashimoto R, Norvell D, Raich A, Aarabi B, Grossman RG, et al. Evaluation of clinical experience using cell-based therapies in patients with spinal cord injury: a systematic review. J Neurosurg Spine. 2012;17(1 Suppl):230–46.
80. Keating A. Mesenchymal stromal cells: new directions. Cell Stem Cell. 2012;10(6):709–16.
81. Hare JM, Fishman JE, Gerstenblith G, DiFede Velazquez DL, Zambrano JP, Suncion VY, et al. Comparison of allogeneic vs autologous bone marrow-derived mesenchymal stem cells delivered by transendocardial injection in patients with ischemic cardiomyopathy: the POSEIDON randomized trial. JAMA. 2012;308(22):2369–79.
82. Miettinen JA, Salonen RJ, Ylitalo K, Niemela M, Kervinen K, Saily M, et al. The effect of bone marrow microenvironment on the functional properties of the therapeutic bone marrow-derived cells in patients with acute myocardial infarction. J Transl Med. 2012;10:66.

83. Mathiasen AB, Jorgensen E, Qayyum AA, Haack-Sorensen M, Ekblond A, Kastrup J. Rationale and design of the first randomized, double-blind, placebo-controlled trial of intramyocardial injection of autologous bone-marrow derived Mesenchymal Stromal Cells in chronic ischemic Heart Failure (MSC-HF Trial). Am Heart J. 2012;164(3):285–91.
84. Ishikawa T, Banas A, Teratani T, Iwaguro H, Ochiya T. Regenerative cells for transplantation in hepatic failure. Cell Transplant. 2012;21(2–3):387–99.
85. Kondziolka D, Wechsler L, Goldstein S, Meltzer C, Thulborn KR, Gebel J, et al. Transplantation of cultured human neuronal cells for patients with stroke. Neurology. 2000;55(4):565–9.
86. Luan Z, Liu W, Qu S, Du K, He S, Wang Z, et al. Effects of neural progenitor cell transplantation in children with severe cerebral palsy. Cell Transplant. 2012;21(Suppl 1):S91–8.
87. Riley J, Federici T, Polak M, Kelly C, Glass J, Raore B, et al. Intraspinal stem cell transplantation in amyotrophic lateral sclerosis: a phase I safety trial, technical note, and lumbar safety outcomes. Neurosurgery. 2012;71(2):405–16 ; discussion 416.
88. Ben-David U, Kopper O, Benvenisty N. Expanding the boundaries of embryonic stem cells. Cell Stem Cell. 2012;10(6):666–77.
89. Serra M, Brito C, Correia C, Alves PM. Process engineering of human pluripotent stem cells for clinical application. Trends Biotechnol. 2012;30(6):350–9.
90. Zhu Y, Wan S, Zhan RY. Inducible pluripotent stem cells for the treatment of ischemic stroke: current status and problems. Rev Neurosci. 2012;23(4):393–402.
91. Wang H, Doering LC. Induced pluripotent stem cells to model and treat neurogenetic disorders. Neural Plast. 2012;2012:346053.
92. van Bekkum DW, Mikkers HM. Prospects and challenges of induced pluripotent stem cells as a source of hematopoietic stem cells. Ann N Y Acad Sci. 2012;1266:179–88.
93. Kao DI, Chen S. Pluripotent stem cell-derived pancreatic beta-cells: potential for regenerative medicine in diabetes. Regen Med. 2012;7(4):583–93.
94. Boral D, Nie D. Cancer stem cells and niche mircoenvironments. Front Biosci (Elite Ed). 2012;4:2502–14.
95. Verga Falzacappa MV, Ronchini C, Reavie LB, Pelicci PG. Regulation of self-renewal in normal and cancer stem cells. FEBS J. 2012;279(19):3559–72.
96. Reya T, Morrison SJ, Clarke MF, Weissman IL. Stem cells, cancer, and cancer stem cells. Nature. 2001;414(6859):105–11.
97. Al-Hajj M, Becker MW, Wicha M, Weissman I, Clarke MF. Therapeutic implications of cancer stem cells. Curr Opin Genet Dev. 2004;14(1):43–7.
98. Dick JE. Acute myeloid leukemia stem cells. Ann N Y Acad Sci. 2005;1044:1–5.
99. Alison MR, Lin WR, Lim SM, Nicholson LJ. Cancer stem cells: in the line of fire. Cancer Treat Rev. 2012;38(6):589–98.
100. Magee JA, Piskounova E, Morrison SJ. Cancer stem cells: impact, heterogeneity, and uncertainty. Cancer Cell. 2012;21(3):83–96.
101. Vermeulen L. de Sousa e Melo F, Richel DJ, Medema JP. The developing cancer stem-cell model: clinical challenges and opportunities. Lancet Oncol. 2012;13(2):e83–9.
102. Aasen T, Raya A, Barrero MJ, Garreta E, Consiglio A, Gonzalez F, et al. Efficient and rapid generation of induced pluripotent stem cells from human keratinocytes. Nat Biotechnol. 2008;26(11):1276–84.
103. Aoi T, Yae K, Nakagawa M, Ichisaka T, Okita K, Takahashi K, et al. Generation of pluripotent stem cells from adult mouse liver and stomach cells. Science. 2008;321(5889):699–702.
104. Hanna J, Markoulaki S, Schorderet P, Carey BW, Beard C, Wernig M, et al. Direct reprogramming of terminally differentiated mature B lymphocytes to pluripotency. Cell. 2008;133(2):250–64.
105. Chambers SM, Studer L. Cell fate plug and play: direct reprogramming and induced pluripotency. Cell. 2011;145(6):827–30.
106. Stadtfeld M, Hochedlinger K. Induced pluripotency: history, mechanisms, and applications. Genes Dev. 2010;24(20):2239–63.

107. Vierbuchen T, Ostermeier A, Pang ZP, Kokubu Y, Sudhof TC, Wernig M. Direct conversion of fibroblasts to functional neurons by defined factors. Nature. 2010;463(7284):1035–41.
108. Ieda M, Fu JD, Delgado-Olguin P, Vedantham V, Hayashi Y, Bruneau BG, et al. Direct reprogramming of fibroblasts into functional cardiomyocytes by defined factors. Cell. 2010;142(3):375–86.
109. Riley PR. An epicardial floor plan for building and rebuilding the mammalian heart. Curr Top Dev Biol. 2012;100:233–51.
110. Lui KO, Bu L, Li RA, Chan CW. Pluripotent stem cell-based heart regeneration: from the developmental and immunological perspectives. Birth Defects Res C Embryo Today. 2012;96(1):98–108.
111. Buckingham M, Meilhac S, Zaffran S. Building the mammalian heart from two sources of myocardial cells. Nat Rev Genet. 2005;6(11):826–35.
112. Bernstein HS, Srivastava D. Stem cell therapy for cardiac disease. Pediatr Res. 2012;71(4 Pt 2):491–9.
113. Ptaszek LM, Mansour M, Ruskin JN, Chien KR. Towards regenerative therapy for cardiac disease. Lancet. 2012;379(9819):933–42.
114. Hotkar AJ, Balinsky W. Stem cells in the treatment of cardiovascular disease--an overview. Stem Cell Rev. 2012;8(2):494–502.
115. Dimarakis I, Menasche P, Habib NA, Gordon MY, editors. Handbook of cardiac stem cell therapy. London: Imperial College Press; 2009. p. 1–285.
116. Mullenix PS, Huddleston SJ, Stojadinovic A, Trachiotis GD, Alexander EP. A new heart: somatic stem cells and myocardial regeneration. J Surg Oncol. 2012;105(5):475–80.
117. Takamiya M, Haider KH, Ashraf M. Identification and characterization of a novel multipotent sub-population of Sca-1(+) cardiac progenitor cells for myocardial regeneration. PLoS One. 2011;6(9):e25265.
118. Ye J, Boyle A, Shih H, Sievers RE, Zhang Y, Prasad M, et al. Sca-1+ cardiosphere-derived cells are enriched for Isl1-expressing cardiac precursors and improve cardiac function after myocardial injury. PLoS One. 2012;7(1):e30329.
119. van Wijk B, Gunst QD, Moorman AF, van den Hoff MJ. Cardiac regeneration from activated epicardium. PLoS One. 2012;7(9):e44692.
120. Senyo SE, Steinhauser ML, Pizzimenti CL, Yang VK, Cai L, Wang M, et al. Mammalian heart renewal by pre-existing cardiomyocytes. Nature. 2013;493(7432):433–6. doi:10.1038/nature11682 . Epub 2012 Dec 5.
121. Eulalio A, Mano M, Ferro MD, Zentilin L, Sinagra G, Zacchigna S, et al. Functional screening identifies miRNAs inducing cardiac regeneration. Nature. 2012;492(7429):376–81. doi:10.1038/nature11739 . Epub 2012 Dec 5.

Chapter 31
Stem Cell Therapy in Heart Failure

Sachil Shah and Alan W. Heldman

Introduction

Despite advances in prevention and treatment, cardiovascular disease (CVD) is still the leading cause of morbidity and mortality in the United States. As mortality from CVD declines, and more of our patients survive acute myocardial infarction, revascularization procedures, arrhythmias, and treatments for congenital and acquired valvular and structural heart disorders, so the prevalence of heart failure (HF) continues to increase with more than 550,000 new cases annually [1]. Half of humans with HF will die within 5 years of onset; it was cited as a contributing cause in more than 280,000 deaths in 2008 [1]. HF is also well-known to be extremely costly, with health care services, medications, and lost productivity equating to a U.S. national burden of $34.4 billion each year [2]. This high clinical and economic cost provides great impetus for the development of new therapeutic approaches for HF.

While it was long taught that that the human heart had no capacity for regeneration because cardiac myocytes existed in a terminally differentiated state, a number of lines of evidence have overturned that idea. While the rate of cell turnover remains a topic of debate [3], demonstration in humans of chimerism of a sex mismatched transplanted heart [4], of mitotic figures in myocardium after infarction [5], and of differential integration of Carbon-14 (from Cold War nuclear bomb tests) [6] suggested that some turnover of myocytes does occur in humans. Demonstration of myocardial regeneration after infarction in animal models [7] initiated a new field for translational research.

S. Shah, MD
Washington Hospital Center/Georgetown University Hospital, Department of Cardiology,
110 Irving Street, Washington, DC 20010, USA
e-mail: shahsachil@gmail.com

A.W. Heldman, MD, FSCAI (✉)
Miami, FL, USA
e-mail: aheldman@gmail.com

H. Eisen (ed.), *Heart Failure*, DOI 10.1007/978-1-4471-4219-5_31

The therapeutic cell types [8], mechanisms of action, routes of administration, and treatable conditions [9] are now beginning to be defined. This chapter will review briefly some of the significant clinical trials in the field of myocardial regeneration for the treatment of heart failure. We argue that a relatively rational progression from translational studies to clinically informative trials [10] is now underway.

Stem Cells

Toronto scientists Till and McCulloch described stem cells in 1963 in their work on the radiation sensitivity of mouse bone marrow cells [11]. Stem cells are cells that can continuously self-renew and undergo differentiation to a cell lineage [12]. Stem cells are described as pluripotent if they can form all the cell types of the adult organism and totipotent if in addition they can form embryonic tissues. Once a stem cell is confined to a certain tissue, its potency is generally limited to differentiation into cell types of that tissue. Besides heart failure [13], other clinical entities being studied for stem cell therapy include vascular disease, wounds, burns, hematological diseases, malignancies, Parkinson's disease, Alzheimer's disease, multiple sclerosis, spinal cord injury, diabetes, and other conditions [14]. Stem cells used in investigational studies could broadly be classified based on their differentiation potential: totipotent embryonic stem cells, adult multipotent stem cells, adult tissue specific stem cells, and 'embryonic-like' induced pluripotent stem cells. Both autologous (i.e., the patient's own) and allogeneic (from a donor) cells are under investigation.

Stem Cells and Cardiac Regeneration

The potential for the human heart to regenerate constitutes a revolutionary paradigm shift in our understanding of myocardial pathophysiology; besides cellular hypertrophy, necrosis, apoptosis, and fibrosis, it appears that under the right conditions we can enable another myocardial response to injury – regeneration. While rate of cell turnover in the human heart is debated, the existence of the phenomenon is a) clearly established, and b) clearly inadequate to recoup the myocytes lost during myocardial infarction. One possible exception might be found in the syndrome of Anomalous Left Coronary Artery from the Pulmonary Artery (ALCAPA, or Bland-White-Garland syndrome); these infants have evidence of myocardial infarction, but if surgically corrected early may recover normal left ventricular function [15]. While the mechanism of this phenomenon is unknown, it seems likely that the regenerative potential of an infant's myocardium might be substantially greater than that of adults'.

As a potential therapeutic intervention in adults, stem cell transplantation may be viewed as an attempt to augment the inadequate endogenous regenerative capacity

of the heart, and to prevent the maladaptive sequelae. Mechanisms by which transplanted stem cells enhance cardiac regeneration include the formation of new cardiac myocytes, new blood vessels, modulation of inflammation, and attenuation of remodeling and fibrosis [16].

Stem Cells for Myocardial Disease

In this section we review broad categories of cell types under study for myocardial regeneration.

Skeletal Myoblasts

Skeletal myoblasts are stem cells located under the basal lamina in skeletal muscle; they were postulated to participate in repair following injury, and were among the first cells to be considered for myocardial regenerative therapy [17]. They can be obtained as an autologous product, have high scalability in culture, and appear to be resistant to ischemia. In animal models skeletal myoblasts appeared promising [18, 19]. Early phase clinical studies did encounter a safety concern and it was speculated that ventricular tachyarrhythmias might arise from failure of the graft electromechanically to couple with endogenous cardiomyocytes [20, 21].

Bone Marrow Derived Stem Cells

The adult bone marrow is home to a vast array of support cells and multipotent precursor lineage stem cells. Bone marrow derived stem cells (BMDSC) are the earliest and most investigated in all of stem cell research. In adult humans, BMDSC can be collected by iliac crest aspiration of marrow with expansion in culture, or obtained by cell sorting from peripheral blood after cytokine mobilization. BMDSC exhibit plasticity in vitro permitting differentiation into many cell types including those of cardiogenic lineage, such as contracting cardiomyocytes, coronary arterioles and capillaries [7]. BMDSCs appear to constitute many different cell types, and of these, preclinical studies [22] and clinical trials have examined several for their potential to promote favourable healing after myocardial infarction. Freshly prepared mononuclear cell fraction of BMDSCs have been the subject of the largest experience to date, but more specific fractions from the bone marrow include precursors of hematopoietic stem cells (HSCs), mesenchymal stem cells (MSCs) and endothelial progenitor cells (EPCs), which are found in varying quantities within the mononuclear population [23].

HSCs are negative for lineage markers (lin^-) but express hematopoietic marker CD45 with Sca-1+, CD34+, CD133+ and c-kit+ (CD117) [24]. The

transdifferentiation of HSC into cardiomyocytes and endothelial cells in the heart has been demonstrated in animal models. Experiments with the administration of c-kit$^+$/lin$^-$ HSC in infarcted rat myocardium demonstrated significant cardiogenesis in conjunction with improved myocardial perfusion, angiogenesis and collateral vessel formation [25], translating into improved myocardial function, whether by transdifferentiation or another mechanism [26]. EPCs have the ability to differentiate into endothelial cells, and exist both in the bone marrow and in the peripheral circulation. EPCs share a common precursor with the HSCs and are CD34+ but are negative for CD45 [27]. Kawamoto et al. demonstrated engraftment, neovascularization and improved cardiac function with both intravenous and intramyocardial delivery of EPCs [28, 29].

MSC constitute a small percentage of the bone marrow; they express Stro-1, CD90, CD106, CD13 but no classic hematopoietic or endothelial cell markers [30, 31], and exhibit the capacity to differentiate into cells of several tissue types, including osteoblasts, chondroblasts and adipocytes. Our lab and others have demonstrated that bone marrow-derived MSCs transplanted into infarcted myocardium result in functional improvement with reduction of infarct scar area [32–34]. MSC also possess immunomodulatory characteristics, inhibiting immune responses during allogeneic transplantation in humans [35]. The use of allograft MSCs in animal models and in human subjects has followed; graft rejection has not been observed, and this approach reduced scar size and improved cardiac function in ischemic cardiomyopathy (ICM) [16, 36, 37].

Cardiac Stem Cells

Cells obtained from the heart with the Lin$^-$/c-kit$^+$ phenotype appear to have the potential to differentiate into functional cardiac myocytes, smooth muscle cells, and endothelial cells in vitro*;* these CSCs have been applied in animal models and in human subjects with the expectation of forming differentiated cardiac myocytes in vivo. CSC harvested from the adult heart (for example, from the right atrial appendage normally incised during many open heart surgeries) also exhibit other markers including Sca-1$^+$ cells [38], side population (SP) cells [39], and ISL-1+ cells. Sca1-positive cells constitute 0.3 % of the myocyte compartment, and appear to have the potential for expressing cardiac transcription factors and transdifferentiating into cardiac myocytes in vivo [40]. Similarly, cellular and animal studies of Sca-1+/CD31cells [41], and SP cells [42] demonstrate cardiomyogenic potential. Together with Islet-1+ and c-kit$^+$ CSCs , these and perhaps other cardiac stem cells exist in niches [43] from which proliferation, migration and regeneration may occur.

Reconstitution of the cardiac stem cell niche has been proposed to underlie the potential efficacy of “cardiospheres,” biologically engineered cultured multicellular structures containing a core of c-kit$^+$ with supporting cells [44, 45], and cells derived from cultured cardiospheres have also advanced through the translational pathway [46].

Pluripotent Stem Cells

Pluripotent stem cells are those which may generate all three germ layers (ectoderm, mesoderm, and endoderm) and which self-renew indefinitely; these include embryonic stem cells (ESC) obtained from the developing embryo. ESC also have the potential for cardiac differentiation [47], but development of these cell types for therapy has been limited compared to other cells. Despite mechanistically feasible findings, both ethical issues and the potential of tumorgenicity [48] have led investigators to other approaches towards pluripotency, including nuclear reprogramming of differentiated adult cells [49, 50]. Like ESC, induced pluripotent stem cells (iPSC) have been shown in small animals to improve heart function after infarction [51].

Umbilical Cord Stem Cells

Human umbilical cord blood is a rich source of both HSC [52] and MSC [53] and these cells maintain proliferative potential which is neither embryonic nor adult, but probably in between [54]. Cord blood-derived cells have been used clinically for the treatment of hematologic diseases [55]. Transdifferentiation into cardiac myocytes and other lineages has been demonstrated [56], and transplantation into infarcted myocardium resulted in neoangiogenesis, reduced infarct size and improved ventricular function in animal models [57–59]. The availability of large quantities of cord blood may favour therapeutic development [60].

Adipose Derived Stem Cells

Paradoxically, as clinicians and epidemiologists bemoan the increasing trend towards obesity in industrialized societies, human adipose tissue also contains cells with multipotent potential [61]. Studies in vitro studies demonstrate ADSC can be persuaded to differentiate into cardiac myocyte-like cells [62, 63]. Showing similar characteristics as MSCs [64, 65], ADSC have been shown to regenerate damaged myocardium in animal studies [66], leading to translational studies with adipose tissue derived products in human subjects.

Cardiovascular Disease Targets for Stem Cell Therapy

Ischemic Cardiomyopathy

Most studies of cell therapy for myocardial disease have focused on that resulting from ischemic damage. Whether in the acute phase of myocardial infarction, or in the later stages of chronic ICM, this closely related set of disorders is

well-understood after decades of clinical and preclinical investigation, and is particularly well-represented by small and large animal models [67]. Nonetheless, important non-ischemic heart diseases also have been subjected to translational investigation for stem cell therapies.

Non-ischemic Cardiomyopathies

In animal models, inherited non-ischemic cardiomyopathy [68–70], anthracycline chemotherapy-associated cardiomyopathy [71, 72], post-myocarditis cardiomyopathy [73, 74], and pacing tachycardia-induced cardiomyopathy [75] have been studied as potential targets for cell therapies. While clinical investigation and trials in these non-ischemic conditions remain fewer than those for acute and chronic ischemic myocardial diseases, translation into early phase human investigation for non-ischemic cardiomyopathies has begun.

Regenerative Mechanisms of Stem Cells

The hope that stem cells could replace damaged heart tissue [19, 22] by transdifferentiation into functioning cardiac myocytes and vascular cells (akin to re-populating a bare patch of lawn with grass seed) has proved a misleading oversimplification. Transdifferentiation may occur as a low-frequency event, but is unlikely to explain the magnitude and temporal course of myocardial regeneration; instead, the modulation and amplifaction of endogenous processes by the administered cell product appears to represent a major mechanism of action [76–78]. In a porcine myocardial infarct model, the administration of bone marrow derived MSCs resulted in 20-fold increase in endogenous c-kit+ CSCs; this principle was further supported by the finding that co-culture with MSCs enriched cardiopoetic cells obtained from heart biopsies [33]. Based on this finding of cell-cell interaction between niche-modulating cells and cardiotypic cells, co-administration of MSCs and CSCs in porcine chronic ICM was twice as effective as either cell type alone [79].

Cytokines which may be involved in this effect include vascular endothelial growth factor (VEGF), basic fibroblast growth factor (bFGF), insulin growth factor 1 (IGF-1), thymosin β4 (TB4), and stromal cell-derived factors 1 (SDF-1) [80], and it is likely that these cytokines are expressed with some temporal and spatial specificity including autocrine feedback, to modulate a local stem cell niche, influencing endogenous stem cells for proliferation, differentiation, cardiac remodelling and repair [81, 82]. Other paracrine effects may alter the metabolism [83] and recruitable contractility [84] of viable cardiac myocytes, and fusion of host cells with transplanted stem cells may occur, with the resulting cell exhibiting some of the characteristics of each contributor [85].

Techniques of Stem Cell Delivery

Cell administration in small animal models typically involved direct myocardial injection of cell suspensions through the epicardium. Large animal preclinical studies opened additional options, most of which have been applied in human subjects, including intracoronary infusion (either continuous or by stopping flow with an occlusive balloon), transendocardial injection (with purpose-built devices), transepicardial injection (typically adjunctive to open heart surgery), retrograde coronary perfusion, and intravenous administration. Each approach has its own logistical and technical advantages and disadvantages [86], and as clinical trials progress the outcomes related to the delivery technique may influence results as much as does the cell product [87].

Intracoronary administration has been frequently used following acute myocardial infarction reperfusion. If the target vessel is patent, the injured territory can accurately be targeted by infusing the culprit coronary, but engraftment will require cells to transmigrate across the endothelial lining, homing to sites of injured myocardium [88]. The potential for cell products to occlude the microvascular space is more than a theoretical concern [89].

Intramyocardial injection, by either transepicardial or transendocardial approaches, avoids these limitations, but increases the complexity of the cell administration procedure. Cells can be delivered directly to injured (or bordering) myocardium, without depending on the uncertainty of coronary transmigration. The spatial accuracy of these techniques has allowed subsequent analyses of the local influences of cells, revascularization, or the combination [90]. Transendocardial stem cell injection (TESI) into the border of an infarct zone appears to confer special benefit with concordant reduction in scar size and improvement in local contractility [91], so it makes sense for approaches to targeting the injection to be incorporated into trial designs [92]. Integration of CT or MR imaging of an infarction with ventriculographic assessment of wall motion permits directed delivery using fluoroscopy as the only real-time modality. Simultaneous biplane fluoroscopy is particularly advantageous when navigating a catheter in the LV chamber. Three-dimensional electromechanical mapping (EMM) [93] adds additional detail to the real-time assessment of potential targets for TESI, providing spatial assessment of myocardial viability and contractility [94].

Intravenous infusion of cells avoids most of the technical challenges of the above approaches, but most cells are likely to be filtered and retained in the pulmonary vasculature [95], reducing the efficiency of this strategy compared to the more direct approaches [96, 97].

Clinical Trials

Comprehensive reviews of clinical trials in the field are regularly published and updated [98, 99], and this chapter will not duplicate those efforts. In order that this chapter might be of more than transient relevance before becoming out of date, we have attempted here to connect the principles of cell biology, cardiac

pathophysiology, and clinical trials design for only some of the more than 100 studies conducted or ongoing.

Acute Myocardial Infarction

Cell therapy studies for acute MI have included more than 1000 patients, mostly receiving BMDSC via intracoronary infusion. Results are mixed. For example, two studies can be compared. In a well-conducted, trial enrolling 101 patients with a first, anterior MI and receiving reperfusion by PCI, Lunde et al. randomized patients to receive bone marrow mononuclear cells (median cell number 68×10^6) by intracoronary infusion with stop-flow balloon occlusion. Control patients were not subjected to sham/placebo interventions. At 6 month cardiac MRI, no benefit was detected from cell infusion [100].

In contrast, the REPAIR-AMI trial randomized 204 patients with an acute MI to receive a ~200 × 106 bone marrow mononuclear cells or placebo 3–7 days after initial coronary intervention, again by stop flow intracoronary infusion. In this case, both LV ejection fraction changes and clinical endpoints seemed to be improved by cell therapy [101].

Among the many potential confounders for these trials, a few might be particularly significant. Important variability exists even among patients meeting the most tightly controlled inclusion criteria; differences in the severity and extent of coronary disease, pre-infarction angina, time to treatment, and others will influence the extent of myocardial injury, the efficacy of its salvage, the rate of recovery of myocardial contractility after reperfusion, and the net effect on global LV function. Ejection fraction, though undoubtedly a powerful marker of future clinical risk, is determined by the estimation of end-diastolic LV volume and end-systolic volume; it may vary substantially both on a beat to beat basis and as loading conditions change. Meta-analyses have been attempted and suggest that bone marrow cell infusion after acute MI may result in improved LVEF, reduced left ventricular end systolic volume (LVESV), and reduce infarct size [102]. Trends suggesting greater benefit in patients with more severely reduced EF are seen in these and other [103] trials of cell therapy for acute MI, including studies based on intravenous administration [104]. However, only large trials, such as the ongoing BAMI (The Effect of Intracoronary Reinfusion of BM-MNC on All Cause Mortality in Acute Myocardial Infarction) trial can approach balancing all these variables.

Chronic Ischemic Cardiomyopathy

In comparison with trials for acute MI, those enrolling patients with ICM include a broader range of cell types and delivery strategies. There is also significant heterogeneity among the outcome measures studied and the techniques used to

characterize changes after cell therapy. Cardiac MRI is particularly useful in this regard, allowing quantification of both global and regional myocardial function, and measurement of the mass of viable myocardium and scar. While MRI remains the most complete technique, CT now approaches MRI in many of these measures. Many patients with ICM have implanted pacemakers and defibrillators, which create artifacts partially obscuring the heart with either MRI or CT. SPECT, PET, and echocardiography have been used as well.

Clinical assessments included in some trials have included the highly subjective (NYHA functional class) and more quantitative (MVO2 max) measures. The potential for placebo effect is particularly great when highly motivated patients with serious conditions undergo procedures with novel therapies [105], reinforcing the value of randomized blinded placebo controlled trials in this arena.

Bone Marrow-Derived Cells for Ischemic Cardiomyopathy

A number of cell products have been derived from adult bone marrow for preclinical and clinical testing. Bone marrow includes a heterogeneous population of cell types, among which there may be significant overlapping features. Whether the study product was a fresh preparation of bone marrow, was characterized by selecting from bone marrow cells for specific surface markers, or was culture expanded, clinical trials of bone marrow-derived cells for chronic ICM are reviewed here.

In 2003 Perin and colleagues published a prospective, nonrandomized, open-label safety and feasibility study of bone marrow derived CD34 marker (+) cells delivered by transendocardial injection, in 14 patients with severe LV dysfunction and ICM versus seven controls [106]. They reported that cell injection was associated with reduction in myocardial ischemia, improvement in global left ventricular function, and mechanical improvement of the injected segments as assessed by single-photon emission computed tomography (SPECT) analysis and EMM respectively. Treated patients also had significant improvements in New York Heart Association (NYHA) functional capacity, Canadian Cardiovascular Society Angina Score (CCSAS), achieved metabolic equivalents (METs) and maximum oxygen consumption (VO_2 max); results also supported the safety of transendocardial stem cell delivery with the NOGA® system.

Randomized trials of bone marrow derived cells have not settled the question of whether this approach is effective. The FOCUS-CCTRN trial [107] randomized 92 patients with ischemic heart disease and LVEF ≤ 0.45 to receive 100×106 autologous bone marrow mononuclear cells, or placebo by transendocardial injection. Injections were targeted to 15 sites of viable myocardium as assessed by NOGA® electromechanical mapping. At 6 months, echocardiographic LV volume and EF, exercise capacity, and SPECT perfusion were not different between groups.

Different endpoints were assessed when our group studied 65 patients with ICM and LVEF < 0.50. The TAC-HFT trial [108] compared autologous bone marrow mononuclear cells (n = 19) vs placebo (n = 10), and autologous culture-expanded bone marrow-derived mesenchymal stem cells (n = 19) vs placebo (n = 11). Cells

were injected at ten sites encompassing an infarct scar as assessed by CT or MRI, and biplane left ventriculography, using the Biocardia Helical Infusion Catheter®, which differs from the NOGA Myostar® in important respects; lacking the electromechanical mapping function of the NOGA system, the Biocardia catheter is navigated to sites selected based on prior cardiac imaging and real-time fluoroscopy. Its needle tip is helical, as compared to the straight needle of the NOGA Myostar. In this study, the transendocardial injection of cultured mesenchymal stem cells was associated with decreasing scar, increasing viable myocardial mass, and improved quality of life and 6 min walk distance.

Again, whether discrepant results relate to different patient populations, different cell types, different delivery strategies, different endpoint measures and techniques, or to the vicissitudes of early phase clinical trials will only begin to be answered when additional trial results come available.

The transepicardial approach to cell delivery has also been studied in patients with ICM undergoing CABG [109, 110]. Patel randomized 20 patients with ICM to undergo off-pump CABG with direct injection of autologous CD34+ cells vs off-pump CABG alone [111]. The treatment group had greater improvement in LVEF compared to controls at 6 months. Stamm and colleagues randomized patients with chronic ICM to receive direct injection of freshly prepared autologous CD133+ bone marrow cells along with CABG (n = 20) vs CABG alone (control, n = 20), and reported improvement in LVEF and myocardial perfusion at 6 months in the cell therapy group [112].

As described above, the intracoronary delivery of cells for acute MI has been studied in a large number of patients, but this approach has also been used for delivery of bone marrow-derived cells in patients with ICM. Small feasibility studies [113–116] suggested this might be safe. Strauer et al. compared 191 patients with ICM who received autologous bone marrow derived mononuclear cells vs 200 patients who chose not to receive cell therapy. Efficacy findings were reported including improved ejection fraction and long-term survival after cell therapy, but the trial design limits certainty of conclusions [117].

Skeletal Myoblasts

Menasche and colleagues reported in 2001 the transfer of autologous skeletal myoblasts into the myocardium by transepicardial injection during CABG in a single patient with ICM [118]. Subsequent work by the same group conducted in a non-randomized open label fashion suggested improvement in regional systolic contractility, but with the new onset of sustained ventricular tachycardia [17]. When randomized placebo-controlled design was employed for 97 patients undergoing coronary bypass with transfer of skeletal myoblasts (400×10^6 or 800×10^6 million) or placebo, there was no improvement in regional or global LV contractility associated with cell treatment; those receiving myoblasts had more arrhythmia events, though total major adverse cardiac events did not differ among groups [119].

Dib administered skeletal myoblasts via transendocardial injection in 12 patients with ICM in an open label unblinded randomized fashion, and compared to 11 control subjects [120]. This trial reported improvement in NYHA class and quality of life with myoblasts; left ventricular volume changes were not statistically different between groups. Arrhythmia events were not increased with cell treatment. While the meaning of changes in serial electromechanical mapping are not known, it is interesting that 3 month follow-up mapping in the patients treated with cells showed increased unipolar electrocardiographic voltage in the treated segments and the hearts as a whole, compared with baseline.

Cardiac Stem Cells

In the SCIPIO trial, autologous cardiac stem cells identified by the c-kit+ marker were obtained from the right atrial appendage of patients undergoing coronary bypass surgery, were expanded in culture, then were returned to the patient a mean of 113 days later. One-half million to one million cells were administered by intracoronary infusion with a stop-flow technique into an infarct territory in a randomized, open-label trial of 16 patients. Among nine patients who had baseline and 4 month cardiac MRI scans, the ejection fraction increased significantly from 27.5 % at baseline (i.e., 4 months after CABG, and before CSC infusion), to 35.1 % after 4 months and to 41.2 % after 12 months, and this seemed to correlate with improved NYHA class and quality of life [121].

Cardiosphere-Derived Cells

In the CADUCEUS trial, heart tissue was obtained by endomyocardial biopsy, a minimally invasive transcatheter procedure. Cardiospheres were prepared by culture from this material, and dispersed cells from these structures were returned to the patient by intracoronary infusion. One important difference from some other ischemic cardiomyopathy trials is that these patients had very recent infarctions; they were enrolled 2–4 weeks after acute MI and were treated (n = 17) 1 ½–3 months after infarction in a randomized 2:1 scheme against control treatment (n = 8). Six months after treatment, MRI showed reduced scar mass, increased viable myocardium, and improved regional contractility. Chamber volume and EF did not differ between groups. Similar findings were reported after 12 month MRI [122].

Non-Ischemic Cardiomyopathy

While the myocardial disease related to coronary ischemia has been the subject of much more preclinical, translational, and clinical study, other forms of cardiomyopathy are important and have motivated investigation as well. Idiopathic dilated

cardiomyopathy (DCM), and specific entities such as familial cardiomyopathies or chemotherapy-associated cardiomyopathy are beginning to be studied with the hope that cell therapy may regenerate or repair damaged myocardium.

Arguero et al. conducted the first clinical trial including bone marrow-derived cells delivery by surgical transepicardial injection, including in five patients with DCM [123]. Similarly, Arom et al. administered peripherally circulating cells by thoracoscopic injection in 20 patients with ischemic cardiomyopathy and 21 patients with DCM [124]. Both studies reported improved LVEF and functional status.

Fischer-Rasokat et al. conducted a study in 33 patients with DCM using an intracoronary infusion of BMDSC. After 3 months, cardiac function improved significantly and at 12 months N-terminal prohormone brain natriuretic peptide (NT-proBNP) serum levels were also decreased [125]. Improvements in quality of life, clinical symptoms, exercise capacity and cardiac function were reported in a similar study conducted by Martino et al. [126].

In the first randomized, open label, controlled trial performed by Seth et al., patients with DCM (n = 24) were administered autologous bone marrow mononuclear cells, and compared to 20 control patients. Cell administration was by intracoronary infusion, during balloon occlusion of the coronary sinus effluent. At 6 months, the treatment group demonstrated significant improvements in the LVEF, NYHA scale, and cardiac volumes compared to controls [127]. A later report from the same group continued to show improved cardiac function and clinical symptoms with treatment (n = 41) compared to control (n = 40) [128].

Vrtovec has reported the long-term follow-up of 110 patients = DCM who were randomized to receive open-label intracoronary infusion of CD34+ cells obtained by GM-CSF mobilization and apheresis, or control. LVEF increased up to 3 years, after which improvement declined, but at 5 years, the patients receiving cells still had higher LVEF and 6-min walk distance, and lower N-terminal B-type natriuretic peptide (a blood biomarker of heart failure.) [129].

Taken in context, these results do suggest that the treatment of non-ischemic cardiomyopathies is feasible and can be considered; randomized blinded placebo controlled trials will be required before firm conclusions can be drawn about efficacy.

Autologous Vs Allogeneic

As surveyed herein, a variety of autologous cell products have been subjected to early stage testing with a variety of strategies. While autologous cells would be expected to avoid the potential of host rejection, compared with the possibility of donor-derived allogeneic products, autologous cells do have important practical and clinical limitations. Depending on the cell type being prepared, tissue acquisition and processing, and culture expansion impose logistical obstacles to treatment when it might be needed. Furthermore, it has been suggested that stem cells from older, sicker patients are marked by smaller number or less potency [130]. Finally, the

requirement to prepare (and perform pre-release quality testing for) a cell product for each individual patient is an expensive undertaking.

Allogeneic cell products, for example from young healthy donor tissue, might overcome these obstacles. Patients with comorbid conditions would be spared tissue harvest, and the product could eventually be prepared in large quantities in advance for administration when a patient's clinical situation is ideal for treatment (with so-called "off the shelf" allogeneic products.) Whether the safety and efficacy of allogeneic cell therapies would be limited by rejection is preliminarily addressed by a few studies.

Mesenchymal stem cells, in particular, seem to have characteristics which do not induce immune rejection. MSC have been transplanted in ischemic and non-ischemic myocardium in large animal models [37], and in human subjects [104] without the use of immunosuppressive drugs. Penn et al. reported the administration of a proprietary allogeneic cell product via a novel coronary adventitial delivery system in 25 patients with acute MI; 19 received cells, and six were enrolled in a non-randomized control registry. Cells were given 2–5 days after infarction. No humoral or cellular immune reactions were detected.

In 2012, Penn conducted a similar study in 25 patients with AMI. Patients receiving MSC demonstrated no immune response, with improvement in LVEF and left ventricular volumes at 4 months, especially in patients receiving the 50 million dose. Improved echocardiographic LVEF was reported for the cell-treated patients [131].

In the POSEIDON study, our group randomized patients with ICM to receive either allogeneic or autologous MSC by fluoroscopically-guided transendocardial injection (TESI). Allogeneic cells did not elicit alloimmune reactions, and both cell types were associated with reduction in the CT scan early contrast enhancement defect [132], with scar reduction and improved regional contractility particularly at sites of TESI, and particularly in regions with severely impaired baseline contractility [91].

Conclusions and the Future

Here we have surveyed a sample of the preclinical and clinical investigation to date in the field of cell therapy for myocardial disease. While a large number of early phase studies have been completed, they are marked by great heterogeneity of purpose and design, so that it is premature to draw many certain conclusions. While it is possible that publication bias has improved the overall picture, the field is notable for a relative absence of trials showing adverse effects of cell therapy, with the exception of possible arrhythmogenesis with skeletal myoblasts, and the procedural risks of applying the therapy.

Particularly in light of the safety findings of phase I trials, and the various demonstrations and suggestions of efficacy summarized here, it is reasonable to hope for results with future trials which might lead clinicians and patients to make rational decisions about regenerative approaches to treating heart disease.

Overreliance on EF as an endpoint may obscure clinically relevant findings, as we see a number of studies showing substantial clinical improvement without parallel increases in EF. While EF is a powerful tool for stratifying risk in many myocardial diseases, it is highly dependent on loading conditions, and is derived from end-diastolic and end-systolic volumes; reduction of both volumes, for example, might indicate favorable remodeling (particularly when accompanied by change in the geometry of the ventricle) even without increase in EF.

The mechanisms of action of exogenously administered cells are now understood to be substantially more complex than merely "re-seeding a bare spot of lawn," and laboratory investigation conducted in parallel with clinical trials will continue to shed light on the ways in which stem cells' interaction with host cells, their secreted products, anti-inflammatory and anti-fibrotic properties, and physical behaviors influence outcomes.

Techniques which manipulate cells, such as overexpression of anti-apoptotic survival genes have shown promise in preclinical studies [133]. The practical implications remain to be seen, particularly with regards regulatory processes. Other approaches to increasing the regenerative potential of cell therapy for myocardial disease will include tissue engineered constructs [134], adjunctive molecular therapies, and combinations of cell types [135].

References

1. Roger VL, Go AS, Lloyd-Jones DM, Benjamin EJ, Berry JD, Borden WB, et al. Executive summary: heart disease and stroke statistics – 2012 update: a report from the American Heart Association. Circulation. 2012;125(1):188–97.
2. Heidenreich PA, Trogdon JG, Khavjou OA, Butler J, Dracup K, Ezekowitz MD, et al. Forecasting the future of cardiovascular disease in the United States: a policy statement from the American Heart Association. Circulation. 2011;123(8):933–44.
3. van Berlo JH, Kanisicak O, Maillet M, Vagnozzi RJ, Karch J, Lin SC, et al. C-Kit+ cells minimally contribute cardiomyocytes to the heart. Nature. 2014;509(7500):337–41.
4. Quaini F, Urbanek K, Beltrami AP, Finato N, Beltrami CA, Nadal-Ginard B, et al. Chimerism of the transplanted heart. N Engl J Med. 2002;346(1):5–15.
5. Beltrami AP, Urbanek K, Kajstura J, Yan S, Finato N, Bussani R, et al. Evidence that human cardiac myocytes divide after myocardial infarction. N Engl J Med. 2001;344(23):1750–7.
6. Bergmann O, Bhardwaj RD, Bernard S, Zdunek S, Barnabe-Heider F, Walsh S, et al. Evidence for cardiomyocyte renewal in humans. Science. 2009;324(5923):98–102.
7. Orlic D, Kajstura J, Chimenti S, Jakoniuk I, Anderson SM, Li B, et al. Bone marrow cells regenerate infarcted myocardium. Nature. 2001;410(6829):701–5.
8. Beltrami AP, Barlucchi L, Torella D, Baker M, Limana F, Chimenti S, et al. Adult cardiac stem cells are multipotent and support myocardial regeneration. Cell. 2003;114(6):763–76.
9. Rubart M, Field LJ. Cardiac regeneration: repopulating the heart. Annu Rev Physiol. 2006;68:29–49.
10. Hare JM, Bolli R, Cooke JP, Gordon DJ, Henry TD, Perin EC, et al. Phase II clinical research design in cardiology: learning the right lessons too well: observations and recommendations from the Cardiovascular Cell Therapy Research Network (CCTRN). Circulation. 2013;127(15):1630–5.
11. Becker AJ, McCulloch EA, Till JE. Cytological demonstration of the clonal nature of spleen colonies derived from transplanted mouse marrow cells. Nature. 1963;197:452–4.

12. Watt FM, Hogan BL. Out of Eden: stem cells and their niches. Science. 2000;287(5457):1427–30.
13. EC P, GV S. What are stem cells and what do they do? In: An essential guide to cardiac cell therapy. New York: Taylor & Francis Ltd; 2006. p. 3–12.
14. Lodi D, Iannitti T, Palmieri B. Stem cells in clinical practice: applications and warnings. J Exp Clin Cancer Res. 2011;30:9 , 9966-30-9.
15. Fratz S, Hager A, Schreiber C, Schwaiger M, Hess J, Stern HC. Long-term myocardial scarring after operation for anomalous left coronary artery from the pulmonary artery. Ann Thorac Surg. 2011;92(5):1761–5.
16. Quevedo HC, Hatzistergos KE, Oskouei BN, Feigenbaum GS, Rodriguez JE, Valdes D, et al. Allogeneic mesenchymal stem cells restore cardiac function in chronic ischemic cardiomyopathy via trilineage differentiating capacity. Proc Natl Acad Sci U S A. 2009;106(33):14022–7.
17. Menasche P, Hagege AA, Vilquin JT, Desnos M, Abergel E, Pouzet B, et al. Autologous skeletal myoblast transplantation for severe postinfarction left ventricular dysfunction. J Am Coll Cardiol. 2003;41(7):1078–83.
18. Atkins BZ, Hueman MT, Meuchel JM, Cottman MJ, Hutcheson KA, Taylor DA. Myogenic cell transplantation improves in vivo regional performance in infarcted rabbit myocardium. J Heart Lung Transplant. 1999;18(12):1173–80.
19. Tambara K, Sakakibara Y, Sakaguchi G, Lu F, Premaratne GU, Lin X, et al. Transplanted skeletal myoblasts can fully replace the infarcted myocardium when they survive in the host in large numbers. Circulation. 2003;108(Suppl 1):II259–63.
20. Siminiak T, Kalawski R, Fiszer D, Jerzykowska O, Rzezniczak J, Rozwadowska N, et al. Autologous skeletal myoblast transplantation for the treatment of postinfarction myocardial injury: phase I clinical study with 12 months of follow-up. Am Heart J. 2004;148(3):531–7.
21. Smits PC, van Geuns RM, Poldermans D, Bountioukos M, Onderwater EEM, Lee CH, et al. Catheter-based intramyocardial injection of autologous skeletal myoblasts as a primary treatment of ischemic heart failure. J Am Coll Cardiol. 2003;42(12):2063–9.
22. Jackson KA, Majka SM, Wang H, Pocius J, Hartley CJ, Majesky MW, et al. Regeneration of ischemic cardiac muscle and vascular endothelium by adult stem cells. J Clin Invest. 2001;107(11):1395–402.
23. Dawn B, Bolli R. Adult bone marrow-derived cells: regenerative potential, plasticity, and tissue commitment. Basic Res Cardiol. 2005;100(6):494–503.
24. Gunsilius E, Gastl G, Petzer AL. Hematopoietic stem cells. Biomed Pharmacother. 2001;55(4):186–94.
25. Kocher AA, Schuster MD, Szabolcs MJ, Takuma S, Burkhoff D, Wang J, et al. Neovascularization of ischemic myocardium by human bone-marrow-derived angioblasts prevents cardiomyocyte apoptosis, reduces remodeling and improves cardiac function. Nat Med. 2001;7(4):430–6.
26. Nygren JM, Jovinge S, Breitbach M, Sawen P, Roll W, Hescheler J, et al. Bone marrow-derived hematopoietic cells generate cardiomyocytes at a low frequency through cell fusion, but not transdifferentiation. Nat Med. 2004;10(5):494–501.
27. Urbich C, Dimmeler S. Endothelial progenitor cells: characterization and role in vascular biology. Circ Res. 2004;95(4):343–53.
28. Kawamoto A, Gwon HC, Iwaguro H, Yamaguchi JI, Uchida S, Masuda H, et al. Therapeutic potential of ex vivo expanded endothelial progenitor cells for myocardial ischemia. Circulation. 2001;103(5):634–7.
29. Kawamoto A, Tkebuchava T, Yamaguchi J, Nishimura H, Yoon YS, Milliken C, et al. Intramyocardial transplantation of autologous endothelial progenitor cells for therapeutic neovascularization of myocardial ischemia. Circulation. 2003;107(3):461–8.
30. Pittenger MF, Martin BJ. Mesenchymal stem cells and their potential as cardiac therapeutics. Circ Res. 2004;95(1):9–20.
31. Chamberlain G, Fox J, Ashton B, Middleton J. Concise review: mesenchymal stem cells: their phenotype, differentiation capacity, immunological features, and potential for homing. Stem Cells. 2007;25(11):2739–49.

32. Shake JG, Gruber PJ, Baumgartner WA, Senechal G, Meyers J, Redmond JM, et al. Mesenchymal stem cell implantation in a swine myocardial infarct model: engraftment and functional effects. Ann Thorac Surg. 2002;73(6):1919–25 ; discussion 1926.
33. Hatzistergos KE, Quevedo H, Oskouei BN, Hu Q, Feigenbaum GS, Margitich IS, et al. Bone marrow mesenchymal stem cells stimulate cardiac stem cell proliferation and differentiation. Circ Res. 2010;107(7):913–22.
34. Schuleri KH, Amado LC, Boyle AJ, Centola M, Saliaris AP, Gutman MR, et al. Early improvement in cardiac tissue perfusion due to mesenchymal stem cells. Am J Physiol Heart Circ Physiol. 2008;294(5):H2002–11.
35. Le Blanc K, Frassoni F, Ball L, Locatelli F, Roelofs H, Lewis I, et al. Mesenchymal stem cells for treatment of steroid-resistant, severe, acute graft-versus-host disease: a phase II study. Lancet. 2008;371(9624):1579–86.
36. Amado LC, Schuleri KH, Saliaris AP, Boyle AJ, Helm R, Oskouei B, et al. Multimodality noninvasive imaging demonstrates in vivo cardiac regeneration after mesenchymal stem cell therapy. J Am Coll Cardiol. 2006;48(10):2116–24.
37. Psaltis PJ, Carbone A, Nelson AJ, Lau DH, Jantzen T, Manavis J, et al. Reparative effects of allogeneic mesenchymal precursor cells delivered transendocardially in experimental non-ischemic cardiomyopathy. JACC Cardiovasc Interv. 2010;3(9):974–83.
38. Oh H, Bradfute SB, Gallardo TD, Nakamura T, Gaussin V, Mishina Y, et al. Cardiac progenitor cells from adult myocardium: homing, differentiation, and fusion after infarction. Proc Natl Acad Sci U S A. 2003;100(21):12313–8.
39. Martin CM, Meeson AP, Robertson SM, Hawke TJ, Richardson JA, Bates S, et al. Persistent expression of the ATP-binding cassette transporter, Abcg2, identifies cardiac SP cells in the developing and adult heart. Dev Biol. 2004;265(1):262–75.
40. Matsuura K, Honda A, Nagai T, Fukushima N, Iwanaga K, Tokunaga M, et al. Transplantation of cardiac progenitor cells ameliorates cardiac dysfunction after myocardial infarction in mice. J Clin Invest. 2009;119(8):2204–17.
41. Wang X, Hu Q, Nakamura Y, Lee J, Zhang G, From AH, et al. The role of the sca-1+/CD31- cardiac progenitor cell population in postinfarction left ventricular remodeling. Stem Cells. 2006;24(7):1779–88.
42. Pfister O, Mouquet F, Jain M, Summer R, Helmes M, Fine A, et al. CD31- but Not CD31+ cardiac side population cells exhibit functional cardiomyogenic differentiation. Circ Res. 2005;97(1):52–61.
43. Urbanek K, Cesselli D, Rota M, Nascimbene A, De Angelis A, Hosoda T, et al. Stem cell niches in the adult mouse heart. Proc Natl Acad Sci U S A. 2006;103(24):9226–31.
44. Smith RR, Barile L, Cho HC, Leppo MK, Hare JM, Messina E, et al. Regenerative potential of cardiosphere-derived cells expanded from percutaneous endomyocardial biopsy specimens. Circulation. 2007;115(7):896–908.
45. Messina E, De Angelis L, Frati G, Morrone S, Chimenti S, Fiordaliso F, et al. Isolation and expansion of adult cardiac stem cells from human and murine heart. Circ Res. 2004;95(9):911–21.
46. Johnston PV, Sasano T, Mills K, Evers R, Lee ST, Smith RR, et al. Engraftment, differentiation, and functional benefits of autologous cardiosphere-derived cells in porcine ischemic cardiomyopathy. Circulation. 2009;120(12):1075–83.
47. Boheler KR, Czyz J, Tweedie D, Yang HT, Anisimov SV, Wobus AM. Differentiation of pluripotent embryonic stem cells into cardiomyocytes. Circ Res. 2002;91(3):189–201.
48. Blum B, Benvenisty N. The tumorigenicity of human embryonic stem cells. Adv Cancer Res. 2008;100:133–58.
49. Takahashi K, Tanabe K, Ohnuki M, Narita M, Ichisaka T, Tomoda K, et al. Induction of pluripotent stem cells from adult human fibroblasts by defined factors. Cell. 2007;131(5):861–72.
50. Yu J, Vodyanik MA, Smuga-Otto K, Antosiewicz-Bourget J, Frane JL, Tian S, et al. Induced pluripotent stem cell lines derived from human somatic cells. Science. 2007;318(5858):1917–20.

51. Yan B, Abdelli LS, Singla DK. Transplanted induced pluripotent stem cells improve cardiac function and induce neovascularization in the infarcted hearts of db/db mice. Mol Pharm. 2011;8(5):1602–10.
52. Broxmeyer HE, Douglas GW, Hangoc G, Cooper S, Bard J, English D, et al. Human umbilical cord blood as a potential source of transplantable hematopoietic stem/progenitor cells. Proc Natl Acad Sci U S A. 1989;86(10):3828–32.
53. Erices A, Conget P, Minguell JJ. Mesenchymal progenitor cells in human umbilical cord blood. Br J Haematol. 2000;109(1):235–42.
54. Salahuddin SZ, Markham PD, Ruscetti FW, Gallo RC. Long-term suspension cultures of human cord blood myeloid cells. Blood. 1981;58(5):931–8.
55. Rocha V, Broxmeyer HE. New approaches for improving engraftment after cord blood transplantation. Biol Blood Marrow Transplant. 2010;16(1 Suppl):S126–32.
56. Kogler G, Sensken S, Airey JA, Trapp T, Muschen M, Feldhahn N, et al. A new human somatic stem cell from placental cord blood with intrinsic pluripotent differentiation potential. J Exp Med. 2004;200(2):123–35.
57. Ma N, Stamm C, Kaminski A, Li W, Kleine HD, Muller-Hilke B, et al. Human cord blood cells induce angiogenesis following myocardial infarction in NOD/scid-mice. Cardiovasc Res. 2005;66(1):45–54.
58. Hu CH, Wu GF, Wang XQ, Yang YH, Du ZM, He XH, et al. Transplanted human umbilical cord blood mononuclear cells improve left ventricular function through angiogenesis in myocardial infarction. Chin Med J. 2006;119(18):1499–506.
59. Henning RJ, Abu-Ali H, Balis JU, Morgan MB, Willing AE, Sanberg PR. Human umbilical cord blood mononuclear cells for the treatment of acute myocardial infarction. Cell Transplant. 2004;13(7–8):729–39.
60. van de Ven C, Collins D, Bradley MB, Morris E, Cairo MS. The potential of umbilical cord blood multipotent stem cells for nonhematopoietic tissue and cell regeneration. Exp Hematol. 2007;35(12):1753–65.
61. Zuk PA, Zhu M, Ashjian P, De Ugarte DA, Huang JI, Mizuno H, et al. Human adipose tissue is a source of multipotent stem cells. Mol Biol Cell. 2002;13(12):4279–95.
62. Gaustad KG, Boquest AC, Anderson BE, Gerdes AM, Collas P. Differentiation of human adipose tissue stem cells using extracts of rat cardiomyocytes. Biochem Biophys Res Commun. 2004;314(2):420–7.
63. Planat-Benard V, Menard C, Andre M, Puceat M, Perez A, Garcia-Verdugo JM, et al. Spontaneous cardiomyocyte differentiation from adipose tissue stroma cells. Circ Res. 2004;94(2):223–9.
64. De Ugarte DA, Morizono K, Elbarbary A, Alfonso Z, Zuk PA, Zhu M, et al. Comparison of multi-lineage cells from human adipose tissue and bone marrow. Cells Tissues Organs. 2003;174(3):101–9.
65. Puissant B, Barreau C, Bourin P, Clavel C, Corre J, Bousquet C, et al. Immunomodulatory effect of human adipose tissue-derived adult stem cells: comparison with bone marrow mesenchymal stem cells. Br J Haematol 2005; 129(1):118–29.
66. Miyahara Y, Nagaya N, Kataoka M, Yanagawa B, Tanaka K, Hao H, et al. Monolayered mesenchymal stem cells repair scarred myocardium after myocardial infarction. Nat Med. 2006;12(4):459–65.
67. McCall FC, Telukuntla KS, Karantalis V, Suncion VY, Heldman AW, Mushtaq M, et al. Myocardial infarction and intramyocardial injection models in swine. Nat Protoc. 2012;7(8):1479–96.
68. Pouly J, Hagege AA, Vilquin JT, Bissery A, Rouche A, Bruneval P, et al. Does the functional efficacy of skeletal myoblast transplantation extend to nonischemic cardiomyopathy? Circulation. 2004;110(12):1626–31.
69. Kondoh H, Sawa Y, Fukushima N, Matsumiya G, Miyagawa S, Kitagawa-Sakakida S, et al. Combined strategy using myoblasts and hepatocyte growth factor in dilated cardiomyopathic hamsters. Ann Thorac Surg. 2007;84(1):134–41.

70. Yoo KJ, Li RK, Weisel RD, Mickle DA, Jia ZQ, Kim EJ, et al. Heart cell transplantation improves heart function in dilated cardiomyopathic hamsters. Circulation. 2000;102(19 Suppl 3):III204–9.
71. Suzuki K, Murtuza B, Suzuki N, Smolenski RT, Yacoub MH. Intracoronary infusion of skeletal myoblasts improves cardiac function in doxorubicin-induced heart failure. Circulation. 2001;104(12 Suppl 1):I213–7.
72. Scorsin M, Hagege AA, Dolizy I, Marotte F, Mirochnik N, Copin H, et al. Can cellular transplantation improve function in doxorubicin-induced heart failure? Circulation. 1998;98(19 Suppl):II151–5 ; discussion II155–6.
73. Nagaya N, Kangawa K, Itoh T, Iwase T, Murakami S, Miyahara Y, et al. Transplantation of mesenchymal stem cells improves cardiac function in a rat model of dilated cardiomyopathy. Circulation. 2005;112(8):1128–35.
74. Werner L, Deutsch V, Barshack I, Miller H, Keren G, George J. Transfer of endothelial progenitor cells improves myocardial performance in rats with dilated cardiomyopathy induced following experimental myocarditis. J Mol Cell Cardiol. 2005;39(4):691–7.
75. Hata H, Matsumiya G, Miyagawa S, Kondoh H, Kawaguchi N, Matsuura N, et al. Grafted skeletal myoblast sheets attenuate myocardial remodeling in pacing-induced canine heart failure model. J Thorac Cardiovasc Surg. 2006;132(4):918–24.
76. Takahashi M, Li TS, Suzuki R, Kobayashi T, Ito H, Ikeda Y, et al. Cytokines produced by bone marrow cells can contribute to functional improvement of the infarcted heart by protecting cardiomyocytes from ischemic injury. Am J Physiol Heart Circ Physiol. 2006;291(2):H886–93.
77. Uemura R, Xu M, Ahmad N, Ashraf M. Bone marrow stem cells prevent left ventricular remodeling of ischemic heart through paracrine signaling. Circ Res. 2006;98(11):1414–21.
78. Gnecchi M, He H, Noiseux N, Liang OD, Zhang L, Morello F, et al. Evidence supporting paracrine hypothesis for Akt-modified mesenchymal stem cell-mediated cardiac protection and functional improvement. FASEB J. 2006;20(6):661–9.
79. Williams AR, Hatzistergos KE, Addicott B, McCall F, Carvalho D, Suncion V, et al. Enhanced effect of combining human cardiac stem cells and bone marrow mesenchymal stem cells to reduce infarct size and to restore cardiac function after myocardial infarction. Circulation. 2013;127(2):213–23.
80. Gnecchi M, He H, Liang OD, Melo LG, Morello F, Mu H, et al. Paracrine action accounts for marked protection of ischemic heart by Akt-modified mesenchymal stem cells. Nat Med. 2005;11(4):367.
81. Kolf CM, Cho E, Tuan RS. Mesenchymal stromal cells. Biology of adult mesenchymal stem cells: regulation of niche, self-renewal and differentiation. Arthritis Res Ther. 2007;9(1):204.
82. Torella D, Ellison GM, Karakikes I, Nadal-Ginard B. Resident cardiac stem cells. Cell Mol Life Sci. 2007;64(6):661–73.
83. Gnecchi M, He H, Melo LG, Noiseaux N, Morello F, de Boer RA, et al. Early beneficial effects of bone marrow-derived mesenchymal stem cells overexpressing Akt on cardiac metabolism after myocardial infarction. Stem Cells. 2009;27(4):971–9.
84. Dhein S, Garbade J, Rouabah D, Abraham G, Ungemach FR, Schneider K, et al. Effects of autologous bone marrow stem cell transplantation on beta-adrenoceptor density and electrical activation pattern in a rabbit model of non-ischemic heart failure. J Cardiothorac Surg. 2006;1:17.
85. Metzele R, Alt C, Bai X, Yan Y, Zhang Z, Pan Z, et al. Human adipose tissue-derived stem cells exhibit proliferation potential and spontaneous rhythmic contraction after fusion with neonatal rat cardiomyocytes. FASEB J. 2011;25(3):830–9.
86. Heldman AW, Hare JM. Cell therapy for myocardial infarction: special delivery. J Mol Cell Cardiol. 2008;44(3):473–6.
87. Hou D, Youssef EA, Brinton TJ, Zhang P, Rogers P, Price ET, et al. Radiolabeled cell distribution after intramyocardial, intracoronary, and interstitial retrograde coronary venous delivery: implications for current clinical trials. Circulation. 2005;112(9 Suppl):I150–6.

88. Bartunek J, Wijns W, Heyndrickx GR, Vanderheyden M. Timing of intracoronary bone-marrow-derived stem cell transplantation after ST-elevation myocardial infarction. Nat Clin Pract Cardiovasc Med. 2006;3(Suppl 1):S52–6.
89. Grieve SM, Bhindi R, Seow J, Doyle A, Turner AJ, Tomka J, et al. Microvascular obstruction by intracoronary delivery of mesenchymal stem cells and quantification of resulting myocardial infarction by cardiac magnetic resonance. Circ Heart Fail. 2010;3(3):e5–6.
90. Karantalis V, DiFede DL, Gerstenblith G, Pham S, Symes J, Zambrano JP, et al. Autologous mesenchymal stem cells produce concordant improvements in regional function, tissue perfusion, and fibrotic burden when administered to patients undergoing coronary artery bypass grafting: The Prospective Randomized Study of Mesenchymal Stem Cell Therapy in Patients Undergoing Cardiac Surgery (PROMETHEUS) trial. Circ Res. 2014;114(8):1302–10.
91. Suncion VY, Ghersin E, Fishman JE, Zambrano JP, Karantalis V, Mandel N, et al. Does transendocardial injection of mesenchymal stem cells improve myocardial function locally or globally? An analysis from the Percutaneous Stem Cell Injection Delivery Effects on Neomyogenesis (POSEIDON) randomized trial. Circ Res. 2014;114(8):1292–301.
92. Trachtenberg B, Velazquez DL, Williams AR, McNiece I, Fishman J, Nguyen K, et al. Rationale and design of the Transendocardial Injection of Autologous Human Cells (bone marrow or mesenchymal) in Chronic Ischemic Left Ventricular Dysfunction and Heart Failure Secondary to Myocardial Infarction (TAC-HFT) trial: a randomized, double-blind, placebo-controlled study of safety and efficacy. Am Heart J. 2011;161(3):487–93.
93. Kornowski R, Leon MB, Fuchs S, Vodovotz Y, Flynn MA, Gordon DA, et al. Electromagnetic guidance for catheter-based transendocardial injection: a platform for intramyocardial angiogenesis therapy. Results in normal and ischemic porcine models. J Am Coll Cardiol. 2000;35(4):1031–9.
94. Wolf T, Gepstein L, Dror U, Hayam G, Shofti R, Zaretzky A, et al. Detailed endocardial mapping accurately predicts the transmural extent of myocardial infarction. J Am Coll Cardiol. 2001;37(6):1590–7.
95. Barbash IM, Chouraqui P, Baron J, Feinberg MS, Etzion S, Tessone A, et al. Systemic delivery of bone marrow-derived mesenchymal stem cells to the infarcted myocardium: feasibility, cell migration, and body distribution. Circulation. 2003;108(7):863–8.
96. Freyman T, Polin G, Osman H, Crary J, Lu M, Cheng L, et al. A quantitative, randomized study evaluating three methods of mesenchymal stem cell delivery following myocardial infarction. Eur Heart J. 2006;27(9):1114–22.
97. Larose E, Proulx G, Voisine P, Rodes-Cabau J, De Larochelliere R, Rossignol G, et al. Percutaneous versus surgical delivery of autologous myoblasts after chronic myocardial infarction: an in vivo cardiovascular magnetic resonance study. Catheter Cardiovasc Interv. 2010;75(1):120–7.
98. Telukuntla KS, Suncion VY, Schulman IH, Hare JM. The advancing field of cell-based therapy: insights and lessons from clinical trials. J Am Heart Assoc. 2013;2(5):e000338.
99. Behfar A, Crespo-Diaz R, Terzic A, Gersh BJ. Cell therapy for cardiac repair – lessons from clinical trials. Nat Rev Cardiol. 2014;11(4):232–46.
100. Lunde K, Solheim S, Aakhus S, Arnesen H, Abdelnoor M, Egeland T, et al. Intracoronary injection of mononuclear bone marrow cells in acute myocardial infarction. N Engl J Med. 2006;355(12):1199–209.
101. Schachinger V, Erbs S, Elsasser A, Haberbosch W, Hambrecht R, Holschermann H, et al. Intracoronary bone marrow-derived progenitor cells in acute myocardial infarction. N Engl J Med. 2006;355(12):1210–21.
102. Martin-Rendon E, Brunskill SJ, Hyde CJ, Stanworth SJ, Mathur A, Watt SM. Autologous bone marrow stem cells to treat acute myocardial infarction: a systematic review. Eur Heart J. 2008;29(15):1807–18.
103. Wollert KC, Meyer GP, Lotz J, Ringes-Lichtenberg S, Lippolt P, Breidenbach C, et al. Intracoronary autologous bone-marrow cell transfer after myocardial infarction: the BOOST randomised controlled clinical trial. Lancet. 2004;364(9429):141–8.

104. Hare JM, Traverse JH, Henry TD, Dib N, Strumpf RK, Schulman SP, et al. A randomized, double-blind, placebo-controlled, dose-escalation study of intravenous adult human mesenchymal stem cells (prochymal) after acute myocardial infarction. J Am Coll Cardiol. 2009;54(24):2277–86.
105. Leon MB, Kornowski R, Downey WE, Weisz G, Baim DS, Bonow RO, et al. A blinded, randomized, placebo-controlled trial of percutaneous laser myocardial revascularization to improve angina symptoms in patients with severe coronary disease. J Am Coll Cardiol. 2005;46(10):1812–9.
106. Perin EC, Dohmann HF, Borojevic R, Silva SA, Sousa AL, Mesquita CT, et al. Transendocardial, autologous bone marrow cell transplantation for severe, chronic ischemic heart failure. Circulation. 2003;107(18):2294–302.
107. Perin EC, Willerson JT, Pepine CJ, Henry TD, Ellis SG, Zhao DX, et al. Effect of transendocardial delivery of autologous bone marrow mononuclear cells on functional capacity, left ventricular function, and perfusion in chronic heart failure: the FOCUS-CCTRN trial. JAMA. 2012;307(16):1717–26.
108. Heldman AW, DiFede DL, Fishman JE, Zambrano JP, Trachtenberg BH, Karantalis V, et al. Transendocardial mesenchymal stem cells and mononuclear bone marrow cells for ischemic cardiomyopathy: the TAC-HFT randomized trial. JAMA. 2014;311(1):62–73.
109. Stamm C, Westphal B, Kleine HD, Petzsch M, Kittner C, Klinge H, et al. Autologous bone-marrow stem-cell transplantation for myocardial regeneration. Lancet. 2003;361(9351):45–6.
110. Archundia A, Aceves JL, Lopez-Hernandez M, Alvarado M, Rodriguez E, Diaz Quiroz G, et al. Direct cardiac injection of G-CSF mobilized bone-marrow stem-cells improves ventricular function in old myocardial infarction. Life Sci. 2005;78(3):279–83.
111. Patel AN, Geffner L, Vina RF, Saslavsky J, Urschel Jr HC, Kormos R, et al. Surgical treatment for congestive heart failure with autologous adult stem cell transplantation: a prospective randomized study. J Thorac Cardiovasc Surg. 2005;130(6):1631–8.
112. Stamm C, Kleine HD, Choi YH, Dunkelmann S, Lauffs JA, Lorenzen B, et al. Intramyocardial delivery of CD133+ bone marrow cells and coronary artery bypass grafting for chronic ischemic heart disease: safety and efficacy studies. J Thorac Cardiovasc Surg. 2007;133(3):717–25.
113. Kuethe F, Richartz BM, Kasper C, Sayer HG, Hoeffken K, Werner GS, et al. Autologous intracoronary mononuclear bone marrow cell transplantation in chronic ischemic cardiomyopathy in humans. Int J Cardiol. 2005;100(3):485–91.
114. Yelda T, Berrin U, Murat S, Aytac O, Sevgi B, Yasemin S, et al. Intracoronary stem cell infusion in heart transplant candidates. Tohoku J Exp Med. 2007;213(2):113–20.
115. Diederichsen AC, Moller JE, Thayssen P, Junker AB, Videbaek L, Saekmose SG, et al. Effect of repeated intracoronary injection of bone marrow cells in patients with ischaemic heart failure the Danish stem cell study – congestive heart failure trial (DanCell-CHF). Eur J Heart Fail. 2008;10(7):661–7.
116. Rouy D, Lebrun F, Berchem G, Delagardelle C, Beissel J, Wagner DR. Cell therapy for severe chronic heart failure: the Luxembourg experience. Biomed Mater Eng. 2008;18(1 Suppl):S27–31.
117. Strauer BE, Yousef M, Schannwell CM. The acute and long-term effects of intracoronary stem cell transplantation in 191 patients with chronic heARt failure: the STAR-heart study. Eur J Heart Fail. 2010;12(7):721–9.
118. Menasche P, Hagege AA, Scorsin M, Pouzet B, Desnos M, Duboc D, et al. Myoblast transplantation for heart failure. Lancet. 2001;357(9252):279–80.
119. Menasche P, Alfieri O, Janssens S, McKenna W, Reichenspurner H, Trinquart L, et al. The Myoblast Autologous Grafting in Ischemic Cardiomyopathy (MAGIC) trial: first randomized placebo-controlled study of myoblast transplantation. Circulation. 2008;117(9):1189–200.
120. Dib N, Dinsmore J, Lababidi Z, White B, Moravec S, Campbell A, et al. One-year follow-up of feasibility and safety of the first U.S., randomized, controlled study using 3-dimensional guided catheter-based delivery of autologous skeletal myoblasts for ischemic cardiomyopathy (CAuSMIC study). JACC Cardiovasc Interv. 2009;2(1):9–16.

121. Bolli R, Chugh AR, D'Amario D, Loughran JH, Stoddard MF, Ikram S, et al. Cardiac stem cells in patients with ischaemic cardiomyopathy (SCIPIO): initial results of a randomised phase 1 trial. Lancet. 2011;378(9806):1847–57.
122. Malliaras K, Makkar RR, Smith RR, Cheng K, Wu E, Bonow RO, et al. Intracoronary cardiosphere-derived cells after myocardial infarction: evidence of therapeutic regeneration in the final 1-year results of the CADUCEUS trial (CArdiosphere-Derived aUtologous stem CElls to reverse ventricUlar dySfunction). J Am Coll Cardiol. 2014;63(2):110–22.
123. Arguero R, Careaga-Reyna G, Castano-Guerra R, Garrido-Garduno MH, Magana-Serrano JA, de Jesus Nambo-Lucio M. Cellular autotransplantation for ischemic and idiopathic dilated cardiomyopathy. Preliminary report Arch Med Res. 2006;37(8):1010–4.
124. Arom KV, Ruengsakulrach P, Jotisakulratana V. Intramyocardial angiogenic cell precursor injection for cardiomyopathy. Asian Cardiovasc Thorac Ann. 2008;16(2):143–8.
125. Fischer-Rasokat U, Assmus B, Seeger FH, Honold J, Leistner D, Fichtlscherer S, et al. A pilot trial to assess potential effects of selective intracoronary bone marrow-derived progenitor cell infusion in patients with nonischemic dilated cardiomyopathy: final 1-year results of the transplantation of progenitor cells and functional regeneration enhancement pilot trial in patients with nonischemic dilated cardiomyopathy. Circ Heart Fail. 2009;2(5):417–23.
126. Martino HF, Oliveira PS, Souza FC, Costa PC, Assunção e Silva E, Villela R, et al. A safety and feasibility study of cell therapy in dilated cardiomyopathy. Braz J Med Biol Res. 2010;43(10):989–95.
127. Seth S, Narang R, Bhargava B, Ray R, Mohanty S, Gulati G, et al. Percutaneous intracoronary cellular cardiomyoplasty for nonischemic cardiomyopathy: clinical and histopathological results: the first-in-man ABCD (Autologous Bone Marrow Cells in Dilated Cardiomyopathy) trial. J Am Coll Cardiol. 2006;48(11):2350–1.
128. Seth S, Bhargava B, Narang R, Ray R, Mohanty S, Gulati G, et al. The ABCD (Autologous Bone Marrow Cells in Dilated Cardiomyopathy) trial a long-term follow-up study. J Am Coll Cardiol. 2010;55(15):1643–4.
129. Vrtovec B, Poglajen G, Lezaic L, Sever M, Domanovic D, Cernelc P, et al. Effects of intracoronary CD34+ stem cell transplantation in nonischemic dilated cardiomyopathy patients: 5-year follow-up. Circ Res. 2013;112(1):165–73.
130. Heiss C, Keymel S, Niesler U, Ziemann J, Kelm M, Kalka C. Impaired progenitor cell activity in age-related endothelial dysfunction. J Am Coll Cardiol. 2005;45(9):1441–8.
131. Penn MS, Ellis S, Gandhi S, Greenbaum A, Hodes Z, Mendelsohn FO, et al. Adventitial delivery of an allogeneic bone marrow-derived adherent stem cell in acute myocardial infarction: phase I clinical study. Circ Res. 2012;110(2):304–11.
132. Hare JM, Fishman JE, Gerstenblith G, Difede Velazquez DL, Zambrano JP, Suncion VY, et al. Comparison of allogeneic vs autologous bone marrow-derived mesenchymal stem cells delivered by transendocardial injection in patients with ischemic cardiomyopathy: the POSEIDON randomized trial. JAMA. 2012:1–11.
133. Noiseux N, Gnecchi M, Lopez-Ilasaca M, Zhang L, Solomon SD, Deb A, et al. Mesenchymal stem cells overexpressing Akt dramatically repair infarcted myocardium and improve cardiac function despite infrequent cellular fusion or differentiation. Mol Ther. 2006;14(6):840–50.
134. Zhang G, Hu Q, Braunlin EA, Suggs LJ, Zhang J. Enhancing efficacy of stem cell transplantation to the heart with a PEGylated fibrin biomatrix. Tissue Eng Part A. 2008;14(6):1025–36.
135. Leri A, Anversa P. Stem cells and myocardial regeneration: cooperation wins over competition. Circulation. 2013;127(2):165–8.

Chapter 32
Origins of Quality Metrics

Howard M. Julien and David J. Whellan

Origins of Quality Metrics

The movement toward the use of quality metrics to shape the delivery of clinical care has its origin in the advent of the evidence based health care (EBHC) movement. EBHC "is the conscientious use of current best evidence in making decisions about the care of individual patients or the delivery of health services" [1, 2]. Evidence based healthcare encompasses the practice of evidence based medicine (EBM) which was best defined by Sackett et al. in their 1996 editorial on the subject. "Evidence based medicine is the conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients" [3]. It lies at the intersection between best external evidence, patient values and expectations, and individual clinical expertise (Fig. 32.1).

EBM is the practice of using data from studies comparing the efficacy of multiple interventions or treatments to guide clinical practice. Quality metrics have their origin in EBM which in turn developed out of application of findings of clinical epidemiology. Parallel to developments in research techniques were social factors that combined to lead to the development of quality measures and the current health care landscape.

The quality measurement and improvement initiative began in the late 1990s with the development of a consensus recognition amongst healthcare providers and

H.M. Julien, MD, MPH (✉)
Division of Cardiovascular Medicine, Perelman School of Medicine,
University of Pennsylvania,
3400 Civic Center Blvd, East Pavillion, Second Floor, Philadelphia, PA 19104, USA
e-mail: Howard.Julien@uphs.upenn.edu

D.J. Whellan, MD, MHS
Department of Medicine, Division of Cardiology, Thomas Jefferson University Hospital,
1015 Chestnut Street, Suite 317, Philadelphia, PA 19107, USA
e-mail: david.whellan@jefferson.edu

H. Eisen (ed.), *Heart Failure*, DOI 10.1007/978-1-4471-4219-5_32

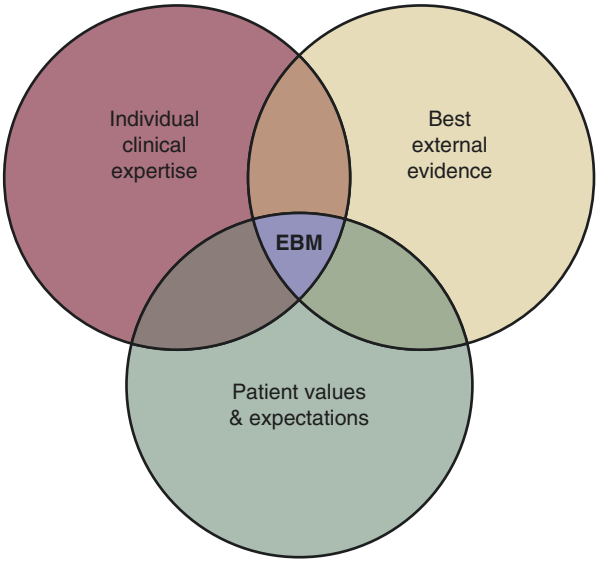


Fig. 32.1 Foundations of evidence based medicine (EBM) [2]

industry leaders that a disconnect existed between the care that should be delivered and that which was actually delivered.

The Institute of Medicine established six aims of improvement to address areas where the health care system underperforms. They postulate that healthcare should be: safe, effective, patient centered, timely, efficient and equitable [4]. National efforts to describe where and to what extent the health care system underperforms led to the passage of the title IX of the Public Health Service Act (42 U.S.C. 299 et seq.). Section 913 (a)(2) of the title outlines the creation of the Agency for Healthcare Research Quality (AHRQ) and charges the agency with generating "an annual report on national trends in the quality of healthcare provided to the American people." This annual report, known as the National Healthcare Quality Report (NHQR) or Quality Report for short, was first published in 2003 and outlined five key findings:

1. High quality health care is not yet a universal reality
2. Opportunities for preventative care are frequently missed
3. Management of chronic diseases presents unique quality challenges
4. There is more to learn
5. Greater improvement is possible

The first national program for the measurement and reporting of hospital quality was started by the Joint Commission in 1998 with its ORYX initiative [5] The Joint Commission (formerly known as the Joint Commission on Accreditation of Healthcare Organizations- JCAHO) is an independent not for profit organization that accredits and certifies more than 19,000 health care organizations and programs in the United States. In 2002, hospitals accredited by the Joint Commission were required to collect and report non-standardized data for two four core health

measures (heart failure, acute myocardial infarction, pregnancy and pneumonia). These data were first made available to the public in 2004 [6].

Overview of Quality Metrics

Any attempt to improve a process first begins with a definition of what the goal of improvement is. In the realm of health care delivery and patient care, this necessitates the definition of quality health care. The most concise definition comes from the National Committee for Quality Assurance (NCQA), a private not-for-profit organization founded in 1990 that collects annual data from providers and health plans and compares the results against developed standards in order to effect change. The NCQA defines quality health care as the "extent to which patients get the care they need in a manner that most effectively protects or restores their health" [7]. According to the NCQA this includes receiving preventative care as well as timely access to effective, evidence based medical treatments. The ultimate goal of these interventions as outlined in their vision and mission statements is to improve/transform health care quality through measurement, transparency and accountability.

The NCQA uses a continuous three stage cycle of measurement, analysis and improvement to drive change. Self-reported data in more than 40 areas are obtained from health plans and providers on an annual basis. The NCQA has developed standards in conjunction with health plans, large employers, patients, doctors and policy makers so that consensus could be reached on which outcomes are important to measure and how to measure them. The comparison of self-reported data on an annual basis with standards established by the NCQA becomes the substrate organizations used to develop focused health care quality improvement initiatives and to create agendas within an organization for subsequent years.

As outlined by the Institute of Medicine (IOM), quality improvement initiatives should aim to develop systems that are safe and designed to avoid injury as well as provide services that are effective, patient centered, delivered efficiently and in an equitable manner. To achieve these aims, quality metrics should have "scientific validity, specification of numerators and denominators, and certainty that a potential measure is interpretable, applicable, and feasible" [4].

Metrics Versus Guidelines

Often confused with guideline recommendations, performance measurements are used to construct a framework for the boundaries of care. As outlined by the American College of Cardiology Foundation and the American Heart Association (ACCF/AHA) task force on performance measures, "performance measures

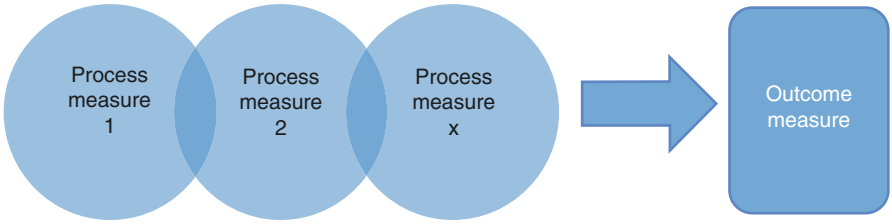


Fig. 32.2 Relationship of process measures to outcome measures

identify aspects of care for which the failure to provide a particular process of care is judged as poor clinical performance" whereas practice guidelines delineate "processes of care that should that should generally be used in patients with a given condition" [8]. As highlighted by the writing committee to develop heart failure clinical performance measures in 2005, development of quality metrics aims to capture implementation of those processes or structural aspects of care whose supporting evidence "is so strong that failure to perform such actions reduces the likelihood that optimal patient outcomes will occur" [9].

Process Versus Outcome Measures

Once the goal of a quality improvement initiative has been identified, the individual(s) or group undertaking the initiative need tools to study existing processes and the outcomes they result in. Outcome measures quantify high level safety, patient care and financial endpoints that indicate how well an organization is meeting its goals. Ideally, outcome measures specify a population to study and a specific timeline over which the measure would be applied.

Process measures assess the specific steps or tasks in a pathway that lead to a specific outcome metric. Several process measures can be studied sequentially to codify the steps that lead to the outcome measure of interest (Fig. 32.2). While outcome measures can be used to measure the overarching goals and directions for a healthcare organization, process measures are used to steer granular interventions towards these goals.

Heart Failure as a Quality Focus: Rationale for Measurement

Improvement in Quality of Care

Health care quality metrics are developed for a wide array of audiences and reasons. Patients and purchasers may use them when deciding on providers and plans, institutions and individual providers may use them as tools to drive performance improvement initiatives, assess resource utilization or compare themselves with

competitors. Donabedian proposed in 1991 that the quality of healthcare could be assessed by assessing its structure, process and outcomes [10]. In the United States, the IOM defines healthcare quality as "the degree to which health services for individuals and populations increase the likelihood of desired health outcomes and are consistent with current professional knowledge" [11].

Process measures provide information about health care delivery that can be used to affect change within a system. Process measures carry the additional benefit of requiring little--if any, risk adjustment for patient illness. The development of a process measure requires identification of an eligible population to which the measure is then applied [12]. An example would be to measure the percentage of all patients with left ventricular systolic dysfunction (eligible population) that have been prescribed and angiotensin converting enzyme inhibitor (ACEI) or an angiotensin receptor blocker (ARB).

- Chassin and colleagues proposed that process measures be judged against 4 criteria in order to maximize their relevance to clinical outcomes [5]. Measures should: be grounded in strong evidence linking the process of care to improved outcomes
- accurately capture whether or not the process of care being measured was performed
- address processes that have few intervening processes of care between the one being measured and the outcome that is targeted
- have small to no chance of inducing adverse events

Rationale for Heart Failure as a Quality Focus

In Crossing the Quality Chasm, the IOM makes the case that focusing on specific conditions provides added meaning to patients as well as those involved in the utilization, delivery, strategic implementation or purchasing of health care [4]. In addition to aligning the multiple stakeholders involved in healthcare delivery and utilization, prioritizing disease conditions can help combat forces that fragment and misalign the health care system and stifle systematic quality improvement efforts.

Heart Failure is an important national public health issue with widespread prevalence, significant morbidity, mortality, and cost implications for patients, providers and payors (both public and private). Of all diagnoses, more Medicare dollars are spent on congestive heart failure diagnosis and treatment than any other in the United States. An estimated five million Americans live with the diagnosis and an additional 550,000 diagnoses are made each year [13]. Understanding of the pathophysiology of the disease has led to the development of non-invasive, pharmacologic and biomechanical tools to diagnose and treat heart failure. Despite these significant advances, evidence indicates that the implementation and use of these new tools falls below that which might be expected.

The NCQA describes the fragmentation of the United States health care system as one in which "episodic care is delivered by a range of providers who are not as well-connected to one another as they should be" [14]. Furthermore, "poorly coordinated care is frequently lower quality, more expensive and can result in poor health outcomes."

Major Organizations Developing Quality Metrics

ACC/AHA/PCPI

In February 2000 the AHA/ACCF Task Force on Performance Measures was created to develop guidelines across the scope of cardiovascular disease care. In 2003 the ACC, AHA and Physician Consortium for Performance Improvement (PCPI) developed measures for heart failure patients that received care in the outpatient setting. The ACCF and AHA first developed inpatient clinical performance measures for adults with chronic heart failure in 2005 [9] Five inpatient measures and 11 outpatient measures were proposed based on 2005 ACCF/AHA class I and class III guideline recommendations for the diagnosis and management of heart failure as well as the Team Management of Patients with Heart Failure: A statement for Healthcare Professionals From the Cardiovascular Nursing Council of the American Heart Association. These measures were most recently updated in May 2012 by the Heart Failure workgroup and published in conjunction with the PCPI. This updated measure set expanded its scope to

Table 32.1 ACC/AHA attributes for satisfactory performance measures [15]

Useful in improving patient outcomes	Evidence-based	
	Interpretable	
	Actionable	
Measure design	Denominator precisely defined	
	Numerator precisely defined	
	Validity	Face validity
		Content validity
		Construct validity
	Reliability	
Measure implementation	Feasability	Reasonable effort
		Reasonable cost
		Reasonable time period for collection

Reprinted with permission from Bonow et al. [15], © 2012

Table 32.2 Heart failure workgroup recommendations for quality measures from the ACCF/AHA/PCPI heart failure performance measure set [15]

Measure Number	Measure Name	Outcome Measure	Process Measure	Patient centered outcome	Measures addressing underuse of patient centered care strategies	Addressing underuse of effective services	Quality improvement only
1	LVEF Assessment (outpatient)		X			X	
2	LVEF Assessment (inpatient)		X			X	
3	Symptom and activity assessment		X		X		
4	Symptom management	X		X			X
5	Patient self-care education		X		X		X
6[a]	Beta blocker therapy for LVSD		X			X	
7[a]	ACEI or ARB therapy for LVSD		X			X	
8	Counseling regarding ICD implantation for patients with LVSD on combination medical therapy					X	X
9[b]	Post discharge appointment for HF patients		X				

Reprinted with permission from Bonow et al. [15], © 2012

[a]Denotes Paired/bundled measures

[b]Addresses care coordination

include guidelines from the European Society of Cardiology and the Heart Failure Society of America (HFSA) [15].

Measures put forth by the (ACCF/AHA/PCPI) in the 2012 update have been streamlined to include both the ambulatory and hospital care settings with the aim of quantifying processes (process measures) in patients with heart failure meant to favorably influence morbidity and mortality (outcome measures). Five outpatient measures and three inpatient measures from the 2005 version of the guidelines were retired with this update. Currently, nine measures exist divided into three groups- outcome measures, process measures and paired/bundled measures (Tables 32.1 and 32.2) [15].

Among measures that were considered for inclusion in the 2012 update but did not make final inclusion were: use of aldosterone antagonists, implementation of cardiac resynchronization therapy (CRT), combined nitrate and hydralazine therapy in addition to standard medical therapy with ACE inhibitors or ARBs and beta blockers for African American patients with heart failure. Reasons for exclusion varied from niche target population (aldosterone antagonists), incomplete definition by existing literature of patient population best served (CRT) and narrow clinical trial data combined with significant systems based barriers to implementation (combined nitrate and hydralazine therapy for African American patients with HF).

The Joint Commission

The Joint Commission announced its first four core measurement areas for hospitals in May 2001. These included acute myocardial infarction and heart failure. The three measures in the heart failure measure set are outlined below (Table 32.3) [16] and are heavily influenced by ACC/AHA guidelines outlined above. The Joint Commission launched its disease specific care certification program in 2002 and to date encompasses at least 26 different programs. Disease specific care certification is available to Joint Commission accredited organizations for 2 year periods with interval reassessment after 1 year [17].

The population for the heart failure measure data set is derived from patients admitted to a hospital for inpatient acute care and discharged to home, homecare

Table 32.3 Joint Commission/CMS heart failure quality measure set [16]

HF set measure ID	Measure short name
HF-1	Discharge instructions[a]
HF-2	Evaluation of LVS function[a]
HF-3	ACEI or ARB for LVSD

Reprinted with permission © Joint Commission Resources: (Heart Failure Core Measure Set). Oakbrook Terrace, IL: Joint Commission on Accreditation of Healthcare Organizations, (Table). (http://www.jointcommission.org/assets/1/6/Heart%20Failure.pdf). Reprinted with permission and electronic copies

[a]Denotes Non-accountability Measure

or court/law enforcement. Patients with a principal ICD-9-CM diagnosis code for heart failure are selected from this population and those with an ICD-9-CM principal or other procedure code of Left ventricular Assist Device or Heart Transplant are excluded. The variables admission date and birthdate are used to calculate age. Patients with ages upon admission greater than 18 years of age and length of stay less than or equal to 120 days were eligible for sampling. Based on Joint Commission specifications, hospitals may choose to sample data on a quarterly or monthly basis with the minimum sample size reported graduated by the initial patient population size.

The HF-1 measure set is a process type performance measure that aims to assess an institution's patient/caregiver education initiatives. It is reasoned that patient/caregiver education initiatives will result in a reduction in patient non-compliance with diet and medications- a key factor behind changes in a heart failure patient's clinical status. Institutions must provide evidence that written instructions or educational materials were given to the patient/caregiver either during the hospitalization or upon discharge. Based on the population listed above the percentage of patients who are sent home with discharge instructions is tabulated. In addition to the standard exclusions listed above, patients that are enrolled in clinical trials or are documented to receive comfort measures only are excluded from the denominator. The instructions/educational material provided is required to address information on activity level, diet, discharge medications, follow-up appointment, weight monitoring and contingency plans if symptoms worsen.

The HF-2 measure set is a process type performance measure that aims to have assessment of Left Ventricular Systolic (LVS) function Similar to the HF-1 measure set, patients that are enrolled in clinical trials or are documented to receive comfort measures only were excluded from the denominator. In addition, patients discharged to another hospital, who left against medical advice, who expired, who were discharged home or to a health care facility for hospice care or had reasons documented by a physician/physician assistant/advanced practice nurse for no LVS function evaluation were all also excluded.

Also a process type performance measure, the HF-3 measure set examines the proportion of heart failure patients that are prescribed an ACE inhibitor or ARB at hospital discharge in comparison to all heart failure patients with left ventricular systolic dysfunction (LVSD). The denominator for this measure once again includes the standard population of patients in the heart failure measure dataset and patients with "chart documentation of a LVEF less than 40% or a narrative description of LVS function consistent with moderate or severe systolic dysfunction." Of the three measures in the Joint Commission HF measure set it is the only one designated as an accountability measure.

The Joint Commission recently relaxed its requirements for reporting heart failure related outcomes for accredited. As of January 1, 2015 hospitals are no longer required to report the core measures listed above. Those that started to report data for calendar year 2014 must continue to do so through the last quarter of 2014 [18].

Table 32.4 Heart failure subset of AHRQ endorsed cardiovascular measures [19]

Number	Measure Name	Organization
0079	Heart failure: LVEF assessment (outpatient setting)	PCPI
0081	Heart failure: ACEI or ARB therapy for left ventricular systolic dysfunction	PCPI
0083	Heart failure: beta-blocker therapy for LVSD	PCPI
0135	Evaluation of left ventricular systolic dysfunction	CMS
0162	ACEI or ARB for left ventricular systolic dysfunction – heart failure patients	CMS
0358	Congestive heart failure (CHF) mortality rate	AHRQ
0229	Hospital 30-day, all-cause, RSMR following HF hospitalization for patients 18 and older	CMS
0330	Hospital 30-day, all-cause, risk-standardized readmission rate following heart failure hospitalization for patients 18 and older	CMS
0277	CHF admission	AHRQ

CHF congestive heart failure, *HF* heart failure, *LVEF* left ventricular ejection fraction, *LVSD* left ventricular systolic

National Quality Forum

The National Quality Forum (NQF) a voluntary consensus standards setting organization published in January 2012 a statement endorsing 39 cardiovascular care quality measures. Of these, nine relate to heart failure and encompass measures that have been delineated by members of consortium groups listed above- CMS, PCPI, AHRQ (Table 32.4) [19].

Performance of Metrics in Clinical Practice

Scrutinio et al. have described the beneficial effect of process of care measures on 1 year post hospital discharge survival. In an analysis of 496 patients with acute decompensated heart failure, eligible for treatment, significant improvement in 1 year mortality was associated with discharge prescription of rennin angiotensin system inhibitors RASIs (RR0.59; $P = 0.015$), beta blockers (RR 0.44; $P < 0.001$) after adjusting for known prognostic risk factors. In addition, the combination therapy, which was not adopted in the ACCF/AHA/PCPI HF performance measure set was also found to have significant improvement in 1 year post hospital discharge survival. Prescription of aldosterone antagonists and planned cardioverter-defibrillator implantation failed to reach statistical significance (RR 0.87 and 0.49 respectively) [20].

Mazimba et al. examined the relationship between adherence to performance metrics and 30 day hospital readmission rates in a retrospective study of 6063 patients admitted with congestive heart failure to one of four hospitals in a regional health system. The study prospectively assessed adherence to four quality mea-

sures- administration of written discharge instructions, LV systolic function measurement, ACE inhibitor or ARB prescribed at discharge, smoking cessation advice given. Readmission rates increased from 16.8 % to 24.8 % over the time period from 2002 to 2008 while adherence to performance measures increased from 95.8 % to 99.9 %. Aside from assessment of LVEF, 30 day readmission rate was not associated with adherence to performance measures. Readmitted patients were found to have twice the odds of not having had their LVEF measured (OR 2.0; $p < 0.00005$; CI 1.45–2.63) [21].

Although clinical trials have been used to develop best care guidelines which have in turn been used to develop quality measures, evidence in the form of clinical trials fails to support this seemingly logical progression. Miller et al. examined the association between JCAHO accreditation scores and AHRQ's Inpatient Quality Indicators and Patient Safety Indicators (IQIs and PSIs). Despite high scores on JCAHO measures by most institutions, IQI and PSI performance varied with no significant relationship between them. JCAHO categorical accreditation decisions were not significantly related to IQI/PSI performance [22].

Accountable Care Organizations

The Patient Protection and Affordable Care Act (PPACA) or simply Affordable Care Act (ACA) was signed into law March 2010. One of the many changes to government sponsored healthcare delivery that it calls for is the creation of accountable care organizations (ACOs) whose goals are to manage and coordinate care for Medicare fee for service beneficiaries. Furthermore, "ACOs that meet quality and performance standards established by the Secretary are eligible to receive payment for shared savings" [23].

These changes come as a part of the shared savings program for Medicare mandated to be enacted no later than January 1, 2012. They are designed to promote accountability for a patient population, coordinate services, and promote "investment in infrastructure and redesigned care processes for high quality and efficient service delivery. Providers of services and suppliers in an ACO continue to receive payments under the original Medicare fee for service program under parts A and B "in the same manner as they would otherwise except that a participating ACO is eligible to receive payment for shared savings." In order to participate, ACOs must serve at least 5000 Medicare fee for service beneficiaries and participate in the shared savings program for at least 3 years.

Measures to assess quality of care provided by ACOs have been broadly divided into three categories: clinical process and outcomes, patient/caregiver experience of care and utilization (i.e. rates of hospital admissions). Furthermore, failure to meet quality performance standards are grounds for termination of agreements with ACOs. Quality of care will be measured using national standards applied to four domains- patient/caregiver experience, care coordination/patient safety, preventative health and at risk populations. Heart failure patients have been identified as one

of these at risk populations and the quality measure assigned is beta blocker therapy left ventricular systolic dysfunction. This quality measure focuses on the population of patients aged 18 or older with heart failure and a current or prior left ventricular ejection fraction less than 40 percent. Beta blocker therapy had to be prescribed within a 12 month period when seen in the outpatient setting or at hospital discharge. Data on this outcome is to be collected using the ACOs group practice reporting option (GPRO) web interface that is designed for clinical quality measure reporting.

Ultimately, quality measure data collected will be used to guide a new pay for performance initiative gradually phased in over the minimum 3 year period of participation in the ACO. In the first year, a pay for reporting policy is applied to all 33 quality measures. In the third year of participation, pay for performance mechanisms will apply to 32 of the 33 quality measures. National benchmark data will be collected and released at the start of the second year when pay for performance begins on many of the quality measures. For the heart failure population, pay for performance with respect to prescription of beta blocker therapy for patients with left ventricular systolic dysfunction is delayed until the third year of participation in the ACO. A minimum attainment level will be set at 30 percent/30th percentile of the performance benchmark with a sliding scale point value assigned up to the maximum attainment value at or above 90 percent/90th percentile of the benchmark of national performance.

Final scores are based upon a composite of the average points obtained within each of the four domains listed above and an overall score that will be used to determine an overall quality performance score and sharing rate. Should an ACO fail to achieve a minimum attainment level on 70 percent of measures in each domain it is at risk of being placed on a hitherto unspecified correction plan.

Bundled Payments

The bundled payments for care improvement (BPCI) initiative was developed by the Center for Medicare and Medicaid Innovation (created by the ACA) as an innovative payment model that develops payment arrangements for organizations based on episodes of care. This is in contrast to the traditional model which calls for payments to be made to providers for each of the services they provide related to a single illness or course of treatment. These new payment arrangements include financial and performance accountability for episodes of care. It is postulated that this payment model will result in the reduction of health care costs for Medicare while increasing coordination among service providers as well as overall quality of care provided.

CMS announced on January 31, 2013 health care organizations that were selected to participate in the bundled payment for care quality improvement initiative. The BPCI initiative is being tested using four implementation models- each of which defines an episode of care differently [24].

In the first model, the episode of care is defined as an inpatient stay in an acute care hospital. Medicare will make separate retrospective payments to hospitals and physicians using the existing Inpatient Prospective Payment System (IPPS) and the Physician Fee Schedule respectively. Payments to hospitals under this model are discounted from the IPPS; however, hospitals and physicians have the opportunity to "share gains arising from the providers' care redesign efforts" [24].

The second and third models call for retrospective payments however, the second implementation model defines the episode as an inpatient stay in an acute care hospital (including all related services and ending 30, 60 or 90 days after discharge) while for the third model and episode of care is triggered by a stay at an acute care hospital and begins at initiation of post-acute care services. These services include participating skilled nursing facilities, inpatient rehabilitation facilities, long-term care hospitals or home health agencies.

Unlike the previous three models, the fourth model calls for a single prospective bundled payment to hospitals for all services provided during the stay by hospitals themselves, physicians and other providers involved with care. Instead of submitting claims to Medicare as per usual, physicians and other providers will submit "no-pay claims" and will receive payment by the hospital from the initial bundled payment. Readmissions for up to 30 days after the initial hospital discharge will be included in the bundled payment amount paid to the hospital.

Controversies

There exist several potential mechanisms explaining discrepancies between improvements over time as determined by quality metrics and actual patient outcomes. Process measures may not accurately capture the implementation of the rationale that they were designed for. The HF-1 performance measure encompasses six different potentially complex components that must be addressed in discharge instructions but does not capture patient understanding of instructions given. General level of education, health literacy and learning style can vary greatly among patient populations and can impact the degree to which interventions are successful. Quality measures that are tied to patient satisfaction may cause health care providers to allocate resources previously directed towards patient care instead towards "customer service" at the expense of clinical outcomes.

The creation of the Medicare shared savings program attempts to reward providers and suppliers for care coordination and delivery of high quality care. It is not clear that delivery of high quality care directly results in health care cost savings. This creates the potential challenge of incentivizing practices that may not be fiscally sustainable in the long-term. Additionally, potential exists for quality metrics to incentivize outdated and even potentially harmful clinical practices if quality metrics and incentives for meeting those practice metrics are not updated on a regular basis in order to keep up with the most current body of scientific evidence [25].

In the largest and most recent prospective study to date, Fonarow et al. examined the association between ACC/AHA performance measures for 5791 patients hospitalized with heart failure at 91 hospitals in the United States in the OPTIMIZE-HF registry and 60 to 90 day mortality [26]. The study found that none of the five ACC/AHA heart failure performance measures- aside from ACEI or ARB use at discharge were associated with a statistically significant reduction in risk of early mortality (60 to 90 days after hospital discharge). Beta blocker use at the time of hospital discharge (which was not one of the ACC/AHA heart failure performance measures at the time of the study) was a significant predictor of reduced risk of mortality (Hazard ratio 0.48; 95 % confidence interval 0.30–0.79; P = 0.004).

Schopfer et al. in their study of heart failure performance measure compliance at 3665 hospitals in the United States found that hospitals in the top quartile of composite compliance had significantly lower 30 day mortality rates than those in the bottom quartile of composite compliance (11.1 % versus 11.5 % $p < 0.001$). No significant difference in 30 day readmission rates were seen (24.7 % versus 24.9 %, $p = 0.098$). These data were limited by the observation that more compliant hospitals in the dataset were located in referral areas with fewer whites, greater proportions of Hispanics and Asians, more high school graduates, more individuals with a graduate degree, and higher household income. These hospitals also had more heart failure admissions per year and were less likely to be a critical access hospital. After adjusting for age, race/ethnicity, income, education, number of HF admissions and type of hospital, hospitals in the top quartile of composite compliance failed to have statistically significant 30 day mortality rates when compared with all other hospitals (11.2 % versus 11.3 %, $p < 0.59$). 30 day hospital readmission rate failed to reach statistical significance for both the adjusted and the unadjusted analysis [27].

Furthermore, regional variation in healthcare costs and practice environments do not seem to be accounted for in pay for performance mechanisms. For more than 20 years the Dartmouth Atlas of Health Care has used administrative data and survey information to chronicle differences in health care resource utilization. Pressures to conform to national quality standards potentially places undue burdens on practitioners in large metropolitan areas where costs of delivering care can be higher.

With the possibility of quality measures being tied to reimbursement in the future, pressure may develop to secure reimbursement through compliance with process measures rather than undertaking initiatives that improve quality of patient care. In the 2012 update to the heart failure performance measure set, the ACCF/AHA recognized that their measure of discharge instructions resulted in “improved adherence without regard to the quality of discharge instructions provided.”

Clinical research has borne tremendous advances in the diagnosis and treatment of heart failure over the past several decades. These advances have been compiled by professional societies into best practice guidelines. In an effort to ensure that all patients receive care that is safe, effective, efficient, timely, patient-centered and equitable -in keeping with IOM recommendations, quality metrics have emerged from the and appear to have an ever growing role in shaping the delivery of health care for patients with heart failure. The basic and clinical science behind the treat-

ment of heart failure is constantly evolving therefore it is imperative that quality measures adapt to reflect changes in best clinical practice.

References

1. Cochrane AL. Effectiveness and efficiency: random reflections on health services. London: Nuffield Provincial Hospitals Trust; 1972.
2. Cochrane Community. http://www.cochrane.org/about-us/evidence-based-health-care (2014). Accessed 21 May 2015. Evidence based medicine tutorial. http://med.fsu.edu/index.cfm?page=medicalinformatics.ebmTutorial. Accessed 1 June 2015.
3. Sackett DL. Evidence based medicine: what it is and what it isn't. BMJ. 1996;312:71–2.
4. Institute of Medicine- Committee on Quality of Health Care in America. Crossing the Quality Chasm: A New Health System for the 21st Century. 3rdrd printing. Washington, DC: National Academy Press, 2002.
5. Chassin MR, Loeb JM, Schmaltz SP, Wachter RM. Accountability measures — using measurement to promote quality improvement. N Engl J Med. 2010;363:683–8.
6. Williams SC, Schmaltz SP, Morton DJ, Koss RG, Loeb JM. Quality of care in U.S. hospitals as reflected by standardized measures, 2002–2004. N Engl J Med. 2005;353:255–64.
7. National Committee for Quality Assurance. http://www.ncqa.org/tabid/142/Default.aspx. Accessed 21 May 2015.
8. Spertus JA, Eagle KA, Krumholz HM, et al. American College of Cardiology and American Heart Association methodology for the selection and creation of performance measures for quantifying the quality of cardiovascular care. J Am Coll Cardiol. 2005;45:1147–56.
9. Bonow RO, Bennett S, Casey DE, et al. ACC/AHA clinical performance measures for adults with chronic heart failure: a report of the American College of Cardiology/American Heart Association Task Force on Performance Measures (Writing Committee to Develop Heart Failure Clinical Performance Measures) endorsed by the Heart Failure Society of America. J Am Coll Cardiol. 2005;46(6):1144–78.
10. Donabedian A. Evaluating quality of medical care. Milbank Mem Fund Q. 1996;44:166–206.
11. Lohr KN, Schroeder SA. A strategy for quality assurance in medicare. N Engl J Med. 1990;322(10):707–12.
12. Rubin HR. The advantages and disadvantages of process-based measures of health care quality. International J Qual Health Care. 2001;13(6):469–74.
13. Thom T, American Heart Association. Heart disease and stroke statistics- 2006 update. Dallas: American Heart Association; 2006.
14. Getting at the heart of the problem. In: Coming home to better care: 2007 annual report. 2007. http://www.ncqa.org/Portals/0/Publications/Resource%20Library/Annual%20Report/NCQA_Annual_2007.pdf. Accessed 21 May 2015.
15. Bonow RO, Ganiats TG, Beam CT, et al. ACCF/AHA/AMA-PCPI 2011 performance measures for adults with heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Performance Measures and the American Medical Association–Physician Consortium for Performance Improvement. J Am Coll Cardiol. 2012;59(20):1812–32.
16. Heart Failure Core Measure Set: The Joint Commission. http://www.jointcommission.org/assets/1/6/Heart%20Failure.pdf. Accessed 21 May 2015.
17. Facts About Disease Specific Care Certification: The Joint Commission. http://www.jointcommission.org/certification/diseasespecific_care.aspx (2014). Accessed 21 May 2015.
18. Heart Failure: The Joint Commission. http://www.jointcommission.org/heart_failure/default.aspx (2015). Accessed 21 May 2015.

19. NQF endorses cardiovascular measures: national quality forum. http://www.qualityforum.org/News_And_Resources/Press_Releases/2012/NQF_Endorses_Cardiovascular_Measures.aspx (2012). Accessed 21 May 2015.
20. Scrutinio D, Passantino A, Ricci VA, Catanzaro R. Association between conformity with performance measures and 1-year postdischarge survival in patients with acute decompensated heart failure. Am J Med Qual. 2013;28(2):160–8.
21. Mazimba S, Grant N, Parikh A, Mwandia G, Makola D, Chilomo C, Redko C, Hahn HS. Heart failure performance measures: do they have an impact on 30-day readmission rates? Am J Med Qual. 2013;28(4):324–9.
22. Miller MR, Pronovost P, Donithan M, Zeger S, Zhan C, Morlock L, Meyer GS. Relationship between performance measurement and accreditation: implications for quality of care and patient safety. Am J Med Qual. 2005;20(5):239–52.
23. Compilation of the social security laws: official social security website. http://www.ssa.gov/OP_Home/ssact/title18/1899.htm. Accessed 21 May 2015.
24. Bundled payments for care improvement (BPCI) initiative: general information: Center for Medicare & Medicaid Services. http://innovation.cms.gov/initiatives/bundled-payments. Accessed 21 May 2015.
25. Loeb JM, Foster N. Process measures, outcome measures, and heart failure. JAMA. 2010;303(1):35–6.
26. Fonarow GC, Abraham WT, Albert NM, Stough WG, Gheorghiade M, Greenberg BH, et al. Association between performance measures and clinical outcomes for patients hospitalized with heart failure. JAMA. 2007;297(1):61–70.
27. Schopfer DW, Whooley MA, Stamos TD. Hospital compliance with performance measures and 30-day outcomes in patients with heart failure. Am Heart J. 2012;164(1):80–6.

Chapter 33
Exercise and Patients with Heart Failure

Donna Mancini

Reduced Exercise Capacity in HF

Heart failure is defined as the inability of the heart to adequately perfuse metabolizing tissues. The classic symptoms of heart failure (CHF) are exertional fatigue and dyspnea. Traditionally it has been hypothesized that the major limitation to exercise performance in CHF patients results from a reduced cardiac output response to exercise leading to skeletal muscle underperfusion and lactic acidosis [1, 2]. However, secondary changes in other organ systems such as skeletal muscle, the vasculature and the lungs play an important role in the genesis of both fatigue and dyspnea [3].

Heart failure can occur in patients with both reduced and preserved systolic function. Exercise performance in patients with reduced systolic function will be the focus of this chapter.

Central Hemodynamic Factors

Cardiac disease can limit an increase cardiac output from a variety of mechanisms including decreased contractility, decreased chronotropic response, active ischemia, obstruction to flow and pulmonary hypertension [4]. In the presence of a reduced cardiac output, the heart is dependent on three principle compensatory mechanisms to maintain normal function. First, the Frank-Starling mechanism, which increases preload to sustain cardiac stroke volume. Second, myocardial hypertrophy occurs, to increase the mass of contractile tissue. Third, the sympathetic nervous system is

D. Mancini, MD
Mt Sinai Icahn School of Medicine, Department of Medicine,
1 Gustav Levy Place, New York, NY 10026, USA
e-mail: dmm31@columbia.edu

H. Eisen (ed.), *Heart Failure*, DOI 10.1007/978-1-4471-4219-5_33

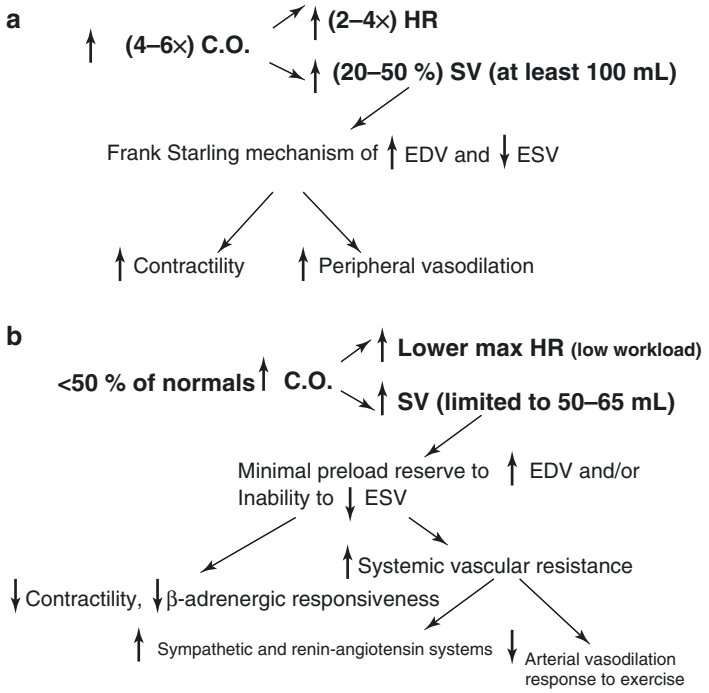


Fig. 33.1 Mechanisms to augment cardiac output (C.O.) in (**a**) healthy persons and (**b**) Patients with heart failure VO_2 = C.O. (HR × SV) (Reprinted from Pina et al. [4], © 2003, with permission from Wolters Kluwer Health)

activated to augment myocardial contractility. In the short term, these compensatory mechanisms serve to preserve cardiac output but with persistent stimulation ultimately become detrimental, contributing to the progression of the disease process. Figure 33.1 shows a schematic illustrating the methods of increasing cardiac output in response to exercise in normal subjects **(a)** and those with systolic heart failure **(b)** [4].

In heart failure patients, decreased exercise capacity has similarly been attributed to a decreased cardiac output response which leads to skeletal muscle underperfusion and intramuscular lactic acidosis [1, 2]. This is based on observations that patients with heart failure exhibit reduced cardiac output responses to exercise compared to normal subjects. Additionally, there is a pronounced increase in filling pressures with the development of marked pulmonary hypertension with pulmonary capillary wedge pressures reaching as high as 50–60 mm Hg [2].

Exercise hemodynamic and ventilatory gas measurements during progressive treadmill exercise in patients with heart failure were first described by Karl Weber in 1981 [5]. This report demonstrated the usefulness of this technique as a non-invasive method for characterizing cardiac reserve and functional status. Weber demonstrated a significant correlation between cardiac output response and oxygen consumption and was able to classify patients into groups of worsening severity on the basis of this non-invasive technique. He found that with worsening heart failure

the cardiac output response is markedly diminished. Several other studies have shown a significant correlation between the peak VO_2 and cardiac output [6–8]. It is this correlation between peak VO_2 and cardiac output which underlies the prognostic value of VO_2 in HF leading to the widespread use of cardiopulmonary exercise testing in the evaluation of these patients.

Peripheral Factors

The peak cardiac output response to exercise is not the sole determinant of exercise performance in HF patients. Patients with similar reductions in left ventricular function estimated using ejection fraction have a wide range of exercise capacity [3]. Furthermore, therapeutic interventions aimed at acutely increasing cardiac output such as positive inotropic drugs do not significantly increase exercise capacity [9, 10]. The discrepancy between enhanced cardiac output and fixed exercise capacity can be explained by abnormalities of skeletal muscle and of the peripheral vasculature. Alterations of skeletal muscle metabolism and mass plays an important role in limiting peak functional capacity in HF patients [11–14]. The changes that occur in the skeletal muscle are critical in the genesis of the primary symptoms of heart failure (dyspnea and fatigue) (Fig. 33.2). Additionally as heart failure becomes progressive the compensatory response to this disease process further negatively impacts skeletal muscle function creating a downward spiral (Fig. 33.3).

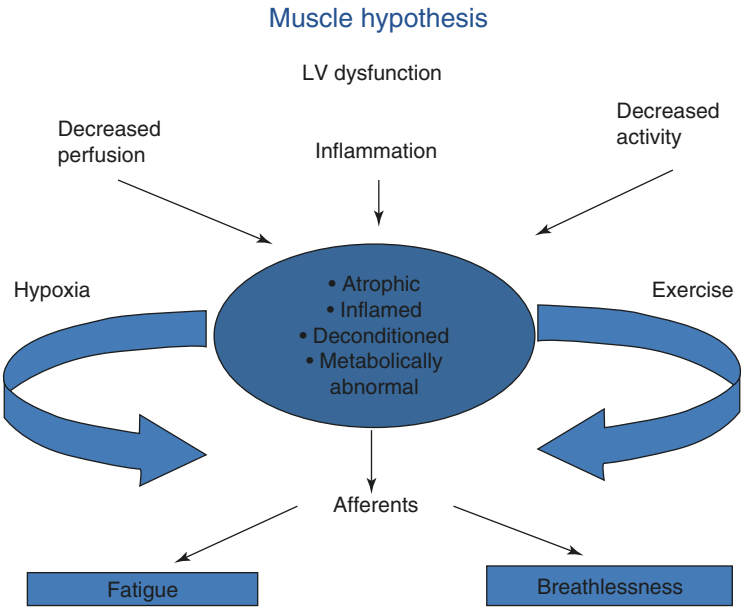


Fig. 33.2 The muscle hypothesis is that the changes in the skeletal muscle result in reduced exercise capacity. Stimulation of ergoreceptors i.e. muscle nerve afferents sensitive to the amount of skeletal muscle work leads to the sensation of dyspnea and fatigue

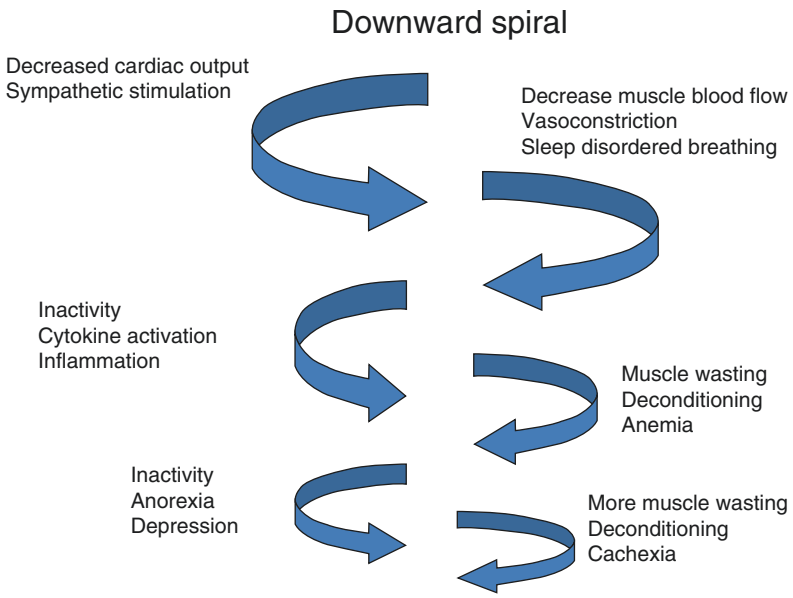


Fig. 33.3 Downward spiral of worsening central cardiac function and increased sympathetic stimulation

CHF patients exhibit generalized skeletal muscle atrophy [11]. Muscle atrophy results from decreased protein synthesis, increased protein degradation or both. CHF is a catabolic state with deficiencies in several anabolic hormones [15–17]. In male CHF patients, deficiencies in circulating total testosterone and insulin-like growth factor are common and these decreases correlate with CHF severity [18]. Growth hormone (GH) resistance and reduction in skeletal muscle IGF-1 concentration contribute to skeletal muscle atrophy in HF by directly reducing protein synthesis [19]. Exercise training has been shown to increase local expression of IGF-1 in normal subjects and HF patients [20]. Patients with HF develop insulin resistance that is related to clinical events and mortality [21].

Chronic low level systemic inflammation, characteristic of the CHF state, also effect changes in skeletal muscle [22] and with the progression of CHF. Inflammatory mediators released into the circulation further activate systemic inflammation and promote muscle atrophy [23, 24].

In addition to skeletal muscle changes, the peripheral circulation undergoes substantial transformations during the progression of HF with an alteration of regional vascular control. These changes occur both at the level of the vascular endothelium and the vascular smooth muscle. Changes in capillary density have been reported in skeletal muscle of patients with HF. Capillary density has been reported to be normal or decreased [25, 26] depending on normalization to muscle fibers number and size. Aerobic training increases capillary density. Nitric oxide (NO)-mediated control of vasomotor tone in CHF [27–29] is attenuated representing endothelial

dysfunction. Of note, aerobic training normalizes endothelial function in patients with HF probably via a mechanism of increased shear stress [30].

Finally, the respiratory muscles are also affected by chronic hypoperfusion and neurohormonal activation which occurs in heart failure [31]. Dyspnea is a complex sensation but weak respiratory muscles coupled with stiff congested lungs as occurs in HF predisposes patients to shortness of breath. Measurement of diaphragmatic work per breath demonstrates dramatic increases in patients with heart failure at rest and during exercise [32]. A reduction in inspiratory and expiratory respiratory muscle strength in patients with HF from both systolic and diastolic dysfunction has been shown [33, 34]. The endurance of the respiratory muscles in HF patients is also diminished compared to normal subjects [35]. The effect of selective respiratory muscle training on exertional dyspnea and exercise capacity has been examined in heart failure subjects. Respiratory muscle endurance, respiratory muscle strength, submaximal and maximal exercise capacity can be significantly improved with selective respiratory muscle training [36, 37].

In summary, exercise capacity is markedly reduced in most patients with CHF due to both a diminished cardiac output with exercise and to secondary changes in skeletal muscle, the peripheral circulation and the lungs. As noted above, most of the individual factors that contribute to reduced exercise capacity in CHF are improved by exercise training.

Exercise Performance and Prognosis in Patients with CHF

As discussed previously, Peak VO_2 is derived from the Fick Principle and is the product of peak cardiac output and maximal arterio-venous oxygen difference. As most sedentary individuals will achieve comparable maximal arterio-venous difference, peak VO_2 provides an indirect assessment of cardiac output reserve. Several peripheral factors may also impact peak VO_2, such as skeletal muscle mass and endothelial function, as well as age, gender and conditioning status.

The use of peak VO_2 to predict prognosis in patients with HF was first described by Szlachcic [38]. In a prospective study of 114 ambulatory patients with severe CHF referred for cardiac transplantation, a VO_2 of less than 14 mL/kg per minute was used as a criterion for acceptance for cardiac transplantation. One-year survival was 94 % in patients with a VO_2 above 14 mL/kg/min. Accepted transplant candidates with a VO_2 below 14 mL/kg per minute had a 1-year survival of 70 %, whereas the patients with a significant co-morbidity and reduced VO_2 had a 1-year survival of 47 %. This approach permitted the identification of candidates whose transplant could be safely deferred [39].

Analysis of peak VO_2 normalized by a predicted maximum based on age, obesity, and gender has been performed to determine if better prognostication can be achieved using percent of predicted peak VO_2. Some investigators have suggested the superiority of this approach, though others have shown no clear benefit [40, 41]. Likely, the additional value of adjusting for sex, age and body composition in any

study cohort is a function of how these characteristics are distributed across the cohort; in studies focusing on middle age men of average weight, both approaches yield similar results [40] while cohorts with greater heterogeneity would likely be better served by reference to sex and age specific prediction equations with adjustment for weight extremes [41].

Since the initial report of the value of peak VO_2 in guiding transplant candidate selection in 1991, there have been many advances in the treatment of heart failure in particular, the use of beta blockade. This therapy has impacted significantly long-term survival without improving peak VO_2. Whether VO_2 retained its predictive power of in the beta-blocker era has been the subject of several reports [42–44]. Consistent across the reports was the sustained utility of this parameter in predicting survival whether cohorts were dichotomized by threshold values of above and below 14 ml/kg/min, or above and below 10 ml/kg/min. The survival for patients on beta blocking agents improved but nevertheless survival separated according to peak VO_2. With the improved survival, a lower cut point than 14 ml/kg/min for referral or listing for cardiac transplant has generally been accepted, with the AHA/ACC guidelines now selecting a peak VO_2 below 10 ml/kg/min with achievement of anaerobic threshold as an absolute indication for transplant (in the absence of significant contraindications). A peak VO_2 of 11–14 ml/kg/min or 55 % of predicted peak VO_2 resulting in major limitation of the patient's daily activities is considered a relative indication for transplant listing [45].

During cardiopulmonary exercise testing other variables are collected that also confer prognostic information. Ventilatory efficiency during exercise, most frequently measured by the VE/VCO_2 ratio or slope, has been found by several investigators to be even more predictive of outcome than peak VO_2 [46–50]. The abnormal VE/VCO_2 response results from increased ventilation–perfusion mismatching and heightened chemosensitivity and ergoreflex responses. This heightened ventilatory response occurs from the onset of exercise and thus unlike peak VO_2, the VE/VCO_2 relation does not require a maximal effort. $VE/VCO_2 > 34$ has been the cut-point selected in many studies but similar to peak VO_2, this parameter is a continuous variable with no absolute cut-point. Frequently in studies, both peak VO_2 and VE/VCO_2 are found to have independent prognostic power, thus, the combination of both VE/VCO_2 and peak VO_2 may provide the strongest way to determine risk. Thus both peak VO_2 and VE/VCO_2 slope provide independent and complementary data on prognosis and should be used together to assess risk [46–50]. VE/VCO_2 correlates more strongly with pulmonary pressures measured during exercise than does peak VO_2. Exercise oscillatory breathing is associated with a poor prognosis. There is no uniform definition of this type of breathing but it is a periodic cycling of hyper and hypopnea with appropriate changes in PET O_2 and PET CO_2. This breathing pattern is observed in about 12–30 % of HF patients during exercise and most patients with exercise oscillatory breathing will have central sleep apnea. Presence of periodic breathing can predict mortality by itself or when combined with the ventilatory slope. In one study of 156 patients with HF, this breathing pattern was strongly correlated with sudden death [51, 52].

Other parameters measured during cardiopulmonary exercise testing also shown to have prognostic power in chronic heart failure include: blood pressure response to exercise (i.e. blunted or failure to increase BP with exercise associated with poor prognosis), the heart rate response to exercise (i.e. chronotropic incompetence), the ventilatory threshold, circulatory power (Peak VO_2 × systolic BP), oxygen kinetics, end tidal Pco_2 and oxygen recovery post exercise [45–53].

As we discussed, the prognostic value of peak VO_2 has been presumed to be as a non-invasive indicator of peak cardiac output response to exercise. Exercise studies in HF patients using both metabolic carts and hemodynamic measurements from Swan Ganz catheters have shown that some measurements such as a reduced left ventricular stroke work index (LVSWI) at peak exercise to be a better prognostic indicator than peak VO_2 [54–57]. As exercise hemodynamic studies are difficult to perform, other investigators have tried to derive other non-invasive parameters which would better approximate this variable. Cohen-Solal [53] proposed 'peak circulatory power' which is the product of the peak VO_2 and the last systolic arterial pressure measurement. The data for this calculation is available from any cardiopulmonary exercise test without the need for special equipment. The value of the 'circulatory power' was assessed in a study involving 175 heart failure patients. During a 25 ± 10 month follow-up, 16 % died and 18 % underwent cardiac transplantation. Multivariable analysis demonstrated that the peak 'circulatory power' (chi-square = 19.9, $P < 0.001$) was the only variable predictive of death or need for transplant. When this was analyzed in terms of quartiles of peak VO_2 or circulatory power, it appeared that prognosis was worse as peak VO_2 declined, but that circulatory power aids in selecting subgroups with particularly poor prognosis—those with both reduced peak VO_2 and reduced blood pressure.

The technology of metabolic carts has improved and new systems now permit non-invasive measurement of cardiac output using inert gas re-breathing techniques [58, 59]. Inert gas rebreathing is a novel, non-invasive method to measure cardiac output during exercise and is reliable, safe and easily performed in patients with CHF [59]. The Innocor rebreathing system uses an oxygen enriched mixture of an inert soluble gas (0.5 % nitrous oxide [N_2O]) and an inert insoluble gas (0.1 % sulfur hexafluoride, [SF_6]) N_2O concentration decreases during the rebreathing maneuver, with a rate proportional to pulmonary blood flow. With the ability to measure cardiac output during exercise, cardiac power can then be derived. Cardiac Power incorporates blood pressure into the exercise hemodynamic assessment. It takes into account both the flow and pressure generating ability of the heart. Tan [60] has argued that it could be viewed as a comprehensive indicator of cardiac function. This technology was applied in 171 consecutive CHF patients during symptom limited bicycle exercise [59]. An accurate measure of peak CO was obtained in 148 patients (85 % of patients). Peak cardiac power was derived from the product of the peak mean arterial blood pressure and CO divided by 451. Duration of follow-up averaged 1 year. Univariable and multivariable analyses were performed using cardiopulmonary exercise variables (i.e., peak VO_2, peak CO, peak cardiac power, VE/VCO_2 slope, and VO_2 at anaerobic threshold). Event-free survival for the entire cohort was 83 % with 5 deaths, 4 LVAD implants and 16 urgent transplants. In this

cohort, peak VO_2 was 12.9 ± 4.5 ml/kg/min and peak cardiac power was 1.7 ± 0.9 watts. Univariable predictors of adverse outcome were peak VO_2, peak CO, peak cardiac power, VE/VCO_2 slope and VO_2 at anaerobic threshold. By multivariable analysis, peak cardiac power and peak CO were predictive of outcome with peak cardiac power being the most powerful independent predictor of outcome (P = 0.01).

As the population ages and more patients survive debilitating myocardial infarctions and/or previously untreatable cardiac disease, there is an ever increasing population of patients with heart failure. When patients approach Stage D, their therapeutic options become increasingly limited. Cardiac transplant and left ventricular assist devices provide (LVAD) the salvage therapies of these patients. With the limited donor supply for transplant, inevitably there will be an increasing number of chronic device patients. The exercise response of patients supported by mechanical assist device will become increasingly important. Despite mechanical support, the exercise capacity of device patients is significantly reduced [61, 62]. The exercise physiology of these patients is unique and results from both the central and peripheral effects of heart failure in conjunction with the limitations of the mechanical device. The right heart is unsupported by the commonly used left ventricular continuous flow pumps. Right ventricular dysfunction is one of the limiting factors for peak exercise performance in these patients particularly since the exercise response is primarily preload mediated. Unlike the earlier pulsatile left ventricular assist devices which had an automatic fill mode which ejected faster with an increase in pump filling, the continuous flow LVADs work with a fixed pump speed (8600–10,000) set with the patient at rest. The speed is selected to optimize unloading of the ventricle and to prevent excessive emptying that results in "suction" (hypotension, arrhythmias). The pump speed of these devices does not change with exercise such that the exercise response is primarily pre-load dependent. Maximum cardiac output of these devices is approximately 10–12 L/min. Additional cardiac output response during exercise can be provided by the native heart working in parallel with the mechanical device. Several long term complications associated with the new continuous flow devices such as anemia and the development of aortic valve leaflet fusion with or without aortic insufficiency can also impact exercise performance [63, 64].

Nevertheless, rest and exercise hemodynamic measurements in LVAD patients are improved compared to unsupported heart failure patients with lower pulmonary pressures and higher cardiac output [61, 62, 64]. Peak VO_2 following support with a continuous flow LVAD averages 12–17 ml/kg/min. The largest study of Heartmate II patients (n = 18) revealed an average percent peak VO_2 of 49 ± 19 % or 15.6 ± 4.7 ml/kg/min 3 months post insertion.

The 6 min walk test is a popularly used assessment of functional capacity in patients with heart failure. It is considered a measure of submaximal exercise performance and thus the level of function needed to perform the activities of daily living. The 6 min walk test, i.e., the distance walked over a period of 6 min, is less subjective than the NYHA functional class, but still can be heavily influenced by the patient's and/or tester's motivation. The 6 min walk test has been shown to provide prognostic information by the Study of Left Ventricular Dysfunction (SOLVD)

investigators who demonstrated in a sub-study of 898 HF patients in their registry that mortality risk was 3.7 times higher in those patients with a 6 min walk distance <350 meters compared to those who walked >450 m. Similarly, the risk of HF hospitalization was 1.4 times higher in those with reduced walk distance [65]. Given the limitations of the current LVADs, the 6 min walk test rather than peak VO_2 has been increasingly used to assess the therapeutic response to mechanical support.

Benefits of Exercise for the Treatment of Chronic Heart Failure

Histologic and metabolic changes of skeletal muscle in HF as described earlier in this chapter may be partially due to muscle disuse [11, 66]. Exercise is a physiologic intervention with a broad variety of positive cardiovascular effects that include changes in lipid metabolism, insulin resistance, weight, arterial hypertension, inflammation and mood [67]. Effects of aerobic exercise on the myocardium have been well established. Regular dynamic exercise increases stroke volume, cardiac output and reduces beta-adrenergic stimulation. Exercise training increases myocardial mass, left ventricular dimensions and stroke volume in healthy subjects [68]. In chronic heart failure, exercise has been shown to improve exercise tolerance and symptoms which is attributed to peripheral adaptations such as improved endothelial function and skeletal muscle strengthening [13].

Many of the central and peripheral changes induced by aerobic training may have a marked therapeutic effect in patients with heart failure. Potential advantages of training in HF (Table 33.1) include central hemodynamic changes such as an increase in stroke volume, and a potential increase in contractility, alteration of autonomic tone with a decrease in sympathetic stimulation, an improvement in endothelial and vascular function with a decrease in peripheral vascular resistance, muscle enzymatic changes with an increased oxidative capacity and decrease in lactate production.

Animal models have been used to investigate the effects of exercise training on the failing heart. Using an ischemic rat model of HF, Musch [69] studied the effects of endurance training. The training protocol consisted of 60 min sessions of treadmill exercise 5 days a week for 10–12 weeks. Following the training program in the rats with heart failure, VO_2 was higher, succinate dehydrogenase activity increased and lactate levels were lower during submaximal exercise. No differences were observed in regional perfusion or in hemodynamic measurements. In this rat model of heart failure, all derived benefits of training were from peripheral mechanisms. Central cardiac function was not altered. Todaka [70] using a pacing-induced model of HF in dogs demonstrated both central and peripheral effects of exercise training. One group received daily treadmill exercise (4.4 km/h, 2 h/day) while the other dogs remained sedentary. At 4 weeks, in-vivo hemodynamic measurements revealed relative preservation of maximum rate of pressure rise and left ventricular end-diastolic pressure in the exercised compared with the sedentary dogs. Subsequent in-vitro

Table 33.1 Benefits of aerobic training

Morphologic	↑ Myocardial mass
	↑ Left ventricular end diastolic volume
	↑ Diameter of coronary arteries
	↑ Myocardial & Skeletal muscle capillary to fiber ratio
Skeletal muscle	↑ Capillary density
	↑ Mitochondrial volume and cristae
	↑ Enzymes citric acid cycle and electron transport chain
	±↑ Myoglobin
	↑ Use of free fatty acids
	↑ Potential to store glycogen
	↑ Local A-VO_2 difference
	↑ Maximal flow rate through muscle
Hemodynamic	↓ Resting HR
	↓ Double product at submaximal workloads
	↑ Stroke volume
	↑ Maximum cardiac output
	↑ Peak VO_2
Metabolic	↑ HDL
	↓ Triglycerides
	↓ Fasting glucose
	↓ Catecholamines
	↑ Lipoprotein lipase
	↓ Hepatic lipase (converts HDL2 HDL3)
	↑ LCAT (esterifies chol with FFA, enhancing chol transport)
	↑ βeta hydroxacyl Co dehydrogenase (↑ βeta oxidation FFA)

Abbreviations: ↑ increase ↓ decrease, *A-V O_2* arterial-venous difference, *HDL* high density lipoprotein, *VLDL* very low density lipoprotein, *FFA* free fatty acid, *LVEDV* left ventricular end diastolic volume, *chol* cholesterol, *LCAT* lipoprotein lipase

analysis of cardiac function revealed similarly depressed systolic functions in both groups. However, whereas the diastolic myocardial stiffness constant was elevated in the sedentary group, it was normal in the exercise training group (32 ± 3 in sedentary dogs, 21 ± 3 in exercised dogs, 20 ± 4 in otherwise normal dogs). Thus, daily exercise training preserved in-vivo hemodynamics and in-vitro measures of diastolic stiffness. The authors concluded that changes in heart function may contribute to the overall beneficial hemodynamic effects of exercise training in this canine model of CHF by a significant effect on diastolic properties.

In patients with CHF, a wide range of hemodynamic changes observed in response to exercise training may also impact on reverse remodeling [13, 14, 67]. One study reported an increase in peak cardiac output [13]. The same workload is

achieved at a lower heart rate and rate-pressure product [13], indicating a more efficient utilization of myocardial work and oxygen consumption. Several studies have attempted to characterize the physiologic mechanisms for the clinical improvement in patients with HF. Sullivan studied 12 patients with HF with a mean VO_2 of 16.3 ml/kg/min and an ejection fraction 21 % [71]. Aerobic training was performed 3–5 h a week for 6 months. With exercise training, peak VO_2 rose 23 % from 16.8 to 20.6 ml/kg/min. Peak cardiac output, peak A-VO_2 difference and peak leg blood flow also significantly increased but ejection fraction was unchanged. Training decreased leg lactate production. Leg blood flow during submaximal exercise did not increase suggesting that the major benefit derived from training was via increased oxygen extraction by the skeletal muscles and the largest proportion of the increase in VO_2 was derived from peripheral adaptation with a possible small central contribution.

Selective arm training [12] in HF patients demonstrated an improvement but not normalization in the skeletal muscle metabolic abnormalities. Percutaneous muscle biopsies of the vastus lateralis showed that aerobic training increased the volume density of mitochondria [72]. Oxidative enzyme activity in skeletal muscle also increased with exercise training indicating improved oxidative function [72].

Various forms of exercise training can be prescribed [73, 74]. The most frequent used method is dynamic aerobic training (e.g. running and cycling) followed by resistance (e.g. strength training) exercises. Dynamic exercise with alternating muscle contraction and relaxation results in a steady rise of systolic blood pressure when intensity increases, while the diastolic pressure varies minimally. In contrast, resistance exercise is characterized by prolonged isometric muscle contraction before relaxation with high interstitial pressure that causes collapse of arterioles and capillaries. Blood pressure increases in relation to intensity and duration of the contraction. Although of minimal benefit with respect to cardiac adaptions, strength training has been shown to also be safe and effective at correcting muscle atrophy and weakness [74], two parameters that are generally less affected by aerobic-type training. The intensity of training programs also vary and can be personalized for the patient and his/her particular problem. Most of the studies done in heart failure subjects have involved dynamic aerobic training at approximately 70 % of peak VO_2.

Belardinelli investigated the value of low intensity exercise training in patients with HF randomized to training versus control groups [75]. The exercise prescription in this study called for 3 weekly training sessions of bicycle exercise at 40 % of peak VO_2 for 8 weeks. Peak VO_2, serum catecholamines, lactate and vastus lateralis skeletal muscle biopsies were performed before and after training. Peak VO_2 increased, serum lactate and catecholamine levels declined during submaximal exercise, and the volume density of mitochondria were enhanced at the conclusion of the study only in the trained group. Similarly, Demopoulus et al. demonstrated the value of low intensity training in patients with severe HF [76]. Using a semirecumbent stationary bicycle, patients trained below 50 % of peak VO_2, 1 h/day, 4x/week, for 3 months. Peak VO_2 rose from 11.5 to 15 ml/kg/min. Peak reactive hyperemia of the calf but not the forearm muscle increased with training. In this study, left

ventricular diastolic wall stress was measured during bicycle exercise at low (<50 %) and more conventional training workloads (70–80 % peak VO_2). Diastolic wall stress was significantly reduced at the lower than at the conventional training rates in these patients.

Skeletal muscle bulk is also reduced in chronic heart failure and could lead to early skeletal muscle fatigue and decreased exercise capacity [11]. Physical deconditioning may contribute to wasting, especially of the leg muscles. The role that physical training plays in increasing leg muscle bulk has yet to be determined but may well contribute to the increased exercise tolerance seen after training.

The effect of aerobic training on endothelial function has also been studied. Isolated forearm training using handgrip exercise resulted in improved flow dependent dilatation [77]. L-NMMA attenuated this improvement implying that the normalization of flow dependent dilatation with training resulted from enhanced endothelial release of nitric oxide. This is an important finding in that it may indicate that with training there is an improvement in skeletal muscle perfusion. Also improvement in the endothelial function of large conduit vessels may decrease impedance to the failing left ventricle and thus improve left ventricular ejection fraction. At this point other investigators have demonstrated increases in skeletal muscle leg perfusion and cardiac output at maximal but not during submaximal activity.

Modulation of "sympathetic overdrive" is another beneficial effect of exercise training. Training increases the parasympathetically mediated component of heart rate variability as well as prolonged exercise duration and increased peak VO_2 [14]. Similarly, the effect of training on autonomic tone assessed by heart rate variability and radiolabeled norepinephrine spillover demonstrated a shift from sympathetic to enhanced vagal activity [14]. Other investigators have demonstrated a decrease in serum catecholamine levels both at rest and during submaximal exercise in these patients following aerobic training [78].

The HF-ACTION trial was a large multicenter, randomized study examining the effects of exercise training on patients with HF (2331 patients with an ejections fraction <35 % enrolled over 4 years). The primary endpoint of the study was overall mortality. The study did not meet its primary endpoint i.e. a significant reduction in all cause mortality or hospitalizations. The sub-study analysis, which adjusted for mortality predictors, did show an exercise dose-dependent benefit in QOL, oxygen uptake, and functional capacity. The observed exercise effect was very modest with an increase of peak VO_2 or only 0.3 ml/min/kg. The study showed that exercise training was safe in patients with HF over an extended period of time in a closely supervised setting with frequent follow-up. Unlike previous studies suggesting that women and older patients may not respond well to exercise training, the HF-ACTION sub-study demonstrated that exercise-related benefits are consistent across sex, race, age, and other subgroups [79]. The modest effect of exercise training on peak functional capacity in the HF-ACTION trial may argue against disuse playing an important role in the pathogenesis of muscle alterations in HF; however these findings may simply reflect the difficulty with adherence to exercise training in a large study population [80]. In the first 3 months where the goal was greater or equal to 90 min of exercise weekly, only 40 % of patients met this goal. By the final year of

the study <30 % were fully adherent with the exercise regimen. A subsequent analysis of the ACTION-HF cohort examining the impact of the volume of exercise performed on clinical events and exercise performance would support the hypothesis that the lack of significance in the ACTION trial primarily was related to the low compliance with therapy. The volume of exercise was computed as hours/week of exercise multiplied by the average exercise intensity in metabolic units. Those patients with a high volume of exercise did show a significant risk reduction for all cause death and hospitalizations as well as greatest increases in peak VO_2. Therefore, the findings of the HF-ACTION trial do not invalidate the documented beneficial effects of exercise training on functional capacity and muscle mass in smaller populations of HF patients.

The ACTION –HF trial focused on ambulatory Stage C heart failure patients. With the development of the new continuous flow devices for left ventricular support (Heartmate II, Heartware) with greater durability, there are increasing number of patients with Stage D HF benefiting from this therapy both as a bridge to transplant as well as destination therapy [81, 82]. Stage D patients are frequently severely debilitated, bedbound, malnourished and often dependent on intravenous medications to support the circulation at rest. Following device implantation, these patients should benefit from intensive rehabilitation. Physical therapy is started in the early post-operative period. Formal cardiac rehab programs post VAD insertion have not been well described. Nevertheless these patients can exercise and rehab could potentially hasten recovery and increase exercise performance. There is minimal data on the impact of aerobic training in these patients. One recent report by Kohli et al. [83] describes the response to training in 22 patients supported by the total artificial heart and 12 LVAD Heartmate II patients. The training protocol used endurance exercise on a motorized treadmill or an upper/lower extremity recumbent stepper. Frequency of training was 3–5 days/week beginning at 5–10 min of exercise at a perceived exertion level of $\leq$ 13 on a Borg scale from 6–20. The aim was to achieve $\geq$ 30 min of continuous aerobic activity. Patients with Heartmate II had an increase in mean arterial pressure with exercise unlike to TAH where exercise mean arterial pressure was flat. For patients with TAH the weekly mean performance on the treadmill increased from 1.6 ± 0.2 Mets at week 1–2.4 ± 0.6 Mets at week 8. The benefit of the aerobic training in LVAD patients was not reported. There is a single case report of training in a HMXVE the formerly used pulsatile pump [84]. There are no reports of isometric training in these patients.

Summary

Reduced exercise capacity is a cardinal symptom of patients with heart failure. Both central and peripheral changes contribute to the reduced functional capacity. Exercise testing provides important prognostic information for the management of these patients. Routine exercise i.e. training is a therapeutic option which has been underutilized and may significantly impact the quality of life and outcomes.

References

1. Wasserman K, Hansen J, Sue D, Whipp B, Casaburi R. Chapter 2: Physiology of exercise. In: Principles of exercise testing and interpretation. 2 ed. Philadelphia: Lea and Febiger; 1994. p. 9–51.
2. Weber K, Janicki J, McElroy P. Determination of aerobic capacity and the severity of chronic cardiac and circulatory failure. Circulation. 1987;76:VI40–5.
3. Clark A, Poole-Wilson P, Coats A. Exercise limitation in chronic heart failure: central role of the periphery. J Am Coll Cardiol. 1996;28:1092–102.
4. Pina I, Apstein C, Balady G, et al. Exercise and heart failure: a statement from the American Heart Association Committee on exercise, rehabilitation and prevention. Circulation. 2003;107:1210–25.
5. Weber K, Kinasewitz G, Janicki J, et al. Oxygen utilization and ventilation during exercise in patients with chronic heart failure. Circulation. 1982;65:1213–23.
6. Wasserman K, Casaburi R. Dyspnea: physiological and pathophysiological mechanisms. Ann Rev Med. 1988;39:503–15.
7. Lang C, Karlin P, Haythe J, et al. Ease of noninvasive measurement of cardiac output coupled with peak VO_2 determination at rest and during exercise in patients with heart failure. Am J Cardiol. 2007;99:404–5.
8. Duscha B, Schulze P, Robbins J, Forman E. Implications of chronic heart failure on peripheral vasculature and skeletal muscle before and after exercise training. Heart Fail Rev. 2008;13:21–37.
9. Maskin C, Forman R, Sonnenblick E, Frishman W, LeJemtel T. Failure of dobutamine to increase exercise capacity despite hemodynamic improvement in severe chronic heart failure. Am J Cardiol. 1983;51:177–82.
10. Wilson J, Martin J, Ferraro N. Impaired skeletal muscle nutritive flow during exercise in patients with congestive heart failure: role of cardiac pump dysfunction as determined by the effect of dobutamine. Am J Cardiol. 1984;53:1308–15.
11. Mancini D, Walter G, Reichek N, et al. Contribution of skeletal muscle atrophy to exercise intolerance and altered muscle metabolism in heart failure. Circulation. 1992;85:1364–73.
12. Adamopoulos S, Coats A, Brunotte F, et al. Physical training improves skeletal muscle metabolism in patients with chronic heart failure. J Am Coll Cardiol. 1993;21:1101–6.
13. Coats A, Adamopoulos S, Meyer T, et al. Effects of physical training in chronic heart failure. Lancet. 1990;335:63–6.
14. Coats A, Adamopoulos S, Radaelli A, et al. Controlled trial of physical training in chronic heart failure. Exercise performance, hemodynamics, ventilation, and autonomic function. Circulation. 1992;85:2119–31.
15. Caminiti G, Volterrani M, Iellamo F, et al. Effect of long-acting testosterone treatment on functional exercise capacity, skeletal muscle performance, insulin resistance, and baroreflex sensitivity in elderly patients with chronic heart failure a double-blind, placebo-controlled, randomized study. J Am Coll Cardiol. 2009;54:919–27.
16. Jankowska E, Biel B, Majda J, et al. Anabolic deficiency in men with chronic heart failure: prevalence and detrimental impact on survival. Circulation. 2006;114:1829–37.
17. Sacca L. Heart failure as a multiple hormonal deficiency syndrome. Circ Heart Fail. 2009;2:151–6.
18. Aukrust P, Ueland T, Gullestad L, Yndestad A. Testosterone: a novel therapeutic approach in chronic heart failure? J Am Coll Cardiol. 2009;54:928–9.
19. Song Y, Li Y, Du J, et al. Muscle-specific expression of IGF-1 blocks angiotensin II-induced skeletal muscle wasting. J Clin Invest. 2005;115:451–8.
20. Schulze PC, Gielen S, Adams V, et al. Muscular levels of proinflammatory cytokines correlate with a reduced expression of insulinlike growth factor-I in chronic heart failure. Basic Res Cardiol. 2003;98:267–74.

21. Doehner W, von Haehling S, Anker S. Insulin resistance in chronic heart failure. J Am Coll Cardiol. 2008;52:239.
22. Mann D, Reid M. Exercise training and skeletal muscle inflammation in chronic heart failure: feeling better about fatigue. J Am Coll Cardiol. 2003;42:869–72.
23. Ferrari R, Bachetti T, Confortini R, et al. Tumor necrosis factor soluble receptors in patients with various degrees of congestive heart failure. Circulation. 1995;92:1479–86.
24. Testa M, Yeh M, Lee P, et al. Circulating levels of cytokines and their endogenous modulators in patients with mild to severe congestive heart failure due to coronary artery disease or hypertension. J Am Coll Cardiol. 1996;28:964–71.
25. Mahy I, Tooke J. Peripheral microvascular function in human heart failure. Clin Sci(Lond). 1995;88:501–8.
26. Duscha B, Kraus W, Keteyian S, et al. Capillary density of skeletal muscle: a contributing mechanism for exercise intolerance in class II-III chronic heart failure independent of other peripheral alterations. J Am Coll Cardiol. 1999;33:1956–63.
27. Katz S, Biasucci L, Sabba C, Strom J, Jondeau G, Galvao M, Solomon S, Nikolic S, Forman R, LeJemtel T. Impaired endothelium-mediated vasodilation in the peripheral vasculature of patients with congestive heart failure. J Am Coll Cardiol. 1992;19:918–25.
28. Kubo S, Rector T, Bank A, et al. Endothelium-dependent vasodilation is attenuated in patients with heart failure. Circulation. 1991;84:1589–96.
29. Teerlink J, Clozel M, Fischli W, Clozel J. Temporal evolution of endothelial dysfunction in a rat model of chronic heart failure. J Am Coll Cardiol. 1993;22:615–20.
30. Hambrecht R, Fiehn E, Weigl C, et al. Regular physical exercise corrects endothelial dysfunction and improves exercise capacity in patients with chronic heart failure. Circulation. 1998;98:2709–15.
31. Mancini D, Nazzaro D, Ferraro N, et al. Demonstration of respiratory muscle deoxygenation during exercise in patients with heart failure. J Am Coll Cardiol. 1991;18:492–8.
32. Mancini D, Henson D, LaManca J, Levine S. Respiratory muscle function and dyspnea in patients with chronic congestive heart failure. Circulation. 1992;86:909–18.
33. Ambrosino N, Opasich C, Crotti P, et al. Breathing pattern, ventilatory drive and respiratory muscle strength in patients with chronic heart failure. Eur Respir J. 1994;7:17–22.
34. Mancini D, Henson D, LaManca J, Levine S. Evidence of reduced respiratory muscle endurance in patients with heart failure. J Am Coll Cardiol. 1994;24:972–81.
35. Mancini D, Henson D, La Manca J, et al. Benefit of selective respiratory muscle training on exercise capacity in patients with chronic congestive heart failure. Circulation. 1995;91:320–9.
36. Dall'Ago P, Chiappa GR, Guths H, et al. Inspiratory muscle training in patients with heart failure and inspiratory muscle weakness: a randomized trial. J Am Coll Cardiol. 2006;47:757–63.
37. Laoutaris I, Dritsas A, Brown MD, et al. Inspiratory muscle training using incremental endurance test alleviates dyspnea and improves functional status in patients with chronic heart failure. Eur J Cardiovasc Prev Rehabil. 2004;11:480–96.
38. Szlachcic J, Massie B, Kramer B, Topic N, Tubau J. Correlates and prognostic implication of exercise capacity in chronic congestive heart failure. Am J Cardiol. 1985;55:1037–42.
39. Mancini D, Eisen H, Kussmaul W, et al. Value of peak exercise oxygen consumption for optimal timing of cardiac transplantation in ambulatory patients with heart failure. Circulation. 1991;83:778–86.
40. Aaronson K, Mancini D. Is percentage of predicted maximal exercise oxygen consumption a better predictor of survival than peak exercise oxygen consumption for patients with severe heart failure? J Heart Lung Transplant. 1995;14:981–9.
41. Stelken A, Younis L, Jennison S, et al. Prognostic value of cardiopulmonary exercise testing using percent achieved of predicted peak oxygen uptake for patients with ischemic and dilated cardiomyopathy. J Am Coll Cardiol. 1996;27:345–52.
42. Lund L, Aaronson K, Mancini D. Predicting survival in ambulatory patients with severe heart failure on beta-blocker therapy. Am J Cardiol. 2003;92:1350–4.

43. Koelling T, Joseph S, Aaronson K. Heart failure survival score continues to predict clinical outcomes in patients with heart failure receiving beta-blockers. J Heart Lung Transplant. 2004;23:1414–22.
44. O'Neill J, Young J, Pothier C, Lauer M. Peak oxygen consumption as a predictor of death in patients with heart failure receiving beta-blockers. Circulation. 2005;111:2313–8.
45. Jessup M, Abraham W, Casey D, et al. 2009 focused update: ACCF/AHA guidelines for the diagnosis and management of heart failure in adults: a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines: developed in collaboration with the International Society for Heart and Lung Transplantation. Circulation. 2009;119:1977–2016.
46. Cohen-Solal A, Laperche T, Morvan D, et al. Prolonged kinetics of recovery of oxygen consumption after maximal graded exercise in patients with chronic heart failure. Analysis with gas exchange measurements and NMR spectroscopy. Circulation. 1995;91:2924–32.
47. Arena R, Myers J, Abella J, et al. The partial pressure of resting end-tidal carbon dioxide predicts major cardiac events in patients with systolic heart failure. Am Heart J. 2008;156:982–8.
48. Arena R, Myers J, Abella J, et al. Development of a ventilatory classification system in patients with heart failure. Circulation. 2007;115:2410–7.
49. Kleber F, Vietzke G, Wernecke K, et al. Impairment of ventilatory efficiency in heart failure: prognostic impact. Circulation. 2000;101:2803–9.
50. Robbins M, Francis G, Pashkow F, et al. Ventilatory and heart rate responses to exercise : better predictors of heart failure mortality than peak oxygen consumption. Circulation. 1999;100:2411–7.
51. Guazzi M, Arena R, Ascione A, et al. Exercise oscillatory breathing and increased ventilation to carbon dioxide production slope in heart failure: an unfavorable combination with high prognostic value. Am Heart J. 2007;153:859–67.
52. Sun X, Hansen J, Beshai J, Wasserman K. Oscillatory breathing and exercise gas exchange abnormalities prognosticate early mortality and morbidity in heart failure. J Am Coll Cardiol. 2010;55:1814–23.
53. Cohen-Solal A, Tabet JY, Logeart D, et al. A non-invasively determined surrogate of cardiac power ('circulatory power') at peak exercise is a powerful prognostic factor in chronic heart failure. Eur Heart J. 2002;23:806–14.
54. Roul G, Moulichon M, Bareiss P, et al. Prognostic factors of chronic heart failure in NYHA class II or III: value of invasive exercise haemodynamic data. Eur Heart J. 1995;16:1387–98.
55. Chomsky D, Lang C, Rayos G, et al. Hemodynamic exercise testing. A valuable tool in the selection of cardiac transplantation candidates. Circulation. 1996;94:3176–83.
56. Mancini D, Katz S, Donchez L, Aaronson K. Coupling of hemodynamic measurements with oxygen consumption during exercise does not improve risk stratification in patients with heart failure. Circulation. 1996;94:2492–6.
57. Metra M, Faggiano P, D'Aloia A, et al. Use of cardiopulmonary exercise testing with hemodynamic monitoring in the prognostic assessment of ambulatory patients with chronic heart failure. J Am Coll Cardiol. 1999;33:943–50.
58. Lang C, Agostoni P, Mancini D. Prognostic significance and measurement of exercise-derived hemodynamic variables in patients with heart failure. J Card Fail. 2007;13:672–9.
59. Lang C, Karlin P, Haythe J, et al. Peak cardiac power output measured non-invasively, is a powerful predictor of outcome in chronic heart failure. Circ Heart Fail. 2009;2:33–8.
60. Tan L. Cardiac pumping capability and prognosis in heart failure. Lancet. 1986;2:1360–3.
61. Mancini D, Goldsmith R, Levin H, et al. Comparison of exercise performance in patients with severe heart failure versus left ventricular assist devices. Circulation. 1998;98:1178–83.
62. Jaski B, Lingie R, Kim J, et al. Comparison of functional capacity in patients with end-stage heart failure following implantation of a left ventricular assist device versus heart transplantation: results of the experience with left ventricular assist device with exercise trial. J Heart Lung Transplant. 1999;18:103.
63. Slaughter M, Pagani F, Rogers J, et al. Clinical management of continuous-flow left ventricular assist devices in advanced heart failure. J Heart Lung Transplant. 2010;29(Suppl):S1.

64. Haft J, Armstrong W, Dyke D, et al. Hemodynamic and exercise performance with pulsatile and continuous flow left ventricular assist device. Circulation. 2007;116:18–5.
65. Bittner V, Weiner D, Yusuf S, et al. Prediction of mortality and morbidity with a 6-minute walk test in patients with left ventricular dysfunction. JAMA. 1993;270:1702–7.
66. Drexler H, Riede U, Munzel T, et al. Alterations of skeletal muscle in chronic heart failure. Circulation. 1992;85:1751–9.
67. Kokkinos P, Narayan P, Papademetriou V. Exercise as hypertension therapy. Cardiol Clin. 2001;19:507–16.
68. Blomqvist C, Saltin B. Cardiovascular adaptations to physical training. Ann Rev Physiol. 1983;45:169–89.
69. Musch T, Moore R, Leathers D, et al. Endurance training in rats with chronic heart failure induced by myocardial infarction. Circulation. 1986;74:431–41.
70. Todaka K, Wang J, Yi G, et al. Impact of exercise training on ventricular properties in a canine model of congestive heart failure. Am J Phys. 1997;272(3 Pt 2):H1382–90.
71. Sullivan MJ, Higginbotham MB, Cobb FR. Exercise training in patients with severe left ventricular dysfunction. Hemodynamic and metabolic effects. Circulation. 1988;78:506–15.
72. Hambrecht R, Niebauer J, Fiehn E, et al. Physical training in patients with stable chronic heart failure: effects on cardiorespiratory fitness and ultrastructural abnormalities of leg muscles. J Am Coll Cardiol. 1995;25:1239–49.
73. Haykowsky M, Liang Y, Pechter D, Jones L, McAlister F, Clark A. A meta-analysis of the effect of exercise training on left ventricular remodeling in heart failure patients: the benefit depends on the type of training performed. J Am Coll Cardiol. 2007;49:2329–36.
74. Spruit M, Eterman R, Hellwig V, et al. Effects of moderate-to-high intensity resistance training in patients with chronic heart failure. Heart. 2009;95:1399–408.
75. Belardinelli R, Georgiou D, Scocco V, et al. Low intensity exercise training in patients with chronic heart failure. J Am Coll Cardiol. 1995;26:975–82.
76. Demopoulos L, Bijou R, Fergus I, et al. Exercise training in patients with severe congestive heart failure: enhancing peak aerobic capacity while minimizing the increase in ventricular wall stress. J Am Coll Cardiol. 1997;29:597–603.
77. Hornig B, Maier V, Drexler H. Physical training improves endothelial function in patients with chronic heart failure. Circulation. 1996;93:210–4.
78. Kiilavuori K, Toivonen L, Naveri H, Leinonen H. Reversal of autonomic derangements by physical training in chronic heart failure assessed by heart rate variability. Eur Heart J. 1995;16:490–5.
79. O'Connor C, Whellan D, Lee K, et al; HF-ACTION Investigators. Efficacy and safety of exercise training in patients with chronic heart failure HF-ACTION randomized controlled trial. JAMA. 2009;301:1439–50.
80. Keteyian S, Leifer E, Houston-Miller N, et al. Relation between volume of exercise and clinical outcomes in patients with heart failure. J Am Coll Cardiol. 2012;60:1899–905.
81. Slaughter M, Rogers J, Milano C, et al. Advanced heart failure treated with a continuous flow left ventricular assist device. N Engl J Med. 2009;361:2241–51.
82. Aaronson K, Slaughter M, Miller L, et al. Use of an intrapericardial ,continuous-flow, centrifugal pump in patients awaiting heart transplantation. Circulation. 2012;125:3191–200.
83. Kohli H, Canada J, Arena R, et al. Exercise blood pressure response during assisted circulatory support : comparison of the total artificial heart with a left ventricular assist device during rehabilitation. J Heart Lung Transplant. 2011;30:1207–13.
84. De Jonge N, Kohlr H, Lahpor J, et al. Exercise performance in patients with end stage heart failure after implantation of a left ventricular assist device and after heart transplantation: an outlook for permanent assisting. J Am Coll Cardiol. 2001;37:1794–9.

Chapter 34
Heart Failure Management and Development of Heart Failure Programs

Jooyoung Julia Shin and Ileana L. Piña

Introduction

Heart failure (HF) as a syndrome is the end stage of a variety of cardiac disorders which include ischemic, valvular disease and dilated cardiomyopathies of different etiologies. The prevalence and incidence of HF continue to grow steadily with projections into 2030 in the order of >8 million individuals [1]. The reasons for this unprecedented growth are many and include aging of the population, better management of acute arrhythmias, the use of defibrillators, and rapid attention to patients with acute coronary syndrome with invasive interventions, among others. The epidemic affects not only the United States but also the rest of the world, with a growing number of patients with heart failure and preserved ejection fraction (HFpEF), which is a piece of this syndrome without many evidence-based therapies [2].

Economic Burden

It is inevitable that with a high incidence of HF, increased costs will accompany the syndrome. The total cost of HF (direct and indirect costs) is expected to increase from $30.7 billion in 2012 to $69.8 billion by 2030, [1]. By 2030, projected cost estimates of treating patients with HF will be $160 billion in direct costs, if one

J.J. Shin, MD (✉)
Albert Einstein College of Medicine, Moses Campus, Advanced Heart Failure and Transplant Cardiology, Montefiore-Einstein Medical Center, Department of Cardiology, 3400 Bainbridge Avenue 7th floor, Bronx, NY 10467, USA
e-mail: Jushin@montefiore.org

I.L. Piña, MD, MPH
Albert Einstein College of Medicine, Division of Cardiology, Montefiore-Einstein Medical Center, 111 East 210th Street North 2- Silver Zone, Bronx, NY 10467, USA
e-mail: ilpina@montefiore.org

H. Eisen (ed.), *Heart Failure*, DOI 10.1007/978-1-4471-4219-5_34

assumes all costs are related to the HF itself and not other diagnoses. Approximately 80 % of the costs are related to hospitalizations and overall nursing care, including skilled nursing facilities [1]. Projections worldwide are equally worrisome, as reported in a worldwide cost assessment and projection of 197 countries. In 2012, the overall economic cost of caring for HF was estimated at $108 billion per annum broken down into direct costs at $65 billion and indirect costs at $43 billion. Notably, countries with high income spend a greater amount on direct costs, unlike countries with middle or low income [3].

Leading Cause of Hospitalization

HF is the leading cause of hospitalizations for Medicare recipients. In parallel, HF is also the leading cause of 30-day rehospitalizations, bringing with it a worse mortality than patients who are stable and managed as outpatient (33 % vs. 8 % annual mortality) [4–6]. Each hospitalization adds to the poor outcome, whether by true worsening of HF, omission (not prescribing guideline directed medical therapy (GDMT)) or commission (removal of GDMT), failure to restart GDMT, and/or prescribing drugs that are not recommended for HF [7, 8]. Multiple medical therapies that have shown to improve survival and decrease hospitalizations are still not being prescribed adequately and are given in low doses without uptitration [9]. Quality improvement programs, such as the Get With the Guidelines (GWTG) registry of the American Heart Association (AHA) have emphasized the use of GDMT in patients who are being discharged after an acute decompensation. As the length of hospital stay has dropped, the 30-day rehospitalization rates have steadily increased leading to the question: “Are patients being discharged prematurely?” Patients who are discharged without adequate decongestion, initiation and planned uptitration of drugs, in addition to inadequate education, medication reconciliation, and a poor diuretic regimen are destined to return to the hospital within 30 days.

Hospitalization Increases Mortality

Most patients who relapse do so within the first 3 weeks, with many of the returned admissions due to something other than another HF decompensation, although it is often related to HF (e.g. excessive diuresis leading to renal insufficiency) [10–12]. Half of admissions are avoidable and are due to a variety of provider and/or patient issues. Failure to understand medication purposes, timing of dosing, or drug-drug interactions often leads to non-adherence. Other reasons include dietary indiscretions, failure to be engaged in self-care and inadequate initiation or uptitration of live-saving therapies by providers. Rather than placing blame on patient behavior, it behooves the provider teams to facilitate patient education and engagement, which often improves adherence to both medications and diet. Education of providers

should also not be ignored in order to overcome the inertia of uptitration of drugs even when the patient looks "well." Education programs with multiple interventions have worked best in changing provider behavior [13].

In the past 5 years there has been an increasing focus on the high readmission rate for HF patients [14]. A HF hospitalization changes the patient's journey, with a combined mortality and readmission rate of 30 % within 90 days after discharge from an admission for decompensated HF [15, 16]. Jencks et al. reported an average readmission rate of 20 % with 50 % or more of patients not seen by a healthcare provider within the first 30 days after discharge [6]. Certainly this trend and the mortality that follows hospitalization is not acceptable and has led to Centers for Medicare and Medicaid Services (CMS) penalties for excessive readmissions.

To address this issue, hospitals have launched internal programs to lower the rate of readmissions. It is important to note that many of the readmissions have other primary diagnoses and only approximately 28–40 % are due to an actual re-exacerbation of heart failure [17]. This fact raises the possibility that other comorbidities may not have been addressed during the initial hospitalization, only to reappear in a clinically significant way.

Yet readmissions have a high variability among different regions of the country as well as among differing types of hospitals, i.e. teaching vs. community [18]. Some of the greatest variability may be related to local culture and practices and not necessarily to failed programs. In a review of 2008 Medicare Provider Analysis and Review (MEDPAR) files, readmissions varied from 11 to 32 % in 306 hospitals across various regions of the U.S and had a strong association between all-cause admission rates and readmissions. The 76 regional centers with the highest quartile of readmission rates for HF had a mean of 28 % while those with the lowest quartile had a mean of 20 %. Those with the highest rates of readmissions were from medium to large hospitals, were in the Northeast and had a higher number of women, African Americans and Hispanics. These differences should not be overlooked when programs are being planned. Yet most interventions have focused only on the transition from hospital to outpatient rather than a broader public health view to reduce incentives to admit patients and use hospital services, i.e., increasing costs.

Furthermore, given the rising number of patients not being discharged to home on their own but rather to skilled nursing facilities or to home with visiting nurses, it is important to examine the readmission rates in these groups of patients [14]. Madigan and colleagues examined the Chronic Conditions Database of Medicare and found that the 30 day rehospitalization rate was 26 with 42 % of patients having cardiac-related diagnoses for the rehospitalization who were using home health care services [19, 20]. The readmission rates had a strong association with the prior number of hospitalizations, the level of disease severity at baseline and the intensity of the visits by the home health care nurse. A more detailed review indicated that many of the rehospitalizations could have been avoided. (See Table 34.1).

In light of the potentially avoidable hospitalizations for home health-care patients and the large percent of those related to HF symptoms, a solid partnership with a HF program can be invaluable by providing an evaluation early into the home health

Table 34.1 Selected potentially avoidable hospitalizations for home health care patients with heart failure using claim indicators by AHRQ designation of Prevention Quality Indicators

AHRQ prevention quality indicators	Primary diagnosis (% of total; N)	Secondary diagnosis (% of total; N)
Heart failure	34 % (6514)	55 %(10,589)
Hypertension	0.14 % (27)	34 %(6588)
COPD	2.6 % (494)	32 % (6184)
Infections	1.6 % (312)	11.5 % (2214)
Dehydration	2.2 % (431)	10.6 % (2041)
Bacterial Pneumonia	4.7 % (913)	6.8 % (1305)
Diabetes, long-term	1.3 % (244)	6.4 % (1235)
Angina without procedure	0.2 % (47)	4.4 % (847)
Diabetes, uncontrolled	0.12 % (23)	1.67 % (311)

Reprinted and adapted from Madigan et al. [20], © 2012, with permission from Blackwell Publishing/Association for Health Services Research; Hospital Research and Educational Trust; Association of University Programs in Health Admin
http://www.qualityindicators.ahrq.gov/pqi_overview.htm; (N = 19,326)

care course, even providing transportation or physician home visits to curb growing symptoms and administering guideline driven therapy by an expert HF team.

Thus, the rehospitalization issue for HF patients is complex and less likely to improve with only a narrow focus. We must target instead the integration of various approaches, including partnering with primary care providers and nurse-driven home health care, as well as with skilled nursing facilities.

The Guideline-Practice GAP

It is a constant and iterative process to encourage practices, whether academic or community-based, to apply the peer-reviewed guidelines for medical and device therapy [21]. The gap still exists in HF registries and is especially guideline-recommended medication doses are still marginal [22, 23]. Gaps in therapy also exist with respect to gender and race; for example, hydralazine and nitrates are used in fewer than ¼ of eligible African American patients with symptomatic HF [24]. Importantly, it has been shown that patients who need admission but are already on HF medical therapy are more likely to be discharged on evidence-based therapies [5].

The source of the inability to uptitrate drugs to their guideline or clinical trial levels is probably multifaceted but includes lack of self-efficacy with uptitration, physician pride that he/she needs no further training or counsel, fears of side effects, and clinical inertia. Educational programs that target quality improvement in applying HF GDMT should be multifactorial [13]. Current requirements for recertification will hopefully help to close the gap as clinicians look internally into their own practice and find places for improvement. Yet, the literature is replete with examples of decreases in poor outcomes, including mortality when GDMT is applied

appropriately and consistently [25]. Patients deserve the best of treatment and the best of care.

Nonetheless, programs that focus on targeted and directed quality improvement have been shown to raise the level of care significantly [5, 26]. Some of these programs are directed to the inpatient stay and others to the transition to outpatient care [27, 28]. Heart failure programs can add a great deal of benefit by actively and vocally supporting such programs within a healthcare system and becoming the champions of quality care as groups that are respected for their clinical quality efforts. Programs are most successful when carried out at a system level and with buy-in from clinicians throughout [29–31].

There are multiple health care delivery settings for heart failure. Prevention of HF would be best and would avoid all the costs and patient burden that follows a HF diagnosis. Prevention is most likely to be delivered by the patient's primary care provider, requires an awareness of the risk factors leading to HF (Stage A), and requires aggressive interventions to improve them, e.g., hypertension or hyperlipidemia. Acute care in the emergency room or hospital observation unit, chronic care in a heart failure clinic, home care with specialized heart failure nurses are all potential sites of therapy. Palliative care can be a partner in all of these settings, except for the Stage A patients.

Why Are Heart Failure Programs Needed?

The disease epidemic of HF results in high utilization and costs of health care. There are several potential causes of high utilization and costs. These include deviation from evidence-based care, poor communication between primary care providers and specialists, poor communication between health-care providers and patients, failure to address psychosocial issues and patient adherence, a lack of coordinated long-term management, and ineffective transitional management from the hospital to home or skilled nursing facility (See Table 34.2). A well-structured specialized

Table 34.2 Why we need HF programs

Realization: *It is impossible for a single practitioner to care for a large number of HF patients using cutting-edge evidence-based care in the current practice environment*
It is equally impossible for a single HF physician to care for the ever growing number of patients
Other providers of care are essential
Teams must be created
In hospital care is fragmented
Measures of quality are being collected by hospitals and systems
Transitions of care are not consistent across episodes
Payment is linked to quality
Penalties exist
Other penalties at the level of the provider are inevitable

heart failure program can address some or most of these problems. Cost reduction is not the only issue driving the establishment of specialized HF programs. Clinical care and continuity of care should constitute top priority. Other issues driving the development of HF programs include research and the reputation of a hospital as a specialized care center.

Planning a HF program needs to take into consideration the social and cultural milieu of the local patient population, which can differ from an inner-city setting to an urban population. The geographic distribution of the target population will dictate the ease to which patients can access clinical care services and prioritize initiatives such as telehealth or home-based visits. The incidence of heart failure, medical co-morbidities and age can also differ by geographic location. Other demographic factors, such as socioeconomic characteristics, health literacy, and ethnicity should be taken into consideration to ensure that care is provided within a culturally appropriate paradigm.

There are multiple goals for a HF clinic, such as improved access to appropriate cost-effective health care, improving patient quality of life and survival while decreasing hospitalizations, control of health care costs, and a means to track quality outcomes. There should be a seamless integration of medical care, pharmacologic intervention, patient education, and patient support.

Criteria have been proposed to identify those patients who could gain most benefit from care in a HF clinic [32]. High-risk markers include recent HF hospitalizations, renal insufficiency, or multiple active comorbidities. Clinics that cannot provide all facets of advanced HF care should partner with a facility that can offer options such as mechanical support and heart transplantation in eligible patients, recognizing that these constitute a small percentage of the total HF population.

Heart Failure Care as Disease Management

Disease management programs have been described as a means to improve the quality of care for patients with chronic illnesses under a multidisciplinary framework in a cost-effective manner. Disease management may be an effective way to treat patients with or at risk for heart failure by increasing quality of care, enhancing adherence to practice guidelines, and expediting accessibility to healthcare services. Disease management may also improve efficiency of delivery of healthcare services by promoting quality while reducing costs. It can do this for the HF population by preventing or minimizing the effects of heart failure through integrative and proactive care. The definition of disease management by the Care Continuum Alliance (formerly the Disease Management Association of America) has helped to standardize the terminology related to the practice of disease management. They define disease management as a multidisciplinary, continuum-based approach to health care delivery that proactively identifies populations with, or at risk for, established medical conditions that: supports the physician/patient relationship and plan of care; emphasizes prevention of exacerbations and complications utilizing cost-effective evidence-based practice guidelines and patient empowerment strategies such as

self-management education; and continuously evaluates clinical, humanistic, and economic outcomes with the goal of improving overall health. In addition, they recommend that all of the following components be in place in order for a program to be considered a disease management program: population identification process; evidence-based practice guidelines; collaborative practice model to include physician and support-service providers; risk identification and matching of interventions with need; patient self-management education (may include behavior modification programs); process and outcomes measurement, evaluation, and management; routine reporting (may include communication with patient, physician and other care providers); and appropriate use of information technology (may include data registries, telehealth and automated decision support tools).

There is a considerable body of clinical evidence supporting the use of disease management strategies for the treatment of patients with heart failure [33–38]. Disease management programs utilize strategies designed to improve adherence to scientific guidelines and established treatment plans. These disease management principles should be practiced consistently in order to maximize the efficiency of resource use within the healthcare system. Ultimately, the goal of disease management programs in HF is to augment quality of patient care while concurrently reducing the public health burden. A team of experts dedicated to the same goal, i.e., the patient's overall well-being, may also improve patient engagement and self-care. The patient is seen as an active member of the team.

The American Heart Association Expert panel on Disease Management recommends the following principles for the development, implementation, and evaluation of disease management programs [39]

- The main goal of disease management should be to improve the quality of care and patient outcomes.
- Scientifically derived, peer-reviewed guidelines should be the basis of all disease management programs. These guidelines should be evidence based and consensus driven.
- Disease management programs should help increase adherence to treatment plans based on the best available evidence.
- Disease management programs should include consensus-driven performance measures.
- All disease management efforts must include ongoing and scientifically based evaluations, including clinical outcomes.
- Disease management programs should exist within an integrated and comprehensive system of care in which the patient-provider relationship is central.
- To ensure optimal patient outcomes, disease management programs should address the complexities of medical comorbidities.
- Disease management programs should be developed for all populations and should particularly address members of the underserved or vulnerable populations.
- Organizations involved in disease management should scrupulously address potential conflicts of interest.

There are a large number of studies that give evidence of some improved outcomes with the use of disease management strategies for the treatment of patients with heart failure. One publication describing 10 observational studies of disease management in HF showed improved symptoms and functional class, reduced hospitalizations and length of stay, improved adherence to HF therapies and improved patient and physician satisfaction [40]. Another study of 9 randomized controlled trials of HF disease management programs showed reduced hospitalizations, readmissions and length of stay, that translated into cost savings but no appreciable impact on mortality [41]. Several other studies showed an improvement in functional class and quality of life, increased adherence to guideline-directed medical therapy and reduced readmission rates [42–45].

Although there are several studies that support disease management programs in the treatment of HF, there still needs to be more scrutiny into what practices and components constitute the most successful of programs. In a more recent study, the Medicare Health Support Pilot Program was a large, randomized study of eight commercial programs for disease management that used nurse-based call centers [46]. The program randomly assigned patients with heart failure to disease management versus usual care to evaluate the effects of the commercial programs on the quality of clinical care, acute care utilization, and Medicare expenditures. This was a large study, enrolling 242,417 patients (163,107 in the intervention group and 79, 310 in the control group). Ultimately, the commercial disease-management programs did not reduce hospital admissions or emergency room visits, as compared with usual care. However, they did observe 14 significant improvements in process-of-care measures, but these modest improvements came at substantial cost, with no demonstrable savings in Medicare expenditures. The authors concluded that commercial disease-management programs using nurse-based call centers achieved only modest improvements in quality-of-care measures, with no demonstrable reduction in the utilization of acute care or the costs of care. The authors further suggested that the findings might be explained by the severity of chronic disease among the patients studied, delays in patients receiving protocol-driven disease management care after hospitalizations, and the lack of integration between specialists and the primary care providers of the patients. Clearly more study is required to determine which components of disease management practice build the more successful programs.

Barriers to adequate HF care include patient-related issues and problems in the care system delivery. Patient barriers include inability to sustain complex self-care management, lack of motivation due to depression or poor functional capacity, and financial concerns. Issues with the delivery of disease management health care include the lack of capacity of high-frequency patient follow-ups (usually 1 week post discharge, then every 1–2 weeks for medication titration and to maintain effective diuresis), and lack of shared communication between multiple health care providers.

Multidisciplinary Structure

HF is a progressive disease characterized by clinical exacerbations that result in the utilization of acute healthcare services. Effective treatment for these patients involves complex drug management, time-consuming patient education and frequent clinical visits [19]. The lack of careful management of patient symptoms results in excessive use of acute emergency and hospital services; indeed, as many as 50 % of HF admissions may be preventable [47]. The goal of HF care is to prevent episodes of clinical exacerbations so as to ensure better quality of life and survival for the patient and offer more efficient use of healthcare resources. HF treatment requires significant adjustments in lifestyle. The prevention of clinical deterioration and maintenance of a good quality of life require the patient to actively participate in the disease management process. For the healthcare provider, successful management of symptomatic HF patients requires frequent follow-up visits and determined efforts to improve patient adherence to medical treatment and lifestyle changes. While current research supports the benefits of some elements of care delivery processes in disease management programs for HF, it does not specify a single, specific healthcare delivery model as the most successful system. In truth, it is likely that a variety of approaches should be tailored to the specific needs of the local patient population and resource availability [40]. In general, care for the HF patient can be improved by a system that emphasizes comprehensiveness of care while preserving efficient healthcare delivery.

Many of the different models of chronic HF care incorporate the following important elements: coordination of care across different providers, patient/caregiver education, patient/caregiver support with a focus on patient self-management and adherence, medication management, rigorous clinical monitoring, and implementation of guideline-directed protocols [48]. The ACC/AHA guidelines state that optimal care is best delivered by a team that includes both a primary care physician and a cardiologist [7] and there is strong evidence supporting the benefit of multidisciplinary programs for the management of HF. For example, in one meta-analysis of 30 randomized-controlled trials of multidisciplinary programs for HF showed a reduction in all-cause hospitalization (13 % lower risk), HF-related admissions (30 %) and mortality (20 %) compared with individuals receiving usual care; interventions involved a physician and at least one other type of health professional such as a nurse, pharmacist, dietician, or social worker [49]. Multiple other studies show that multidisciplinary interventions for HF management may improve patient adherence, functional status, reduce risk of hospital admissions, reduce length of hospital stay, confer improved survival, and reduce healthcare costs [30, 41, 48–58].

In 2008, the Heart Failure Society of America published a consensus statement that described the integral elements of a HF clinic, which focused on the systems and procedures that would provide the most consistent application of evidence-based guidelines and, ultimately, ensure optimal patient care [59]. The authors specified the follow areas: disease management, functional assessment, quality of life

assessment, medical therapy and drug evaluation, device evaluation, nutritional assessment, follow-up, advance planning, communication, provider education, and quality assessment. The authors acknowledged that these areas had not been subjected to standard trial methodology and that few studies had adequate power or statistical design to show that specialized HF clinics decreased mortality for HF patients. As described above, however, there are many studies demonstrating improved quality of life, functional status, and patient satisfaction, with reduced hospitalizations for patients followed in HF clinics [41]. The current era of Patient Centered Outcomes Research (PCORI) may be able to compare strategies of HF care using patient reported outcomes, such as quality of life and satisfaction with the care.

Most specialized HF clinics practice a multidisciplinary approach that may include physicians, nurses, pharmacists, nutritionists, social workers, exercise physiologists, and other health care professionals with specialized training and skills in HF management [60, 61]. With consistent application of GDMT and the common goals of improving patient well-being and increasing the efficiency of healthcare deliver, the multidisciplinary team establishes a long-term relationship with an individual patient to optimize medical therapy, provide frequent clinical follow-up with ready access to care in the case of decompensation, administer thorough patient and caregiver education, and create seamless coordination of care between multiple care providers. Comprehensive education of the patient and family with a focus on increasing adherence to therapy and self-care can improve HF outcomes. Numerous clinical studies provide strong evidence for the effectiveness of multidisciplinary disease management of HF and the components of HF management programs consistent across these studies include multidisciplinary teams of health professionals, intensive patient education and support for self-management, and ready access to providers.

A successful multidisciplinary HF clinic requires adequate financial resources to support provider training and the framework for coordinated healthcare delivery and quality assessment. This includes a provider to patient ratio that will support individualized and comprehensive patient care.

Management of the HF Patient

A systematic approach to the assessment of the HF patient provides the crux of effective HF management. The ongoing management of the HF patient should address the following components: etiology and ongoing factors contributing to myocardial dysfunction, circulatory status, related co-morbidities, goals for ongoing therapy, psychological and social vulnerabilities, patient preferences and end-of-life decisions (Table 34.3) [62]. Important elements of HF management include symptom review, medication titration, education of the patient, care provider and family, self-management support, management of comorbidities, telephone support, psychosocial and care provider support, and palliative care. The frequency of office

Table 34.3 Ongoing assessment in heart failure [62]

Cause of and contributing factors to left ventricular dysfunction:
Original cause (e.g. ischemia, alcohol)
Additional exacerbating factors (e.g. tachycardia, anemia, infection, pulmonary emboli, obesity, excessive alcohol consumption, use of recreational drugs, use of nonsteroidal anti-inflammatory agents, thyroid disease)
Current circulatory status:
Resting profile – evidence of congestion or hypoperfusion
Cardiovascular reserve – activity level, evidence of limitation
Potential to improve current status with adjustment of therapy – therapy for fluid retention and symptomatic hypotension
Related risks:
Symptoms of dysrhythmias
Risk or symptoms for embolic events
Recurrent ischemic events
Defining goals for ongoing therapy:
Establishment of clinical stability
Maintenance of clinical stability
Modulation of disease progression – target dosages of ACE inhibitors and beta-blockers
Behavioral, psychological, and social risks:
Non-adherence and factors that contribute to it
Anxiety and depression
Social isolation
Patient preferences and end-of-life decisions

Reprinted and adapted from Grady et al. [62]; © 2000, with permission from Wolters Kluwer Health

visits and HF treatment should be guided by established protocols to ensure uniform practice and the attainment of optimal guideline-directed medical and device therapies. Patients should ideally be seen within a week of hospital discharge and every 2 weeks if they exhibit unstable symptoms. Stable HF patients should be followed at a minimum frequency of every 3 months. Recent evidence from GWTG implies that a visit that occurs early, within 1 week of discharge can lead to a decrease in hospitalizations [31].

The assessment of functional capacity remains an important component of the initial and follow-up evaluation of HF patients. There are three well-validated methods to assess functional status in HF patients, New York Heart Association (NYHA) class, the 6-minute walk test (6MWT), and cardiopulmonary exercise stress (CPET) testing [63–66]. BNP testing may also be useful, but its purpose in guiding outpatient management of HF is currently undergoing study. Baseline NYHA functional classification should be assessed then reassessed with every visit. An objective assessment of functional status with either 6MWT or CPET should also be performed initially then serially to determine response to clinical interventions. CPET is also important to risk stratifying patients potentially needing advanced therapies such as mechanical assist device or cardiac transplantation. Peak oxygen uptake

(VO_2) obtained during CPET is one of the most powerful predictors of mortality in this population and may also serve to deliver an individualized exercise prescription. Serial measurements of health status, such as through the Minnesota Living with Heart Failure Questionnaire or Kansas City Cardiomyopathy Questionnaire, can also predict survival and hospitalization risk for patients with HF [67–69].

Evidence-based practice guidelines for the pharmacologic and device therapy of HF have been published by several professional organizations [7, 70]. These guidelines are best put in protocol form for HF management clinics in order to ensure uniform practice across all healthcare providers and to expedite up-titration and optimization to the target dosages of guideline-directed HF medications. A comprehensive drug evaluation can reduce hospital admission rates and improve survival [51, 60, 71–74]. A look at adherence to the medication regimen should be done with each visit, with a focus on strategies to improve patient adherence and involvement in HF care.

Nutritional assessment and education can be done by a physician extender or nutritionist as part of the holistic approach to HF care. Sodium and fluid indiscretion accounts for at least 18 % of preventable readmissions for HF [75] and time should be spent devoted to teaching patients about salt and fluid restriction, especially those with frequent acute exacerbations of HF. Early identification and intervention for cachexia are also important since cachexia is a marker for poor outcomes in HF [76].

Effective communication is extremely important to improved patient outcomes. Shared decision-making between the healthcare provider and patient leads to better adherence and patient satisfaction [77]. In addition, clear communication between different healthcare providers decreases the incidence of medication errors and conflicting treatment plans. HF patients usually have many comorbidities and all of the care provided by their various providers should be well-coordinated to decrease discrepancies and improve patient outcomes and the efficiency of healthcare delivery.

Each HF patient should have an individualized care management plan for the long-term care of their disease. Components of the care management plan include HF management goals, treatment plans, a list of problems such as lifestyle changes, medication administration, and means of transportation, and clear contact information for their various healthcare providers. A copy of the care management plan should be given to the patient and his or her care provider, as well as each health care provider that is involved in the care of the patient. HF patient education should provide information on their medical condition, lifestyle changes that need to be made, medications, and the predicted course of their condition. The patients' family member and care providers should also be educated on HF. Standardized HF educational resources, such as booklets or support group meetings, are very useful to meet the education objectives of patients and their care providers.

Patient self-management is a care model whereby the patient is actively engaged in and takes responsibility for their healthcare. This model requires an informed and motivated patient. By promoting self-management in the care of HF, patients are

empowered to understand their disease and treatments, and to be able to recognize the signs of HF decompensation before they become emergent.

Telephone services to assess symptoms, up-titrate medications, provide education, or offer emotional support, complement the face-to-face clinical care of the HF patient. This should be delivered by a nurse proficient at HF care and these phone interactions should be guided by evidence-based protocols.

Advanced heart failure therapies are required for a relatively small proportion of people with HF and these patients should be managed intensively in a tertiary hospital with capability for mechanical support devices and/or heart transplantation. For those patients with end-stage HF for whom advanced therapies are not appropriate, involvement of palliative care services can improve the quality of life of patients with HF and their families facing death. Health professionals treating HF patients should have some training in palliative care philosophy.

Home Care and Telemonitoring

HF disease management programs can incorporate home care and telemonitoring into their systems of care [78]. Some studies have shown that multidisciplinary interventions that included home-based components were the most effective in the care of the HF patient [79]. Home care may be provided by home health care vendors that employ visiting nurses or other home health care professionals [80]. Home-based visitation by physicians has also been reported as another strategy to improve outcomes for HF patients [81]. Home care visits have been shown to decrease risk of all-cause and HF-related admissions [49].

The HF clinic can utilize telemonitoring technology to monitor patients who cannot make frequent visits, either due to geographic limitations or an inability to leave their homes [82, 83]. Telemonitoring is the use of telecommunications or other electronic information processing technologies to monitor patient health status at a distance. Telemonitoring devices include those that monitor vital signs and weight. Physiologic data such as body weight, blood pressure, and heart rate can be captured electronically on a scheduled or ad hoc basis for review and intervention, if needed. Remote analysis of intrathoracic impedance may also be used to monitor for worsening HF [84, 85]. Telemonitoring has been shown to improve outcomes in HF patients, such as decreased admissions and reduced risk of mortality [49]. Some of the published evidence suggests that telemonitoring may be as effective as other disease management programs for decreasing patient risk of hospitalization and increasing quality of life [86–88] while other studies show no difference in patient outcomes [89, 90]. Careful examination of some telemonitoring programs will show that beyond the early study time-period, adherence to the intervention drops off, making it nearly impossible to determine true efficacy in an intent-to-treat analysis. It may be more important, therefore, to examine the system in which telemonitoring is deployed, rather than the type of telemonitoring used.

Hospital to Clinic Transition

HF is a chronic disease that cannot be holistically treated if only acute exacerbations are addressed. Continuity of care needs to be the main focus of HF care in order to ensure the best patient outcomes. When a patient is hospitalized for acute decompensated HF, inadequate discharge planning is a major contributor to early rehospitalization rates [75]. Patients should have an early outpatient follow-up after a HF hospitalization or emergency department visit. The use of risk models may help guide follow-up care [91–93]. Higher risk patients should receive follow-up within 72 h; this can be accomplished as a telephone contact, home health visit, or clinic visit. Starting care management strategies during the inpatient hospital stay has been shown to reduce the risk of hospital readmission [94, 95].

Physical Rehabilitation

Consensus-driven guidelines recommend that all stable patients with HF should be referred to a specifically designed physical activity program and that exercise therapy should accompany GDMT. Data suggest that rehabilitation programs may result in improved physical functioning and an improvement in health-related quality of life for HF patients. The HF-ACTION trial found a modest improvement in outcomes and a much better improvement when patients adhered to the exercise program. The trial also demonstrated excellent safety in aerobic training throughout the study. However, there are limited data as to whether home-based or organized exercise programs would best meet their needs [96–99]. As in most long-term programs, the patients in HF-ACTION had a drop in adherence to the exercise intervention despite multiple interventions to enhance patient compliance [100]. Future studies are needed to determine if aerobic training also could improve outcomes in HFpEF patients, although small trials are consistently positive. Furthermore, the issue of adherence and modalities or interventions to improve exercise compliance are critically needed.

Assessing Quality in HF Care

The assessment of quality in HF care can be divided into outcome, process, and structural components [101, 102]. Outcome measures, such as survival and quality of life, are the most important quality measures from the perspective of both patient and healthcare provider. Process of care measures are the most accepted indicators of quality for hospitals and individual providers. Adoption of many of these process measures have been shown to improve outcomes in randomized trials.

Outcome measures that should be followed include: mortality, HF readmission rate, the percentage of HF patients on maximally tolerated guideline directed medical therapy, functional status, quality of life, and patient satisfactions. Process measurements include the number of patients referred to multidisciplinary HF care, the percentage of HF patients with documented assessment of cardiac function, and those for whom an advanced care plan has been addressed. Hospitals and HF clinics can have formal evaluations of their outcome measures by such organizations such as The Joint Commission and the American Heart Association Get With the Guidelines Heart Failure Program.

Conclusion

Advances in the treatment of HF and early interventions to prevent clinical decompensation delay disease progression and improve survival. After initial evaluation and the implementation of guideline-directed medical therapy, outpatient HF management strategies focus on the maintenance of patient stability (Fig. 34.1). Patient education, a focus on self-management and adherence, and discharge planning may further contribute to clinical stability and improved patient outcomes.

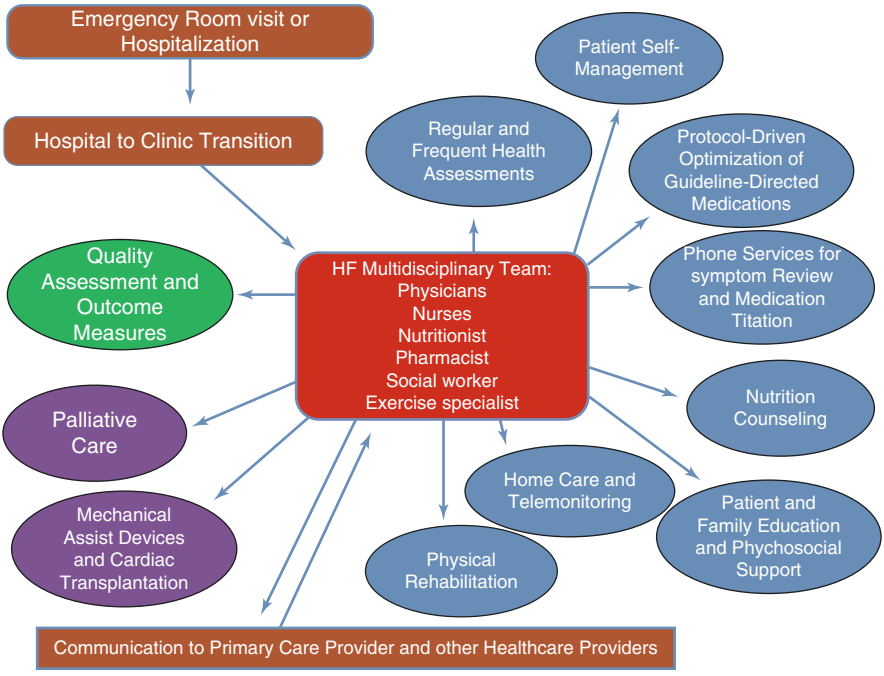


Fig. 34.1 Communication to primary care provider and other healthcare providers

Multidisciplinary disease-management HF programs may help improve HF patient outcomes, including decreased symptoms, improved quality of life, reduced rates of hospital admission, and decreased healthcare costs.

The principals of effective HF care include: a patient-centered multidisciplinary approach, rigorous adherence to evidence-based treatment through written protocols, early detection of exacerbations, development of individualized management plans, promotion of patient self-management, continuity of care, and continuous monitoring of program outcomes and quality improvement.

References

1. Heidenreich PA, Albert NM, Allen LA, Bluemke DA, Butler J, Fonarow GC, et al. Forecasting the impact of heart failure in the United States: a policy statement from the American Heart Association. Circ Heart Fail. 2013;6(3):606–19.
2. Ambrosy AP, Fonarow GC, Butler J, Chioncel O, Greene SJ, Vaduganathan M, et al. The global health and economic burden of hospitalizations for heart failure: lessons learned from hospitalized heart failure registries. J Am Coll Cardiol. 2014;63(12):1123–33.
3. Cook C, Cole G, Asaria P, Jabbour R, Francis DP. The annual global economic burden of heart failure. Int J Cardiol. 2014;171(3):368–76.
4. Hong Y, LaBresh KA. Overview of the American Heart Association "Get With the Guidelines" Programs: Coronary Heart Disease, Stroke, and Heart Failure. Crit Pathw Cardiol. 2006;5(4):179–86.
5. Krantz MJ, Ambardekar AV, Kaltenbach L, Hernandez AF, Heidenreich PA, Fonarow GC. Patterns and predictors of evidence-based medication continuation among hospitalized heart failure patients (from Get With the Guidelines-Heart Failure). Am J Cardiol. 2011;107(12):1818–23.
6. Jencks SF, Williams MV, Coleman EA. Rehospitalizations among patients in the Medicare fee-for-service program. N Engl J Med. 2009;360(14):1418–28.
7. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey Jr DE, Drazner MH, et al. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation. 2013;128(16):1810–52.
8. Blackledge HM, Tomlinson J, Squire IB. Prognosis for patients newly admitted to hospital with heart failure: survival trends in 12 220 index admissions in Leicestershire 1993–2001. Heart. 2003;89(6):615–20.
9. Yancy CW, Fonarow GC, Albert NM, Curtis AB, Stough WG, Gheorghiade M, et al. Adherence to guideline-recommended adjunctive heart failure therapies among outpatient cardiology practices (findings from IMPROVE HF). Am J Cardiol. 2010;105(2):255–60.
10. Krumholz HM, Baker DW, Ashton CM, Dunbar SB, Friesinger GC, Havranek EP, et al. Evaluating quality of care for patients with heart failure. Circulation. 2000;101(12):E122–40.
11. Gheorghiade M, Shah AN, Vaduganathan M, Butler J, Bonow RO, Rosano GM, et al. Recognizing hospitalized heart failure as an entity and developing new therapies to improve outcomes: academics', clinicians', industry's, regulators', and payers' perspectives. Heart Fail Clin. 2013;9(3):285-2vi.
12. Butler J, Fonarow GC, Gheorghiade M. Need for increased awareness and evidence-based therapies for patients hospitalized for heart failure. JAMA. 2013;310(19):2035–6.
13. Piña IL, Bruckman D, Lance C, Hitch J, Gee J, Schaub K, et al. Quality improvement in heart failure: a randomized educational intervention to change provider behavior. Congest Heart Fail. 2012;18(5):245–53.

14. Fang J, Mensah GA, Croft JB, Keenan NL. Heart failure-related hospitalization in the U.S., 1979 to 2004. J Am Coll Cardiol. 2008;52(6):428–34.
15. Gheorghiade M, Abraham WT, Albert NM, Greenberg BH, O'connor CM, She L, et al. Systolic blood pressure at admission, clinical characteristics, and outcomes in patients hospitalized with acute heart failure. JAMA. 2006;296(18):2217–26.
16. Ross JS, Chen J, Lin Z, Bueno H, Curtis JP, Keenan PS, et al. Recent national trends in readmission rates after heart failure hospitalization. Circ Heart Fail. 2010;3(1):97–103.
17. Aranda Jr JM, Johnson JW, Conti JB. Current trends in heart failure readmission rates: analysis of Medicare data. Clin Cardiol. 2009;32(1):47–52.
18. Epstein AM, Jha AK, Orav EJ. The relationship between hospital admission rates and rehospitalizations. N Engl J Med. 2011;365(24):2287–95.
19. Madigan E, Schmotzer BJ, Struk CJ, DiCarlo CM, Kikano G, Pina IL, et al. Home health care with telemonitoring improves health status for older adults with heart failure. Home Health Care Serv Q. 2013;32(1):57–74.
20. Madigan EA, Gordon NH, Fortinsky RH, Koroukian SM, Pina I, Riggs JS. Rehospitalization in a national population of home health care patients with heart failure. Health Serv Res. 2012;47(6):2316–38.
21. Brocco S, Zamboni M, Fantin F, Marchesan M, Schievano E, Zambon F, et al. Quality of care in congestive heart failure in the elderly: epidemiological evidence of a gap between guidelines and clinical practice. Aging Clin Exp Res. 2010;22(3):243–8.
22. Fonarow GC, Albert NM, Curtis AB, Stough WG, Gheorghiade M, Heywood JT, et al. Improving evidence-based care for heart failure in outpatient cardiology practices: primary results of the Registry to Improve the Use of Evidence-Based Heart Failure Therapies in the Outpatient Setting (IMPROVE HF). Circulation. 2010;122(6):585–96.
23. Heywood JT, Fonarow GC, Yancy CW, Albert NM, Curtis AB, Gheorghiade M, et al. Comparison of medical therapy dosing in outpatients cared for in cardiology practices with heart failure and reduced ejection fraction with and without device therapy: report from IMPROVE HF. Circ Heart Fail. 2010;3(5):596–605.
24. Golwala HB, Thadani U, Liang L, Stavrakis S, Butler J, Yancy CW, et al. Use of hydralazine-isosorbide dinitrate combination in African American and other race/ethnic group patients with heart failure and reduced left ventricular ejection fraction. J Am Heart Assoc. 2013;2(4):e000214.
25. Fonarow GC, Albert NM, Curtis AB, Gheorghiade M, Liu Y, Mehra M, et al. Incremental reduction in risk of death associated with use of guideline-recommended therapies in patients with heart failure: a Nested Case-Control Analysis of IMPROVE HF. J Am Heart Assoc. 2012;1(1):16–26.
26. Fonarow GC, Yancy CW, Albert NM, Curtis AB, Stough WG, Gheorghiade M, et al. Improving the use of evidence-based heart failure therapies in the outpatient setting: the IMPROVE HF performance improvement registry. Am Heart J. 2007;154(1):12–38.
27. American Heart Association "Get With the Guidelines". www.americanheart.org. 2007.
28. Yancy CW, Abraham WT, Albert NM, Clare R, Stough WG, Gheorghiade M, et al. Quality of care of and outcomes for African Americans hospitalized with heart failure: findings from the OPTIMIZE-HF (Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients With Heart Failure) registry. J Am Coll Cardiol. 2008;51(17):1675–84.
29. Hernandez AF, Hammill BG, O'connor CM, Schulman KA, Curtis LH, Fonarow GC. Clinical effectiveness of beta-blockers in heart failure: findings from the OPTIMIZE-HF (Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure) Registry. J Am Coll Cardiol. 2009;53(2):184–92.
30. Gonseth J, Guallar-Castillon P, Banegas JR, Rodriguez-Artalejo F. The effectiveness of disease management programmes in reducing hospital re-admission in older patients with heart failure: a systematic review and meta-analysis of published reports. Eur Heart J. 2004;25(18):1570–95.
31. Hernandez AF, Greiner MA, Fonarow GC, Hammill BG, Heidenreich PA, Yancy CW, et al. Relationship between early physician follow-up and 30-day readmission among Medicare beneficiaries hospitalized for heart failure. JAMA. 2010;303(17):1716–22.

32. Adams Jr KF, Fonarow GC, Emerman CL, LeJemtel TH, Costanzo MR, Abraham WT, et al. Characteristics and outcomes of patients hospitalized for heart failure in the United States: rationale, design, and preliminary observations from the first 100,000 cases in the Acute Decompensated Heart Failure National Registry (ADHERE). Am Heart J. 2005;149(2):209–16.
33. Ahmed A, Kiefe CI, Allman RM, Sims RV, DeLong JF. Survival benefits of angiotensin-converting enzyme inhibitors in older heart failure patients with perceived contraindications. J Am Geriatr Soc. 2002;50(10):1659–66.
34. Akosah KO, Schaper AM, Haus LM, Mathiason MA, Barnhart SI, McHugh VL. Improving outcomes in heart failure in the community: long-term survival benefit of a disease-management program. Chest. 2005;127(6):2042–8.
35. Discher CL, Klein D, Pierce L, Levine AB, Levine TB. Heart failure disease management: impact on hospital care, length of stay, and reimbursement. Congest Heart Fail. 2003;9(2):77–83.
36. Gillespie JL. The value of disease management—part 1: balancing cost and quality in the treatment of congestive heart failure. A review of disease management services for the treatment of congestive heart failure. Dis Manag. 2001;4(2):41–51.
37. Heidenreich PA, Ruggerio CM, Massie BM. Effect of a home monitoring system on hospitalization and resource use for patients with heart failure. Am Heart J. 1999;138(4 Pt 1): 633–40.
38. Krumholz HM, Currie PM, Riegel B, Phillips CO, Peterson ED, Smith R, et al. A taxonomy for disease management: a scientific statement from the American Heart Association Disease Management Taxonomy Writing Group. Circulation. 2006;114(13):1432–45.
39. Faxon DP, Schwamm LH, Pasternak RC, Peterson ED, McNeil BJ, Bufalino V, et al. Improving quality of care through disease management: principles and recommendations from the American Heart Association's Expert Panel on Disease Management. Circulation. 2004;109(21):2651–4.
40. Rich MW, Beckham V, Wittenberg C, Leven CL, Freedland KE, Carney RM. A multidisciplinary intervention to prevent the readmission of elderly patients with congestive heart failure. N Engl J Med. 1995;333(18):1190–5.
41. McAlister FA, Lawson FM, Teo KK, Armstrong PW. A systematic review of randomized trials of disease management programs in heart failure. Am J Med. 2001;110(5):378–84.
42. Whellan DJ, Gaulden L, Gattis WA, Granger B, Russell SD, Blazing MA, et al. The benefit of implementing a heart failure disease management program. Arch Intern Med. 2001;161(18):2223–8.
43. Fonarow GC, Stevenson LW, Walden JA, Livingston NA, Steimle AE, Hamilton MA, et al. Impact of a comprehensive heart failure management program on hospital readmission and functional status of patients with advanced heart failure. J Am Coll Cardiol. 1997;30(3):725–32.
44. de la Porte PW, Lok DJ, van Veldhuisen DJ, van Wijngaarden J, Cornel JH, Zuithoff NP, et al. Added value of a physician-and-nurse-directed heart failure clinic: results from the Deventer-Alkmaar heart failure study. Heart. 2007;93(7):819–25.
45. Bueno H, Ross JS, Wang Y, Chen J, Vidan MT, Normand SL, et al. Trends in length of stay and short-term outcomes among Medicare patients hospitalized for heart failure, 1993-2006. JAMA. 2010;303(21):2141–7.
46. McCall N, Cromwell J. Results of the Medicare Health Support disease-management pilot program. N Engl J Med. 2011;365(18):1704–12.
47. Ojeda S, Anguita M, Delgado M, Atienza F, Rus C, Granados AL, et al. Short- and long-term results of a programme for the prevention of readmissions and mortality in patients with heart failure: are effects maintained after stopping the programme? Eur J Heart Fail. 2005;7(5):921–6.
48. Rich MW. Management of heart failure in the elderly. Heart Fail Rev. 2002;7(1):89–97.
49. Holland R, Battersby J, Harvey I, Lenaghan E, Smith J, Hay L. Systematic review of multidisciplinary interventions in heart failure. Heart. 2005;91(7):899–906.

50. Philbin EF. Comprehensive multidisciplinary programs for the management of patients with congestive heart failure. J Gen Intern Med. 1999;14(2):130–5.
51. Stewart S, McAlister FA, McMurray JJ. Heart failure management programs reduce readmissions and prolong survival. Arch Intern Med. 2005;165(11):1311–2.
52. Halcomb E, Davidson P, Daly J, Yallop J, Tofler G. Australian nurses in general practice based heart failure management: implications for innovative collaborative practice. Eur J Cardiovasc Nurs. 2004;3(2):135–47.
53. Whellan DJ, Hasselblad V, Peterson E, O'connor CM, Schulman KA. Metaanalysis and review of heart failure disease management randomized controlled clinical trials. Am Heart J. 2005;149(4):722–9.
54. Windham BG, Bennett RG, Gottlieb S. Care management interventions for older patients with congestive heart failure. Am J Manag Care. 2003;9(6):447–59.
55. Bruggink-Andre de la Porte PW, Lok DJ, van Wijngaarden J, Cornel JH, Pruijsers-Lamers D, van Veldhuisen DJ, et al. Heart failure programmes in countries with a primary care-based health care system. Are additional trials necessary? Design of the DEAL-HF study. Eur J Heart Fail. 2005;7(5):910–20.
56. Rich MW. Heart failure disease management: a critical review. J Card Fail. 1999;5(1):64–75.
57. van der Wal MH, Jaarsma T, van Veldhuisen DJ. Non-compliance in patients with heart failure; how can we manage it? Eur J Heart Fail. 2005;7(1):5–17.
58. Moser DK. Heart failure management: optimal health care delivery programs. Annu Rev Nurs Res. 2000;18:91–126.
59. Hauptman PJ, Rich MW, Heidenreich PA, Chin J, Cummings N, Dunlap ME, et al. The heart failure clinic: a consensus statement of the Heart Failure Society of America. J Card Fail. 2008;14(10):801–15.
60. Gattis WA, Hasselblad V, Whellan DJ, O'connor CM. Reduction in heart failure events by the addition of a clinical pharmacist to the heart failure management team: results of the Pharmacist in Heart Failure Assessment Recommendation and Monitoring (PHARM) Study. Arch Intern Med. 1999;159(16):1939–45.
61. Gohler A, Januzzi JL, Worrell SS, Osterziel KJ, Gazelle GS, Dietz R, et al. A systematic meta-analysis of the efficacy and heterogeneity of disease management programs in congestive heart failure. J Card Fail. 2006;12(7):554–67.
62. Grady KL, Dracup K, Kennedy G, Moser DK, Piano M, Stevenson LW, Young JB. Team management of patients with heart failure: a statement for healthcare professionals. Circulation. 2000;102(19):2443–56.
63. Williams SG, Jackson M, Ng LL, Barker D, Patwala A, Tan LB. Exercise duration and peak systolic blood pressure are predictive of mortality in ambulatory patients with mild-moderate chronic heart failure. Cardiology. 2005;104(4):221–6.
64. Genth S, Zotz R, Darius H, Treese N, Sigmund M, Hanrath P, et al. Comparison of NYHA classification with cardiopulmonary function in patients with chronic heart failure. Z Kardiol. 1996;85(6):428–34.
65. van den Broek SA, van Veldhuisen DJ, de Graeff PA, Landsman ML, Hillege H, Lie KI. Comparison between New York Heart Association classification and peak oxygen consumption in the assessment of functional status and prognosis in patients with mild to moderate chronic congestive heart failure secondary to either ischemic or idiopathic dilated cardiomyopathy. Am J Cardiol. 1992;70(3):359–63.
66. Rostagno C, Galanti G, Comeglio M, Boddi V, Olivo G, Gastone Neri SG. Comparison of different methods of functional evaluation in patients with chronic heart failure. Eur J Heart Fail. 2000;2(3):273–80.
67. Konstam V, Gregory D, Chen J, Weintraub A, Patel A, Levine D, et al. Health-related quality of life in a multicenter randomized controlled comparison of telephonic disease management and automated home monitoring in patients recently hospitalized with heart failure: SPAN-CHF II trial. J Card Fail. 2011;17(2):151–7.
68. Heidenreich PA. Department of Veterans Affairs Quality Enhancement Research Initiative (QUERI) Chronic Heart Failure QUERI Center Application Strategic Plan. 2008. Report.

69. Kosiborod M, Krumholz HM, Jones PG, Pitt B, Spertus JA. The relationship between anemia, change in hematocrit over time and change in health status in patients with heart failure after myocardial infarction. J Card Fail. 2008;14(1):27–34.
70. Lindenfeld J, Albert NM, Boehmer JP, Collins SP, Ezekowitz JA, Givertz MM, et al. HFSA 2010 comprehensive heart failure practice guideline. J Card Fail. 2010;16(6):e1–194.
71. Varma S, McElnay JC, Hughes CM, Passmore AP, Varma M. Pharmaceutical care of patients with congestive heart failure: interventions and outcomes. Pharmacotherapy. 1999;19(7):860–9.
72. Luzier AB, Forrest A, Feuerstein SG, Schentag JJ, Izzo Jr JL. Containment of heart failure hospitalizations and cost by angiotensin-converting enzyme inhibitor dosage optimization. Am J Cardiol. 2000;86(5):519–23.
73. Pearson GJ, Cooke C, Simmons WK, Sketris I. Evaluation of the use of evidence-based angiotensin-converting enzyme inhibitor criteria for the treatment of congestive heart failure: opportunities for pharmacists to improve patient outcomes. J Clin Pharm Ther. 2001;26(5):351–61.
74. Sadik A, Yousif M, McElnay JC. Pharmaceutical care of patients with heart failure. Br J Clin Pharmacol. 2005;60(2):183–93.
75. Vinson JM, Rich MW, Sperry JC, Shah AS, McNamara T. Early readmission of elderly patients with congestive heart failure. J Am Geriatr Soc. 1990;38(12):1290–5.
76. Anker SD, Coats AJ. Cachexia in heart failure is bad for you. Eur Heart J. 1998;19(2):191–3.
77. McNutt RA. Shared medical decision making: problems, process, progress. JAMA. 2004;292(20):2516–8.
78. Heart Failure Society Of America. HFSA 2006 comprehensive heart failure practice guideline. J Card Fail. 2006;12(1):e1–2.
79. Hamner JB. State of the science: posthospitalization nursing interventions in congestive heart failure. ANS Adv Nurs Sci. 2005;28(2):175–90.
80. Stewart S, Horowitz JD. Home-based intervention in congestive heart failure: long-term implications on readmission and survival. Circulation. 2002;105(24):2861–6.
81. Kornowski R, Zeeli D, Averbuch M, Finkelstein A, Schwartz D, Moshkovitz M, et al. Intensive home-care surveillance prevents hospitalization and improves morbidity rates among elderly patients with severe congestive heart failure. Am Heart J. 1995;129(4):762–6.
82. de Lusignan S, Wells S, Johnson P, Meredith K, Leatham E. Compliance and effectiveness of 1 year's home telemonitoring. The report of a pilot study of patients with chronic heart failure. Eur J Heart Fail. 2001;3(6):723–30.
83. Grancelli H, Varini S, Ferrante D, Schwartzman R, Zambrano C, Soifer S, et al. Randomized Trial of Telephone Intervention in Chronic Heart Failure (DIAL): study design and preliminary observations. J Card Fail. 2003;9(3):172–9.
84. Jerant AF, Azari R, Nesbitt TS. Reducing the cost of frequent hospital admissions for congestive heart failure: a randomized trial of a home telecare intervention. Med Care. 2001;39(11):1234–45.
85. Ypenburg C, Bax JJ, van der Wall EE, Schalij MJ, van Erven L. Intrathoracic impedance monitoring to predict decompensated heart failure. Am J Cardiol. 2007;99(4):554–7.
86. Louis AA, Turner T, Gretton M, Baksh A, Cleland JG. A systematic review of telemonitoring for the management of heart failure. Eur J Heart Fail. 2003;5(5):583–90.
87. Cleland JG, Louis AA, Rigby AS, Janssens U, Balk AH. Noninvasive home telemonitoring for patients with heart failure at high risk of recurrent admission and death: the Trans-European Network-Home-Care Management System (TEN-HMS) study. J Am Coll Cardiol. 2005;45(10):1654–64.
88. Schofield RS, Kline SE, Schmalfuss CM, Carver HM, Aranda Jr JM, Pauly DF, et al. Early outcomes of a care coordination-enhanced telehome care program for elderly veterans with chronic heart failure. Telemed J E Health. 2005;11(1):20–7.
89. Chaudhry SI, Mattera JA, Curtis JP, Spertus JA, Herrin J, Lin Z, et al. Telemonitoring in patients with heart failure. N Engl J Med. 2010;363(24):2301–9.

90. Koehler F, Winkler S, Schieber M, Sechtem U, Stangl K, Bohm M, et al. Telemedical Interventional Monitoring in Heart Failure (TIM-HF), a randomized, controlled intervention trial investigating the impact of telemedicine on mortality in ambulatory patients with heart failure: study design. Eur J Heart Fail. 2010;12(12):1354–62.
91. Selker HP, Griffith JL, D'Agostino RB. A time-insensitive predictive instrument for acute hospital mortality due to congestive heart failure: development, testing, and use for comparing hospitals: a multicenter study. Med Care. 1994;32(10):1040–52.
92. Lee DS, Austin PC, Rouleau JL, Liu PP, Naimark D, Tu JV. Predicting mortality among patients hospitalized for heart failure: derivation and validation of a clinical model. JAMA. 2003;290(19):2581–7.
93. Levy WC, Mozaffarian D, Linker DT, Sutradhar SC, Anker SD, Cropp AB, et al. The Seattle Heart Failure Model: prediction of survival in heart failure. Circulation. 2006;113(11):1424–33.
94. Phillips CO, Singa RM, Rubin HR, Jaarsma T. Complexity of program and clinical outcomes of heart failure disease management incorporating specialist nurse-led heart failure clinics. A meta-regression analysis. Eur J Heart Fail. 2005;7(3):333–41.
95. Balinsky W, Muennig P. The costs and outcomes of multifaceted interventions designed to improve the care of congestive heart failure in the inpatient setting: a review of the literature. Med Care Res Rev. 2003;60(3):275–93.
96. Beswick AD, Rees K, Griebsch I, Taylor FC, Burke M, West RR, et al. Provision, uptake and cost of cardiac rehabilitation programmes: improving services to under-represented groups. Health Technol Assess. 2004;8(41):iii-x.
97. Austin J, Williams R, Ross L, Moseley L, Hutchison S. Randomised controlled trial of cardiac rehabilitation in elderly patients with heart failure. Eur J Heart Fail. 2005;7(3):411–7.
98. Haykowsky M, Vonder Muhll I, Ezekowitz J, Armstrong P. Supervised exercise training improves aerobic capacity and muscle strength in older women with heart failure. Can J Cardiol. 2005;21(14):1277–80.
99. Senden PJ, Sabelis LW, Zonderland ML, Hulzebos EH, Bol E, Mosterd WL. The effect of physical training on workload, upper leg muscle function and muscle areas in patients with chronic heart failure. Int J Cardiol. 2005;100(2):293–300.
100. O'connor CM, Whellan DJ, Lee KL, Keteyian SJ, Cooper LS, Ellis SJ, et al. Efficacy and safety of exercise training in patients with chronic heart failure: HF-ACTION randomized controlled trial. JAMA. 2009;301(14):1439–50.
101. Donabedian A. Quality assurance: corporate responsibility for multihospital systems. QRB Qual Rev Bull. 1986;12(1):3–7.
102. Donabedian D. What students should know about the health and welfare systems. Nurs Outlook. 1980;28(2):122–5.

Chapter 35
Inflammation and Heart Failure

Kyung-Hee Kim, Diana Kim, and Howard J. Eisen

Small Animal Models of Heart Failure

Heart failure is a leading cause of death and continues to provide significant socioeconomic burdens worldwide [1]. Heart failure is a clinical syndrome attributed to various causes. Although most patients share the final stage of left ventricular (LV) dysfunction, the pathophysiology from initial myocardial damage to LV dysfunction differs in every patient [2]. Therefore, the study of heart failure requires various animal models that mimic the pathogenetic features of heart failure in humans. In this respect, animal models of LV hypertrophy that lead to heart failure have been useful for providing a new insight into the complex pathogenesis of heart failure and for testing novel heart failure therapeutic options before clinical experience [3]. Many investigators have scaled down from large animal models to small models because they are easier to manipulate, cheaper to maintain, and similar to the human cardiovascular system. Moreover, recent advances in echocardiography and micronanometer conductance catheters have made it possible to reliably evaluate cardiac function in small animal models [4, 5]. The role of these models for understanding the disease and developing new treatment cannot be overemphasized. Additionally, the costs are much lower; thus, the experiment is more feasible. The current section will focus upon new aspects of rat models of heart failure. The

K.-H. Kim, MD (✉)
Division of Cardiology, Department of Internal Medicine, Sejong General Hospital, Hyohyunro 489 street Bucheon, Kyunggi-do, Republic of Korea
e-mail: learnbyliving9@gmail.com

D. Kim, BA
Drexel University College of Medicine, Philadelphia, PA, USA
e-mail: dhk45@drexel.edu

H.J. Eisen, MD
Division of Cardiology, Drexel University College of Medicine, Hahnemann University Hospital, 245 North 15th Street, Mailstop#1012, Philadelphia, PA 19102, USA
e-mail: heisen@drexelmed.edu

H. Eisen (ed.), *Heart Failure*, DOI 10.1007/978-1-4471-4219-5_35

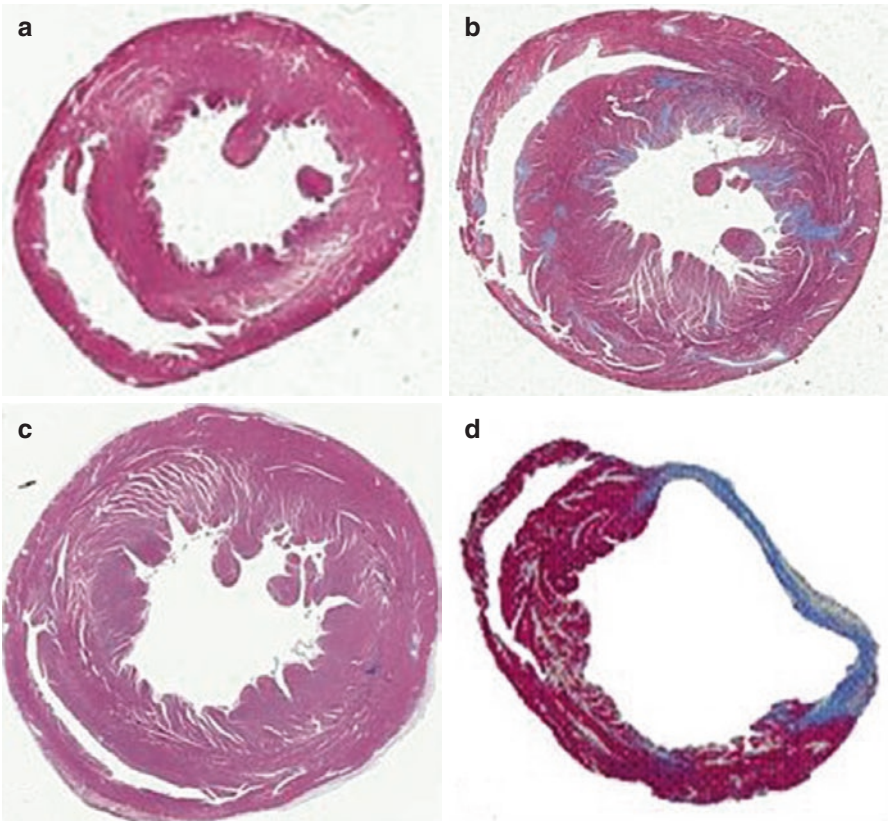


Fig. 35.1 Animal models of heart failure. (**a**) Sham (**b**) Pressure overloaded model after suprarenal ligation (**c**) Volume overloaded model after mitral regurgitation (**d**) Mixed load remodeling model after myocardial infarction

sections below describe three clinical conditions that can result in heart failure: pressure overloaded model (concentric hypertrophy), volume overloaded model (eccentric hypertrophy), mixed load ventricular remodeling model (Fig. 35.1) [6]. Regardless of the initial stimulus, for example, hypertension, ischemia, or volume overload, the heart counters insults with hypertrophy where inflammatory plays a major role. Before we will discuss the inflammatory pathophysiology of the heart failure, we mention the major animal models of heart failure. The authors recognize that the complexities of the human diseases that lead to HF are difficult to mimic in most animal models. All of the to-be-mentioned small animal models have advantages and limitations, and the transfer from experimental to human heart failure needs critical evaluation. However, many new therapeutic strategies that have shown success in different animal models of heart failure have subsequently proven to be useful in human heart failure. With these limitations in mind, this section of the chapter gives an overview of the various animal models of heart failure

according to the pathophysiology-based human classification of heart failure. In the next section of the chapter, we will discuss the pathophysiology of heart failure focused on inflammation and how it is clinically presented.

Rat Pressure Overload Models

Aortic Banding

Models involving an abnormal pressure load have been most useful in the study of the pathogenesis of hypertrophy, subcellular failure, and vascular changes. There are numerous surgical methods to induce pressure overload in rats, but the ascending aortic banding is one of the more widely used surgical models, in which a stricture is placed around the ascending aorta of weanling rats [7, 8]. Compared with ascending aortic banding, abdominal aortic banding model is more physiologic model like human clinical settings. Abdominal aortic banding is also a well-established model for inducing hypertrophy due to pressure overload in animals and it has been used extensively for many decades [9, 10]. The abdominal aorta is exposed above the left renal artery and a silk thread is passed under it. A 23 cannula is placed longitudinally on the aorta and both aorta and cannula is tied. The cannula is then removed, leaving an aortic lumen determined by the diameter of the cannula (Fig. 35.2). The skin is closed by clipping and covered with tar spray. Kim and colleagues [11] have used this model extensively to explore the new phosphodiesterase 5 inhibitors (PDE 5 inhibitors), udenafil therapy to prevent heart failure and

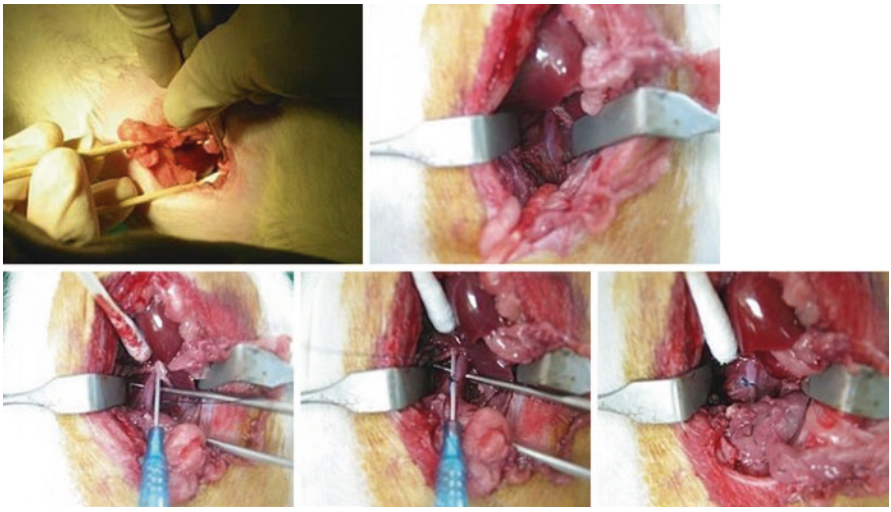


Fig. 35.2 The procedure of pressure overload model; suprarenal ligation

decreased inflammatory markers in pressure overloaded failing heart. They showed that udenafil-attenuated myocardial fibrosis and apoptosis. Udenafil also decreased myocardial matrix metalloproteinase-9 expression and augmented serum interleukin-10 concentration. Long-term udenafil use prevented cardiac remodeling and improved exercise capacity and survival in rats exposed to pressure-overload cardiac hypertrophy.

Rat Volume Overload Models

Aortocaval Fistula

Much less is known about signal systems for volume overload than those for pressure loads because there are fewer volume overload models. It is of interest that, as opposed to LV pressure overload, LV volume overload is associated with a decrease in interstitial collagen surrounding cardiomyocytes [12, 13]. The pure volume overload of aortocaval fistula (ACF) in the rat causes a LV stretch stimulus without an increase in LV pressure due to the arterial-venous shunt. As in the human with a pure volume overload, this results in an adverse LV eccentric remodeling involving increases in LV end-diastolic pressure and LV end-diastolic dimension to wall thickness ratio over a period of time. Heart failure is induced in this model by surgical creation of an arteriovenous (AV) fistula between the abdominal aorta and inferior vena cava, distal to the origin of the renal arteries [14, 15].

Mitral Regurgitation Model in Rats

Mitral regurgitation (MR) is the most common type of valvular heart disease that induces LV volume overload. In their pioneering work, Pu et al. [16] developed an MR rat model for the first time. However, their report lacked details about the animal model, LV remodeling, exercise capacity, and histological findings that are critically important for future research. Kim et al. [17] established a reliable small animal model of chronic MR using rats and verified the pathophysiological features of this model using serial echocardiography. After anesthesia, an intracardiac echocardiographic catheter is inserted into the esophagus for transesophageal echocardiography. A lateral thoracotomy is performed, and a needle is inserted into the LV via apical puncture and is advanced toward the mitral valve to create a hole in the leaflet and induce MR under the guidance of transesophageal echocardiography. Using this model, they evaluated that sildenafil attenuated LV remodeling and prevents exercise intolerance in a rat model of chronic MR likely due to the antiapoptotic, anti-inflammatory effects of sildenafil. They used transcriptional profiling of cardiac apical tissues which revealed that gene sets related to inflammatory response,

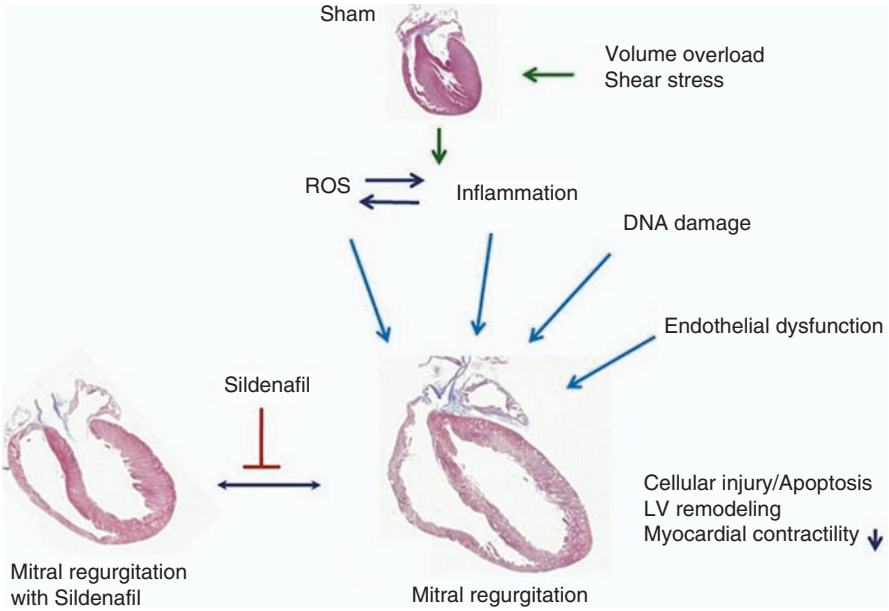


Fig. 35.3 Mitral regurgitation causes progressive left ventricular dilatation, wall thinning, and cardiomyocyte elongation, which recapitulates eccentric remodeling with inflammation cell infiltration, extracellular matrix degradation and activation of DNA damage pathway. The anti- inflammatory and antiapoptotic effects of sildenafil seemed to play a key role in preventing LV remodeling

DNA damage response, cell cycle checkpoint, and cellular signaling pathways were significantly enriched by genes with reciprocal changes in sildenafil treatment group (Fig. 35.3).

Rat Ischemic Injury/Myocardial Infarction Model (Mixed Load Ventricular Remodeling Model)

Various methods have been applied to induce MI and/or ischemia in animals via occlusions of coronary arteries. Left ventricular MI in rats has been established by Pfeffer et al. [18] In brief, after anesthesia, orotracheal intubation and thoracotomy, the heart is rapidly exteriorized and the LCA is ligated in the proximal segment using a thin thread. The occlusion of the artery can be recognized by blanching of the tissue distal to the ligation. Rats with infarctions greater than 46 % develop congestive HF after 21 days with elevated filling pressures, reduced cardiac output, and a minimal capacity to respond to pre- and after-load stress. The degree of

impairment of LV function is directly related to the extent of myocardial loss. In comparison to the permanent occlusion model, the reperfusion MI model leads to a higher infiltration of inflammatory cells, attenuated fibrotic remodeling and enhanced neovascularization in the area of infarction [19].

Methodological Considerations

HF animal models must be carefully characterized to ensure that they have the critical features that have been described above. The level of characterization will ultimately be determined by the study design and the available equipment and resources. Several additional points are worth considering as work continues in animal models: (1) Our first concern was that heart size and gender have been neglected in some previous experiments. In our pilot study, we found that rats showed rapid growth of the heart between 8 and 10 weeks of age (LVESD, 3.40 ± 0.15 mm vs. 4.02 ± 0.27 mm; LVEDD, 6.41 ± 0.34 mm vs. 7.31 ± 0.34 mm for 8 vs. 10 weeks of age, $p < 0.01$); thus, this period was not optimal for evaluating LV remodeling (Fig. 35.4). (2) When considering new treatment approaches, experiments that determine whether treatment reverses ventricular remodeling are more relevant than animal studies of prevention of heart failure; (3) Complete hemodynamic assessment of the animals used is essential, including assessment of both static and dynamic parameters as well as structural remodeling in determining the magnitude of these parameters. Assessment of ventricular cardiac performance is also of importance; (4) Assessment of the functional capacity of both diseased and treated animals to determine whether improvement in hemodynamics and cardiac function afforded by pharmacological intervention is clinically significant; (5) Longer-term studies on the effects of treatment must be performed with effects on survival and toxicity being included. We will mention shortly the approaches that have been used routinely to reliably characterize small-animal heart failure models are outlined below.

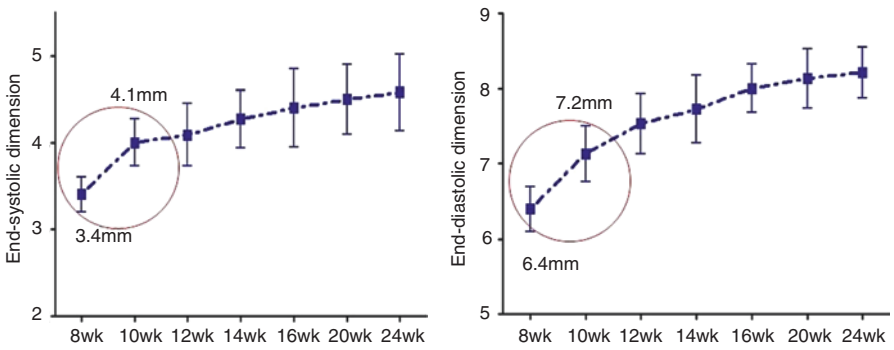


Fig. 35.4 In Kim et al. pilot study, they found that rats showed rapid growth of the heart between 8 and 10 weeks of age (LVESD, 3.40 ± 0.15 mm vs. 4.02 ± 0.27 mm; LVEDD, 6.41 ± 0.34 mm vs. 7.31 ± 0.34 mm for 8 vs. 10 weeks of age, $p < 0.01$); thus, this period was not optimal for evaluating LV remodeling

In Vivo Cardiac Function

Transthoracic echocardiography can be used to evaluate cardiac function in anesthetized or conscious rats [17, 20–22]. LV septal and posterior wall thickness (SWT and PWT, respectively) and the LV end diastolic/systolic dimension (EDD/ESD, respectively) can be measured using M-mode echocardiography at the papillary muscle level. The LV ejection fraction (EF) and LV mass can be estimated by established formulas [23]. Transthoracic 2-dimensional guided M-mode echocardiography and pulsed-wave Doppler wave can be performed by using a variety of commercially available echocardiograph machines (Fig. 35.5). Serial measurements should be performed to evaluate structural and functional progression of heart failure or to evaluate the efficacy of therapeutics. Recent miniaturization and refinement of imaging technology for rats such as high-field-strength MRI machines (9.4 T) have facilitated noninvasive characterization of the pulmonary and systemic circulation in rodents [24, 25]. However, cardiac MRI of small animal model needs lots of time to get the image, so anesthesia time could affect the result of study.

In Vivo Measurements of Exercise Capacity

Measurements of exercise capacity is very important parameters in patients with heart failure. Exercise capacity of rats can be measured by several methods. Kim et al. used the Rotal Rod Treadmill [17]. The rats ran on a knurled drum as the drum rotated to avoid falling off. Animals were trained two times before the test to adjust the treadmill. Treadmill speed was gradually increased from 3 revolutions per minute (rpm) to 15 rpm every 1 minute, and maximum exercise time was recorded. Guazzi et al. [26] measure maximal exercise capacity with a conventional

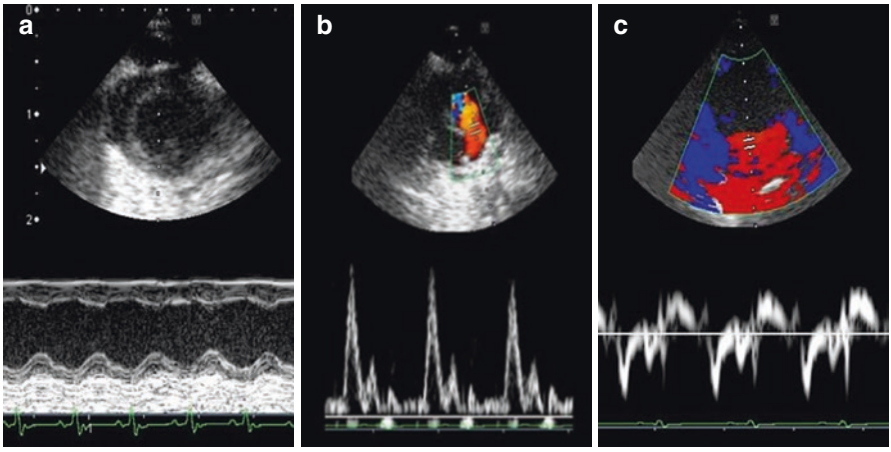


Fig. 35.5 Echocardiography (**a**) 2D & M-mode. Color Doppler. (**b**) Spectral Doppler. Mitral inflow. (**c**) Tissue Doppler. Mitral annulus

motor-driven treadmill. They had the 2-week acclimatization period. During the first week of acclimatization, this consisted of 3 sessions of slow walking on the treadmill for 10 to 15 minutes each. During the second week of acclimatization, rats underwent 3 maximal exercise capacity tests, with the final 2 averaged. If there is special chamber, maximal VO_2 can be measured. The animals were placed on a treadmill and enclosed in an airtight metabolic chamber. This chamber was adapted for the determination of O_2 uptake (VO_2) by using an open-circuit method [27].

In Vivo Measurements of Loading Cardiac Conditions

Thanks to advances in microcatheter technology, ventricular pressure-volume relationships has been successfully translated to small animal models, including rats, allowing for detailed characterization of cardiovascular function. This method is unique for providing measures of ventricular performance that are more specific to the heart and less affected by vascular loading conditions. Pacher et al. showed the protocol in depth and detail in Nature Protocols [4]. Despite its invasiveness, this sophisticated methodology has great potential for characterizing cardiac function in various rodent- models of cardiovascular disease.

Conclusions

There is not yet a perfect preclinical model that accurately reproduces all the clinical pathological features of human heart failure. However, it is also clear that animal models have provided, and will continue to provide, valuable insight into the numerous pathways that contribute to the development and maintenance of heart failure. These models will allow us to investigate important interactions between the various triggers, which have been implicated in heart failure, their impact on signaling pathways, and their temporal evolution into the structural and functional abnormalities, which characterize the myocardial dysfunction process. Use of both classic and newly developed animal models will allow us to continue to rigorously test new hypotheses regarding pathogenesis and evaluate the ability of newly developed agents for prevention and reversal of established disease. Careful and rigorous clinical trials will be required to establish safety and efficacy of any heart failure therapy or mechanism in human patients.

Pathophysiology

Heart failure is described by a complex pathophysiology that includes more than just the cardiovascular system. Heart failure is often thought of in the context of the "neurohormonal hypothesis." This hypothesis states that that neurohormonal influences involving imbalance of sympathetic and parasympathetic tone as well as

disruption of the renin-angiotensin-aldosterone system contribute to heart failure [28]. Additionally, deleterious systemic inflammation involving various cytokines has been observed to further the progression of chronic heart failure, as postulated by the "cytokine hypothesis" [29]. Although the relationship between inflammatory cytokines and the neuroendocrine system has not been fully elucidated, studies show that the two systems influence each other to advance the status of heart failure [30]. Further, recent studies have shown that the two systems may interact with each other in the pathogenesis of this disorder [31]. This section will discuss the role of inflammation and neurohormonal influences in the pathophysiology of heart failure, as well as other aspects of heart failure syndrome such as cachexia, endothelial dysfunction, and reduced skeletal muscle blood flow.

Cytokines in Heart Failure

Elevated circulating levels of pro-inflammatory cytokines are seen with heart failure. The most important cytokines are TNF-α, IL-6, and IL-1. A number of chemokines, including macrophage chemoattractant protein (MCP)-1, IL-8, and macrophage inflammatory protein (MIP)-1α are also associated with heart failure; these levels of chemokines increase with heart failure progression. Increased expression of inflammatory cytokines and chemokines has been demonstrated by Damas et al. at both the protein and mRNA levels in a study of patients with heart failure; particularly high levels of these pro-inflammatory cytokines and chemokines were found in the coronary circulation [32]. The pro-inflammatory effects seem to be unopposed due to the absence of anti-inflammatory cytokines such as IL-10. The result of this imbalance leads to a systemic inflammatory effect [33]. The causes of inflammation in heart failure are manifold. The initial inflammation in early stages of myocardial infarction activates an immune response that can potentially explain some of the pro-inflammatory signals in heart failure. Moreover, mechanical overload and shear stress cause cytokine expression in various cell types including the endothelium, leukocytes, and even the cardiomyocytes themselves, suggesting these are native molecules made not just by the immune system but within the heart tissue itself. The consequential effects of these pro-inflammatory cytokines include release of radical nitric oxide, oxidative stress, and apoptosis among many other outcomes. Here, we describe the individual roles of TNF-α, IL-6, IL-1, TLRs and MMPs for their contribution to the pro-inflammatory state during heart failure and their intrinsic connection to neurohormonal activation.

Tumor Necrosis Factor Alpha (TNF-α)

TNF-α is a cytokine released by myocardial cells in response to damage and thought to be the one of most important mediators of HF progression. TNF-α exerts its effects via TNF-α receptors (TNFR), which are ubiquitously expressed.

Circulating levels in TNF-α levels are elevated in patients with CHF and increases as heart failure worsens [34], demonstrating a positive association between TNF-α and the progression of HF. TNFR then modulates myocardial function through two ways: (1) instantaneous activation of the sphingomyelinase signaling pathway that occurs within minutes of ligand interaction and (2) a slower, delayed response that involves the inhibition of β-adrenergic by nitric oxide [35]. TNFR-1, one subtype of the TNF receptor, is more abundantly expressed and mediates the majority of TNF-α's deleterious effects such as remodeling, hypertrophy, nuclear factor-kappa-B production, and apoptosis. TNF-α mediates its apoptotic effects through its effect on the death domain within the cytoplasmic portion of the TNF receptor-1, and secondarily activating NF-kB. Additionally, cytokines exert a cytotoxic effect on cardiomyocytes, leading to necrosis [36]. NF-kB effects and necrosis, together, further compromise the composition and function of the heart. TNFR-2, which is less commonly expressed, actually provides a protective effect for the heart. A study with patients with myocardial infarction by Valgimigli et al. demonstrated that TNFR-1 was the most powerful independent risk factor for HF and death [37]. Yet despite the contradictory effects of the TNFR-1 and TNFR-2, Hamid et al. implicated that both receptors are necessary in precipitating the pathophysiological consequences of TNF-α [38], including left ventricular dysfunction and remodeling, cardiac myocyte apoptosis, development of anorexia and cachexia, reduced skeletal muscle blood flow, and endothelial dysfunction, and other effects.

Interleukin 6

Increased concentrations of circulatory IL-6 are also strongly associated with advancement of HF. Moreover, in hospitalized patients with CAD, IL-6 levels were significantly associated with all-cause and cardiovascular mortality [39]. IL-6 type cytokines mediate their signals through the ubiquitously expressed glycoprotein (gp) 130 receptor subunit, which is central to the inflammatory effects observed in HF.

Short-term activation of IL-6R confers protective effects during ischemia partly through its classical, membrane-bound signaling. However, constitutive, persistent activation of gp130 present during heart failure states contributes to cardiac hypertrophy, myocardial dysfunction, and muscle wasting via IL-6 trans-signaling pathway [40]. Nevertheless, it has also been shown in genetic models of IL-6 that IL-6 is not necessary for the pathogenesis of heart failure. Fuchs et al. showed that IL-6 knockout mice did not have differences in LV dysfunction and hypertrophy after MI compared to regular mice. They postulated that there were redundancies between this system and the JAK/STAT pathways such that there were compensatory mechanisms through alternative receptors [41].

Interleukin 1

IL-1 works synergistically with TNF-α to depress myocardial contractility in a dose-dependent manner. IL-1, similar to TNF-α, is a potent inducer of myocardial apoptosis and hypertrophy in vitro [42, 43]. Further, it is involved in arrhythmogenesis, leading to exacerbation of HF [44]. Recent studies have suggested that TNF and IL-1 may have negative inotropic effect on the heart indirectly through activation and release of IL-8 [45, 46]. Preclinical studies suggest that IL-1 blockade has a positive effect on the failing heart, and clinical trials are under way to investigate the role of IL-1 blockade in improving symptomatic outcomes in patients with HF [47].

Toll-like Receptors

Toll-like receptors (TLRs) are also speculated to be an important link to inflammation in HF. TLRs are pattern-recognition receptors that are primarily involved in initiating the innate immune responses in the presence of conserved microbial molecules. Studies show that in HF that arises after acute myocardial infarction, TLRs are activated on monocytes. For example, in a study of patients with acute myocardial infarction by Satoh et al., TLR4 levels on monocytes positively correlated with IL-6 and TNF-α levels [48], indicating that activation of TLR4 through a myocytic inflammation reaction is associated with HF post-MI. This evidence is strengthened by inflammatory cytokines' upregulatory effect on TLR2 and TLR4 of vascular endothelial cells, which is likely to contribute to endothelial cell-related inflammation in HF. Additionally, enhanced effects of TLR2 and TLR4 are seen in injured myocardium, which subsequently recruit cells of innate immunity that may contribute to the myocardial inflammation in HF progression. The link between TLR and inflammation can be explained by TLRs' capacity to respond to not only microbes, but also to molecules released from injured cells, such as fibronectin and heat shock protein 60 [49].

Matrix Metalloproteases

Inflammatory cytokines, particularly TNF-α, are important regulators of myocardial activity of a proteolytic system called matrix metalloproteinases (MMPs) and their inhibitors, tissue inhibitors of metalloproteinases (TIMPS). During left ventricular remodeling and heart failure, a fine balance exists between matrix metalloproteinases, which are responsible for digesting extracellular matrix, and TIMPs, their inhibitors. It has been shown that through the different stages after MI leading

to heart failure that there are important spatial and temporal changes that correspond to functional outcomes. TNF-α, along with numerous other cytokines, is overexpressed by cardiomyocytes and causes the induction of MMP activity. The increased MMP proteolytic activity relative to TIMP activity results in disturbance of fibrillar collagen and ultimately fosters ventricular dilation. Thus, TNF-α is seen to influence left ventricular (LV) remodeling, a marked characteristic of heart failure, through the induction of MMP species. Interestingly, this phenomenon is short-lived. As time progresses, the MMP activity appears to decrease in response to TNF-α and TIMP increases, leading to increased collagen content and cardiac fibrosis [50].

Neurohormonal Activation

It has been well documented that heart failure is characterized by neurohormonal activation, in addition to inflammatory events. Neurohormonal activation is a process that involves renin-angiotensin-aldosterone system (RAAS) and the adrenergic system. Both systems are activated almost simultaneously upon damage to the myocardium, resulting in an increase of norepinephrine, angiotensin II, endothelin, TNF-α and aldosterone [51], in order to improve the mechanical state of the heart.

Angiotensin II (Ang II), a major factor in RAAS, is a robust vasoconstrictor of the renal efferent arterioles and systemic circulation that is produced during states of low cardiac output. Ang II also stimulates release of norepinephrine, from sympathetic nerve terminals and induces the release of aldosterone and AVP, both of which increase circulating blood volume through retention of sodium and/or water. Low cardiac output also activates SNS, which promotes vasoconstriction of peripheral vessels. While these effects can be beneficial in restoring cardiac output in a functional heart, persistent activation of both systems can have catastrophic effects on cardiac function, particularly in an already compromised heart. A mechanism through which this may occur is through the combined vasopressor effects by RAAS and SNS, which induce a large increase in left ventricular afterload. This, in turn, results in elevated myocardial demand, pulmonary capillary wedge pressure, and left ventricular end-diastolic pressure, all of which contribute to progression of HF. Furthermore, increased blood volume by aldosterone and AVP results in increased intracardiac pressure, pulmonary congestion, and edema [52]. Excessive sympathetic activity is also directly correlated to cardiac myocyte apoptosis, hypertrophy, and focal myocardial necrosis [53]. Additionally, Ang II also directly induces cardiac myocyte necrosis and modifies the myocardial matrix structure [54], latter by promoting reactive perivascular and interstitial fibrosis. It is not surprising, then, that the degree of neurohormonal activation is correlated with severity of HF. Francis et al. studied neurohormonal activation among patients with left ventricular dysfunction with and without congestive heart failure, which demonstrated plasma norepinephrine, plasma AVP, and plasma renin increase as heart failure progresses [55]. Further, the extent of neurohormonal activation is correlated with prognosis of

HF. For example, the Cooperative North Scandinavian Enalapril Survival Study demonstrated that levels of angiotensin, ANP (atrial natriuretic peptide), norepinephrine, and epinephrine were significantly higher in patients who died than those who survived in a study of patients with severe heart failure randomized to treatment with enalapril or placebo [56]. The association between neurohormonal activation and long-term prognosis of HF is well evidenced by studies that demonstrate improvement in cardiac function and reduced mortality after administration of inhibition of neurohormonal activation in patients with HF. In the Metoprolol CR/XL Randomised Intervention Trial in-Congestive Heart Failure (MERIT-HF) study, metrolol, a beta blocker, given once daily in addition to optimum standard therapy improved survival of patients with chronic heart failure [57]. β-blockade is thought to suppress many deleterious hemodynamic and metabolic effects of SNS and at least partially interfere with the RAAS in patients with HF [58]. Analogously, ACE inhibitors and angiotensin II receptor blockers suppress neurohormonal activation by inhibiting the effects of angiotensin.

It is important to note that inflammatory and neurohormonal activation in HF progression are not independent processes. Studies have demonstrated that angiotensin II has significant proinflammatory effects in the vascular wall, inducing activation of leukocytes and synthesis of adhesion molecules, ROS, and inflammatory cytokines, which facilitate in endothelial dysfunction and vascular inflammation [59]. Further, activation of the SNS primarily suppresses the activity of the innate immune system while it modulate the cells of the acquired immune system [60]. Gurantz et al. demonstrated that TNF-α and IL-1 are directly related to increasing angiotensin II receptor density in the myocardium [30]. Further interplay between these two systems is further detailed in pre-clinical animal studies, suggesting a complex process that needs to be better understood.

Clinical Disease

Heart failure can either be acute or chronic, and is characterized by inability of the ventricle to fill with or eject blood. The inability leads to decreased cardiac output that can no longer meet the body's nutritional demands. Moreover, blood backs up and becomes congested in the lungs, liver, and systemic circulation. This leads to a variety of symptoms: dyspnea, orthopnea, paroxysmal or intermittent nocturnal dyspnea, fatigue, cyanosis, and edema. As described in previous sections, activation of neurohormonal and inflammatory systems occurs both in response to heart failure in the body's attempt to restore blood pressure and blood volume and thus, cardiac output.

The most common cause of heart failure is coronary artery disease, accounting for nearly 70 percent of heart failure cases [61]. It has become even more important now that improvements in the treatment of acute MI with reperfusion therapy have led to increased survivors. A combination of factors, including ischemia, infarct size, ventricular remodeling, mechanical stress, cardiomyocyte death contribute to

global cardiac dysfunction and heart failure [62]. Outside of coronary artery disease, heart failure is also associated with uncontrolled hypertension, alcohol abuse, drug abuse, hyperthyroidism, and abnormalities of the heart valves. Viral infection and myocarditis are also associated with heart failure, although they are rare causes. Here we discuss the inflammatory etiologies behind the pathogenesis of these clinical diseases, and discuss their relationship to anemia, cardiac cachexia, pulmonary hypertension and systemic inflammation.

Clinical Etiologies for Inflammation in Heart Failure

Essential hypertension is another common yet unrecognized cause of heart failure that leads to a pro-inflammatory state. In essential hypertension, there is increased afterload on the heart due to increased peripheral vascular resistance. These changes often modulate mechanical and immunogenic factors that lead to endothelial dysfunction, media growth, ECM deposition, and inflammation. In animal models of hypertension, evidence of inflammation has been found in the vessels of the vasculature. Furthermore, C-reactive protein (CRP) and IL-6 are also associated with vascular lesions in hypertension and associated with impaired cardiovascular outcomes [63]. In other experimental models and humans, pro-inflammatory cytokines related to the RAAS system have been implicated in hypertensive vessels, further corroborating this process. Thus, inflammation is an underlying cause of both hypertension that ultimately precipitates in heart failure [64].

Another cause of heart failure is alcoholic cardiomyopathy, which presents with a dilated cardiomyopathy. Often times, this cardiomyopathy is reversible with complete abstinence from alcohol. In this disease, alcohol precipitates a chronic inflammatory process that can potentially contribute to heart failure. Studies have shown that there are high levels of pro-inflammatory cytokines in patients with alcoholic liver disease [65]. Moreover, the genetic makeup of pro and anti-inflammatory cytokines in humans has been closely associated with the development of alcohol-related diseases. In these situations, chronic alcohol use actually precipitates chronic inflammation through lipopolysaccharides (LPS), a bacterial component, through transmigration in the gut. In the healthy individual, LPS is detoxified and is prevented from inducing a systemic inflammatory response. However, in the chronic alcoholic, the liver dysfunction leads to a systemic response to LPS, leading to pro-immunogenic signals like TNF-α and TLR stimulation, which are also two of the previously described inflammatory mediators in the progression of heart failure [66].

Thyroid hormone disarray has been closely linked to heart failure, both in hyper and hypothyroid states. In patients with pre-existing heart disease, hyperthyroid states can exacerbate poor contractility and output. Hyperthyroidism can also independently decrease ventricular contractility through sustained sinus tachycardia or atrial fibrillation. Oppositely, low thyroid hormone levels alter cardiac gene expression and increases systemic vascular resistance, precipitating heart failure [67].

Although thyroid dysfunction directly affects the heart, many etiologies for thyroid dysfunction are immune in nature. For example, Hashimoto's thyroiditis and other auto-immune thyroiditis diseases are precipitates by imbalances in humoral and cell-mediated immune responses, leading to pro-inflammatory conditions that mimic some of the systemic inflammatory signs observed in heart failure. One such example is IL-6, which is found to play a significant role in the pathogenesis of Hashimoto's thyroiditis, and is also a cytokine found to be responsible for heart failure progression [68].

Heart valve dysfunction leads directly to heart failure by altering the pressure volume relationships in the heart and exacerbating remodeling. Recent studies have shown that there may be a role of inflammation between heart valve dysfunction and cardiac failure. For example, stenotic aortic valves are often found to exhibit significant infiltration from mononuclear inflammatory cells [69]. Other signs of inflammation have been found in rheumatic and non-rheumatic causes of valvular dysfunction [70], suggesting the potential link to the inflammation in heart failure.

Myocarditis is a disease that is completely inflammatory in etiology that leads to heart failure. It is characterized by inflammatory infiltrates in the myocardium. Myocarditis is either infectious or autoimmune in nature, and much of what is known has been elucidated from experimental models suggesting the role for pro-inflammatory cytokines and various cell-mediated responses. The most common etiology is coxsackievirus B3 (CVB3), which progresses to a chronic myocarditis leading to heart failure in genetically susceptible individuals. On a molecular level, CVB3 has been shown to both directly cause cell death. Moreover, it has been observed that for certain subtypes of CVB3, some myocytes recover due to an immune response, specifically through NK cells, antibodies, macrophages, T cells, interferon-α, and interferon-β. Thus, immune response that succeeds infection with CVB3 is important in preventing direct cell death and necrosis of myocardial tissue in response to replicating virus. However, it is important to note that inflammation induced against CVB3 infection may also lead to autoimmunity, thus resulting in detrimental effects. In similar experiments, Neu et al. [71] found that autoantibodies were formed in response to cardiac myosin after CVB3 infection. Autoantibodies (humoral) to other proteins including antinucleotide translocator (ANT), branched chain ketoacidic dehydrogenase, and extracellular matrix proteins were also found in further mouse models of myocarditis, which were also detected in the serum of human myocarditis patients.

Inflammation and Heart Failure Clinical Syndromes

To understand the role of inflammation in the body, it is important to understand its role in precipitating the clinical syndromes found in anemia, cachexia, pulmonary hypertension and systemic inflammation.

Anemia is found in one third of cases, and is often times related to kidney insufficiency present in approximately one half of heart failure and commonly precipitated

by renal vasoconstriction and ischemia. Consequently, the kidney is unable to produce erythropoietin (EPO) to sufficient levels, thus causing anemia. Anemia can also be directly caused by the immune system, as recent studies show. For example, excessive production of TNF-α and IL-6 in CHF can cause reduced EPO secretion and even interfere with the ability for EPO to signal within the bone marrow. These cytokines have been shown to inhibit EPO production on the transcriptional and transductional level [72]. Moreover, these pro-inflammatory cytokines also reduce iron supply in the bone marrow. Hepcidin, a peptide hormone that is made in the liver and coordinates iron metabolism, also serves as a link between anemia and inflammation. During highly inflammatory processes, hepcidin increases at the cytokine level, corresponding to release of CRP and amyloid protein. Anemia induces progression of cardiac function not only by causing tachycardic stress and increased volume, but also by reducing renal blood flow and fluid retention. Anemia is also found to be more commonly associated with mortality in heart failure [73, 74].

In cachexia, body wasting is commonly thought to be related to heart failure and is related to reduced LVEF. It is also associated with generalized loss of tissue, including fat and bone from reduced total mass. There is increasing information that neurohormonal and immune abnormalities contribute to this clinical progress. For example, cardiac cachexia is related to plasma levels of inflammatory cytokines, such as TNF-α. Moreover, it has also been related to neuroendocrine activation leading to a tipping of the scale towards catabolic process vs anabolic process [75]. Pro-inflammatory cytokines are also playing an important role in maintaining the catabolic processes. For example, TNF-α increases expression of a catabolic hormone leptin and IL-1 reduced neuropeptide Y, both of are involved in catabolic events. Endotoxin and cytokines induce expression of leptin, TNF-α contributes to obesity-related hyperleptinemia, while IL-1 effects on the CNS leads to release of neuropeptide Y. Decreased bowel perfusion due to the heart failure and dietary deficiencies have also been observed to play a role. Moreover, IL-6 activation requires an excess of essential amino acids, leading to catabolism of skeletal muscle mass. TNF-α also activates protein breakdown in striated muscle and leads to a wasting process [76].

Resultant decreased blood oxygen from decreased cardiac output and anemia can cause hypoxic vasoconstriction in the pulmonary circulation. Moreover, the neurohormonal activation can further corroborate this, leading to pulmonary hypertension and often times right-sided heart failure. Moreover, increased blood in area of the pulmonary arterial wall triggers inflammation [77], contributing to fatigue and dyspnea. Monocytes and macrophages are found in pulmonary lesions, activating IL-6 and IL-10 as well as presenting antigens to T cells. These plaques found in pulmonary hypertension contribute to the clinical syndrome of pulmonary hypertension in heart failure and contribute to symptoms of edema. TNF-α, for example, ameliorate pulmonary pressure and has been shown significantly higher levels in pulmonary hypertensive states [78].

CRP levels are frequently elevated in heart failure, and commonly plays a role in also contributing to the pathogenesis of comorbid diseases such as COPD. Moreover, there are specific roles in a continuum between the heart and lung, which are related

to CRP and IL-6, called the cardiopulmonary continuum. Moreover, autoantigens and oxidized LDL trigger activation of T-cells, macrophages, and mast cells leading to IFN-γ and TNF-α secretion, also activating MMPs. TNF-α is very important in the cardiopulmonary phenomenon. CRP is elevated by TNF-α and IL-6, which can then continue to worsen atherosclerotic levels and can increase fibrinogen and increase prothrombotic risk [79].

References

1. Stewart S, MacIntyre K, Capewell S, McMurray JJ. Heart failure and the aging population: an increasing burden in the 21st century? Heart. 2003;89(1):49–53 http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=1767504&tool=pmcentrez&rendertype=abstract. Accessed 3 Jan 2016.
2. Mosterd A, Hoes AW. Clinical epidemiology of heart failure. Heart. 2007;93(9):1137–46. doi:10.1136/hrt.2003.025270.
3. Patten RD, Hall-Porter MR. Small animal models of heart failure: development of novel therapies, past and present. Circ Heart Fail. 2009;2(2):138–44. doi:10.1161/CIRCHEARTFAILURE.108.839761.
4. Pacher P, Nagayama T, Mukhopadhyay P, Bátkai S, Kass DA. Measurement of cardiac function using pressure-volume conductance catheter technique in mice and rats. Nat Protoc. 2008;3(9):1422–34. doi:10.1038/nprot.2008.138.
5. Monnet E, Chachques JC. Animal models of heart failure: what is new? Ann Thorac Surg. 2005;79(4):1445–53. doi:10.1016/j.athoracsur.2004.04.002.
6. Opie LH, Commerford PJ, Gersh BJ, Pfeffer MA. Controversies in ventricular remodelling. Lancet (London, England). 2006;367(9507):356–67. doi:10.1016/S0140-6736(06)68074-4.
7. Nagayama T, Hsu S, Zhang M, et al. Sildenafil stops progressive chamber, cellular, and molecular remodeling and improves calcium handling and function in hearts with pre-existing advanced hypertrophy caused by pressure overload. J Am Coll Cardiol. 2009;53(2):207–15. doi:10.1016/j.jacc.2008.08.069.
8. Litwin SE, Katz SE, Weinberg EO, et al. Serial echocardiographic-Doppler assessment of left ventricular geometry and function in rats with pressure-overload hypertrophy. Chronic angiotensin-converting enzyme inhibition attenuates the transition to heart failure. Circulation 1995;91(10):2642–54. http://www.ncbi.nlm.nih.gov/pubmed/7743628. Accessed 26 Nov 2015.
9. Ganguly PK, Lee SL, Beamish RE DN. Altered sympathetic system and adrenoceptors during the development of cardiac hypertrophy. SciCurve. http://scicurve.com/paper/2476018. Accessed 3 Jan 2016.
10. Hiyoshi H, Yayama K, Takano M, Okamoto H. Stimulation of cyclic GMP production via AT2 and B2 receptors in the pressure-overloaded aorta after banding. Hypertension. 2004;43(6):1258–63. doi:10.1161/01.HYP.0000128022.24598.4f.
11. Kim H-L, Kim Y-J, Kim K-H, et al. Therapeutic effects of udenafil on pressure-overload cardiac hypertrophy. Hypertens Res. 2015;38(9):597–604. doi:10.1038/hr.2015.46.
12. Ryan TD, Rothstein EC, Aban I, et al. Left ventricular eccentric remodeling and matrix loss are mediated by bradykinin and precede cardiomyocyte elongation in rats with volume overload. J Am Coll Cardiol. 2007;49(7):811–21. doi:10.1016/j.jacc.2006.06.083.
13. Brower GL, Chancey AL, Thanigaraj S, et al. Cause and effect relationship between myocardial mast cell number and matrix metalloproteinase activity. Am J Physiol Heart Circ Physiol. 2002;283(2):H518–25. doi:10.1152/ajpheart.00218.2000.
14. Stumpe KO, Sölle H, Klein H, Krück F. Mechanism of sodium and water retention in rats with experimental heart failure. Kidney Int 1973;4(5):309–17. http://www.ncbi.nlm.nih.gov/pubmed/4762578. Accessed 3 Jan 2016.

15. Garcia R, Diebold S. Simple, rapid, and effective method of producing aortocaval shunts in the rat. Cardiovasc Res 1990;24(5):430–2. http://www.ncbi.nlm.nih.gov/pubmed/2142618. Accessed 3 Jan 2016.
16. Pu M, Gao Z, Li J, Sinoway L, Davidson WR. Development of a new animal model of chronic mitral regurgitation in rats under transesophageal echocardiographic guidance. J Am Soc Echocardiogr. 2005;18(5):468–74. doi:10.1016/j.echo.2004.10.005.
17. Kim K-H, Kim Y-J, Ohn J-H, et al. Long-term effects of sildenafil in a rat model of chronic mitral regurgitation: benefits of ventricular remodeling and exercise capacity. Circulation. 2012;125(11):1390–401. doi:10.1161/CIRCULATIONAHA.111.065300.
18. Pfeffer MA, Pfeffer JM, Fishbein MC, et al. Myocardial infarct size and ventricular function in rats. Circ Res 1979;44(4):503–12. http://www.ncbi.nlm.nih.gov/pubmed/428047. Accessed 3 Jan 2016.
19. Vandervelde S, van Amerongen MJ, Tio RA, et al. Increased inflammatory response and neovascularization in reperfused vs. non-reperfused murine myocardial infarction. Cardiovasc Pathol. 2006;15(2):83–90. doi:10.1016/j.carpath.2005.10.006.
20. Popović ZB, Benejam C, Bian J, et al. Speckle-tracking echocardiography correctly identifies segmental left ventricular dysfunction induced by scarring in a rat model of myocardial infarction. Am J Physiol Heart Circ Physiol. 2007;292(6):H2809–16. doi:10.1152/ajpheart.01176.2006.
21. Kokubo M, Uemura A, Matsubara T, Murohara T. Noninvasive evaluation of the time course of change in cardiac function in spontaneously hypertensive rats by echocardiography. Hypertens Res. 2005;28(7):601–9. doi:10.1291/hypres.28.601.
22. Watson LE, Sheth M, Denyer RF, Dostal DE. Baseline echocardiographic values for adult male rats. J Am Soc Echocardiogr. 2004;17(2):161–7. doi:10.1016/j.echo.2003.10.010.
23. Reffelmann T, Kloner RA. Transthoracic echocardiography in rats. Evalution of commonly used indices of left ventricular dimensions, contractile performance, and hypertrophy in a genetic model of hypertrophic heart failure (SHHF-Mcc-facp-Rats) in comparison with Wistar rats during. Basic Res Cardiol. 2003;98(5):275–84. doi:10.1007/s00395-003-0401-3.
24. Badea CT, Bucholz E, Hedlund LW, et al. Imaging methods for morphological and functional phenotyping of the rodent heart. Toxicol Pathol. 2006;34(1):111–7.
25. Herold V, Parczyk M, Mörchel P, et al. In vivo measurement of local aortic pulse-wave velocity in mice with MR microscopy at 17.6 Tesla. Magn Reson Med. 2009;61(6):1293–9. doi:10.1002/mrm.21957.
26. Guazzi M, Brenner DA, Apstein CS, Saupe KW. Exercise intolerance in rats with hypertensive heart disease is associated with impaired diastolic relaxation. Hypertension 2001;37(2):204–8. http://www.ncbi.nlm.nih.gov/pubmed/11230272. Accessed 3 Jan 2016.
27. Rolim NPL, Mattos KC, Brum PC, et al. The decreased oxygen uptake during progressive exercise in ischemia-induced heart failure is due to reduced cardiac output rate. Braz J Med Biol Res. 2006;39(2):297–304. doi:10.1590/S0100-879X2006000200018.
28. Oikonomou E, Tousoulis D, Siasos G, et al. The role of inflammation in heart failure: new therapeutic approaches. Hellenic J Cardiol. 2011;52(1):30–40. http://www.ncbi.nlm.nih.gov/pubmed/21292605. Accessed 8 Nov 2015.
29. Seta Y, Shan K, Bozkurt B, et al. Basic mechanisms in heart failure: the cytokine hypothesis. J Card Fail 1996;2(3):243–9. http://www.ncbi.nlm.nih.gov/pubmed/8891862. Accessed 8 Nov 2015.
30. Gurantz D, Cowling RT, Varki N, et al. IL-1beta and TNF-alpha upregulate angiotensin II type 1 (AT1) receptors on cardiac fibroblasts and are associated with increased AT1 density in the post-MI heart. J Mol Cell Cardiol. 2005;38(3):505–15. doi:10.1016/j.yjmcc.2004.12.015.
31. Yndestad A, Damås JK, Øie E, et al. Role of inflammation in the progression of heart failure. Curr Cardiol Rep 2007;9(3):236–41. http://www.ncbi.nlm.nih.gov/pubmed/17470337. Accessed 8 Nov 2015.
32. Damås JK, Gullestad L, Aass H, et al. Enhanced gene expression of chemokines and their corresponding receptors in mononuclear blood cells in chronic heart failure–modulatory effect

of intravenous immunoglobulin. J Am Coll Cardiol 2001;38(1):187–93. http://www.ncbi.nlm.nih.gov/pubmed/11451272. Accessed 8 Nov 2015.
33. Yndestad A, Damås JK, Oie E, et al. Systemic inflammation in heart failure–the whys and wherefores. Heart Fail Rev. 2006;11(1):83–92. doi:10.1007/s10741-006-9196-2.
34. Torre-Amione G, Kapadia S, Benedict C, et al. Proinflammatory cytokine levels in patients with depressed left ventricular ejection fraction: a report from the Studies of Left Ventricular Dysfunction (SOLVD). J Am Coll Cardiol. 1996;27(5):1201–6. doi:10.1016/0735-1097(95)00589-7.
35. Mann DL. Inflammatory mediators and the failing heart: past, present, and the foreseeable future. Circ Res 2002;91(11):988–98. http://www.ncbi.nlm.nih.gov/pubmed/12456484. Accessed 8 Nov 2015.
36. Cohn JN, Ferrari R, Sharpe N. Cardiac remodeling—concepts and clinical implications: a consensus paper from an international forum on cardiac remodeling. J Am Coll Cardiol. 2000;35(3):569–82. doi:10.1016/S0735-1097(99)00630-0.
37. Valgimigli M, Ceconi C, Malagutti P, et al. Tumor necrosis factor-alpha receptor 1 is a major predictor of mortality and new-onset heart failure in patients with acute myocardial infarction: the Cytokine-Activation and Long-Term Prognosis in Myocardial Infarction (C-ALPHA) study. Circulation. 2005;111(7):863–70. doi:10.1161/01.CIR.0000155614.35441.69.
38. Hamid T, Gu Y, Ortines RV, et al. Divergent tumor necrosis factor receptor-related remodeling responses in heart failure: role of nuclear factor-kappaB and inflammatory activation. Circulation. 2009;119(10):1386–97. doi:10.1161/CIRCULATIONAHA.108.802918.
39. Su D, Li Z, Li X, et al. Association between serum interleukin-6 concentration and mortality in patients with coronary artery disease. Mediators Inflamm. 2013;2013:726178. doi:10.1155/2013/726178.
40. Askevold ET, Gullestad L, Dahl CP, et al. Interleukin-6 signaling, soluble glycoprotein 130, and inflammation in heart failure. Curr Heart Fail Rep. 2014;11(2):146–55. doi:10.1007/s11897-014-0185-9.
41. Fuchs M, Hilfiker A, Kaminski K, et al. Role of interleukin-6 for LV remodeling and survival after experimental myocardial infarction. FASEB J. 2003;17(14):2118–20. doi:10.1096/fj.03-0331fje.
42. Bujak M, Frangogiannis NG. The role of IL-1 in the pathogenesis of heart disease. Arch Immunol Ther Exp (Warsz). 2009;57(3):165–76. doi:10.1007/s00005-009-0024-y.
43. Abbate A, Salloum FN, Vecile E, et al. Anakinra, a recombinant human interleukin-1 receptor antagonist, inhibits apoptosis in experimental acute myocardial infarction. Circulation. 2008;117(20):2670–83. doi:10.1161/CIRCULATIONAHA.107.740233.
44. Anker SD, von Haehling S. Inflammatory mediators in chronic heart failure: an overview. Heart. 2004;90(4):464–70 http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=1768165&tool=pmcentrez&rendertype=abstract. Accessed 8 Nov 2015.
45. Mann DL. Innate immunity and the failing heart: the cytokine hypothesis revisited. PubMed – NCBI. http://proxy.library.upenn.edu:2080/pubmed?otool=upennlib&term=25814686. Accessed 8 Nov 2015.
46. Hofmann U, Heuer S, Meder K, et al. The proinflammatory cytokines TNF-alpha and IL-1 beta impair economy of contraction in human myocardium. Cytokine. 2007;39(3):157–62. doi:10.1016/j.cyto.2007.07.185.
47. Van Tassell BW, Raleigh JMV, Abbate A. Targeting interleukin-1 in heart failure and inflammatory heart disease. Curr Heart Fail Rep. 2015;12(1):33–41. doi:10.1007/s11897-014-0231-7.
48. Satoh M, Shimoda Y, Maesawa C, et al. Activated toll-like receptor 4 in monocytes is associated with heart failure after acute myocardial infarction. Int J Cardiol. 2006;109(2):226–34. doi:10.1016/j.ijcard.2005.06.023.
49. Knuefermann P, Vallejo J, Mann DL. The role of innate immune responses in the heart in health and disease. Trends Cardiovasc Med 2004;14(1):1–7. http://www.ncbi.nlm.nih.gov/pubmed/14720467. Accessed 8 Nov 2015.

50. Bradham WS, Bozkurt B, Gunasinghe H, et al. Tumor necrosis factor-alpha and myocardial remodeling in progression of heart failure: a current perspective. Cardiovasc Res 2002;53(4):822–30. http://www.ncbi.nlm.nih.gov/pubmed/11922892. Accessed 15 Oct 2015.
51. Sigurdsson A, Swedberg K. The role of neurohormonal activation in chronic heart failure and postmyocardial infarction. Am Heart J. 1996;132(1 Pt 2 Su):229–34. http://www.ncbi.nlm.nih.gov/pubmed/8677861. Accessed 8 Nov 2015.
52. Chatterjee K. Neurohormonal activation in congestive heart failure and the role of vasopressin. Am J Cardiol. 2005;95(9A):8B–13B. doi:10.1016/j.amjcard.2005.03.003.
53. Jackson G, Gibbs CR, Davies MK, Lip GY. ABC of heart failure. Pathophysiology. BMJ 2000;320(7228):167–70. http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=1128747&tool=pmcentrez&rendertype=abstract. Accessed 8 Nov 2015.
54. Weber KT, Janicki JS. Angiotensin and the remodelling of the myocardium. Br J Clin Pharmacol. 1989;28 Suppl 2:141S–9S; discussion 149S–150S. http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=1379855&tool=pmcentrez&rendertype=abstract. Accessed 8 Nov 2015.
55. Francis GS, Benedict C, Johnstone DE, et al. Comparison of neuroendocrine activation in patients with left ventricular dysfunction with and without congestive heart failure. A substudy of the Studies of Left Ventricular Dysfunction (SOLVD). Circulation 1990;82(5):1724–9. http://www.ncbi.nlm.nih.gov/pubmed/2146040. Accessed 8 Nov 2015.
56. Swedberg K, Eneroth P, Kjekshus J, Wilhelmsen L. Hormones regulating cardiovascular function in patients with severe congestive heart failure and their relation to mortality. CONSENSUS Trial Study Group. Circulation 1990;82(5):1730–6. http://www.ncbi.nlm.nih.gov/pubmed/2225374. Accessed 8 Nov 2015.
57. MERIT-HF Study Group. Effect of metoprolol CR/XL in chronic heart failure: Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF). Lancet 1999;353(9169):2001–7. http://www.ncbi.nlm.nih.gov/pubmed/10376614. Accessed 7 May 2015.
58. Packer M, Lee WH, Kessler PD, et al. Role of neurohormonal mechanisms in determining survival in patients with severe chronic heart failure. Circulation 1987;75(5 Pt 2):IV80–92. http://www.ncbi.nlm.nih.gov/pubmed/2882867. Accessed 8 Nov 2015.
59. Brasier AR, Recinos A, Eledrisi MS. Vascular inflammation and the renin-angiotensin system. Arterioscler Thromb Vasc Biol 2002;22(8):1257–66. http://www.ncbi.nlm.nih.gov/pubmed/12171785. Accessed 8 Oct 2015.
60. Nance DM, Sanders VM. Autonomic innervation and regulation of the immune system (1987-2007). Brain Behav Immun. 2007;21(6):736–45. doi:10.1016/j.bbi.2007.03.008.
61. Gheorghiade M, Bonow RO. Chronic heart failure in the United States: a manifestation of coronary artery disease. Circulation 1998;97(3):282–9. http://www.ncbi.nlm.nih.gov/pubmed/9462531. Accessed 8 Nov 2015.
62. Minicucci MF, Azevedo PS, Polegato BF, et al. Heart failure after myocardial infarction: clinical implications and treatment. Clin Cardiol. 2011;34(7):410–4. doi:10.1002/clc.20922.
63. Pauletto P, Rattazzi M. Inflammation and hypertension: the search for a link. Nephrol Dial Transplant. 2006;21(4):850–3. doi:10.1093/ndt/gfl019.
64. Savoia C, Schiffrin EL. Inflammation in hypertension. Curr Opin Nephrol Hypertens. 2006;15(2):152–8. doi:10.1097/01.mnh.0000203189.57513.76.
65. McClain CJ, Barve S, Deaciuc I, et al. Cytokines in alcoholic liver disease. Semin Liver Dis. 1999;19(2):205–19. doi:10.1055/s-2007-1007110.
66. Wang HJ, Zakhari S, Jung MK. Alcohol, inflammation, and gut-liver-brain interactions in tissue damage and disease development. World J Gastroenterol 2010;16(11):1304–13. http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=2842521&tool=pmcentrez&rendertype=abstract. Accessed 8 Nov 2015.
67. Schmidt-Ott UM, Ascheim DD. Thyroid hormone and heart failure. Curr Heart Fail Rep 2006;3(3):114–9. http://www.ncbi.nlm.nih.gov/pubmed/16914103. Accessed 8 Nov 2015.
68. Figueroa-Vega N, Alfonso-Pérez M, Benedicto I, et al. Increased circulating pro-inflammatory cytokines and Th17 lymphocytes in Hashimoto's thyroiditis. J Clin Endocrinol Metab. 2010;95(2):953–62. doi:10.1210/jc.2009-1719.

69. Wallby L, Lars W, Steffensen T, et al. Role of inflammation in nonrheumatic, regurgitant heart valve disease. A comparative, descriptive study regarding apolipoproteins and inflammatory cells in nonrheumatic heart valve disease. Cardiovasc Pathol. 2007;16(3):171–8. doi:10.1016/j.carpath.2006.10.004.
70. Wallby L. Signs of inflammation in different types of heart valve disease: The VOCIN study. http://urn.kb.se/resolve?urn=urn:nbn:se:liu:diva-11330. Accessed 8 Nov 2015.
71. Neu N, Rose NR, Beisel KW, et al. Cardiac myosin induces myocarditis in genetically predisposed mice. J Immunol 1987;139(11):3630–6. http://www.jimmunol.org/content/139/11/3630.abstract. Accessed 8 Nov 2015.
72. Jelkmann W. Proinflammatory cytokines lowering erythropoietin production. J Interferon Cytokine Res 1998;18(8):555–59. http://www.ncbi.nlm.nih.gov/pubmed/9726435. Accessed 8 Nov 2015.
73. Silverberg DS, Wexler D, Iaina A. The role of anemia in the progression of congestive heart failure. Is there a place for erythropoietin and intravenous iron? J Nephrol. 2004;17(6):749–61. http://www.ncbi.nlm.nih.gov/pubmed/15593047. Accessed 8 Nov 2015.
74. Caramelo C, Just S, Gil P. Anemia in heart failure: pathophysiology, pathogenesis, treatment, and incognitae. Rev Española Cardiol (English Ed). 2007;60(8):848–60. doi:10.1016/S1885-5857(08)60029-8.
75. Anker SD, Sharma R. The syndrome of cardiac cachexia. Int J Cardiol 2002;85(1):51–66. http://www.ncbi.nlm.nih.gov/pubmed/12163209. Accessed 8 Nov 2015.
76. von Haehling S, Genth-Zotz S, Anker SD, Volk HD. Cachexia: a therapeutic approach beyond cytokine antagonism. Int J Cardiol 2002;85(1):173–83. http://www.ncbi.nlm.nih.gov/pubmed/12163222. Accessed 8 Nov 2015.
77. Gursoy M, Salihoglu E, Hatemi AC, et al. Inflammation and congenital heart disease associated pulmonary hypertension. Heart Surg Forum 2015;18(1):E38–41. http://www.ncbi.nlm.nih.gov/pubmed/25881225. Accessed 8 Nov 2015.
78. Groth A, Vrugt B, Brock M, et al. Inflammatory cytokines in pulmonary hypertension. Respir Res. 2014;15:47. doi:10.1186/1465-9921-15-47.
79. Ukena C, Mahfoud F, Kindermann M, et al. The cardiopulmonary continuum systemic inflammation as “common soil” of heart and lung disease. Int J Cardiol. 2010;145(2):172–6. doi:10.1016/j.ijcard.2010.04.082.

Index

H. Eisen (ed.), *Heart Failure*, DOI 10.1007/978-1-4471-4219-5

F

G

H

Q

T

W