Wolfgang Krüger

Acute Heart Failure

Putting the Puzzle of Pathophysiology and Evidence Together in Daily Practice

Second Edition

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Foreword to the Second Edition

Since the publication of the first edition in 2009, quite a substantial amount of new insights in the pathobiology of acute heart failure have been gained. This second edition incorporates these new findings and integrates them into the "big puzzle" and concept of acute heart failure syndromes. Indeed, we have not only discovered more details about this syndrome but this new knowledge substantially helps us to understand the overall context of this malady. The new views may hopefully open ways to develop new and better therapeutic strategies, particularly for patients with heart failure and preserved ejection fraction where a scientifically based effective treatment could not yet be established.

Aarau, Switzerland — Wolfgang Krüger

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Extraordinary thanks appertain to my sons Lenn and Finn for their invaluable editorial input and help with the chapter drawings and figures.

I have a profound appreciation of the understanding and patience of my wife Manuela for letting me write this edition.

Contents

Abbreviations

A II	Angiotension II
ACCP	American College of Chest Physicians
ACS	Acute coronary syndrome
AF	Atrial fibrillation
AHA	American Heart Association
AHF	Acute heart failure
AHFS	Acute heart failure syndromes
AKI	Acute kidney injury
AMI	Acute myocardial infarction
AR	Aortic valve regurgitation
ARBs	Angiotension receptor blockers
ARDS	Acute respiratory distress syndrome
ATN	Acute tubular necrosis
BMI	Body mass index
BNP	Brain natriuretic peptide
BP	Blood pressure
BUN	Blood urea nitrogen
CAD	Coronary artery disease
CF	Cardiac function
cGMP	Cyclic guanosine monophosphate
CI	Cardiac index
CO	Cardiac output
COPD	Chronic obstructive lung disease
CPI	Cardiac power index
CPO	Cardiac power output
CPP	Coronary perfusion pressure
CRS	Cardio-renal syndrome
CS	Cardiogenic shock
CVP	Central venous pressure
DD	Diastolic dysfunction
DOB	Dobutamine
dp/dt	Change in (left) ventricular pressure per time
DPG	Diastolic pressure gradient (or difference)
DVI	Diastolic ventricular interaction

Ea	Effective arterial elastance
ECM	Extracellular matrix
ED	Endothelial dysfunction
Ees	End-systolic chamber elastance
EF	Ejection fraction; ejection fraction of the left ventricle mainly named EF, but sometimes also LV-EF; RV-EF (ejection fraction right ventricle)
ESC	European Society of Cardiology
ESV	End-systolic volume
EVLW(I)	Extra vascular lung water (index)
FS	Fractional shortening
GEDV	Global end diastolic volume
GFR	Glomerular filtration rate
HF	Heart failure
HFpEF	Heart failure with preserved EF
HFrEF	Heart failure with reduced EF
HHD	Hypertensive heart disease
HR	Heart rate
HTN	Hypertension
ICP	Intracerebral pressure
IHD	Ischemic heart disease
IL-6	Interleukin 6
IR	Insulin resistance
ITBV(I)	Intrathoracic blood volume (index)
IVS	Interventricular septum
i.v.	intravenous
LA	Left atrium
LA-P	Left atrial pressure
LAVI	Left atrial volume index
LEVO	Levosimendan
LHD	Left heart disease
LV	Left ventricle
LVEDA	Left ventricular end-diastolic area
LVEDD	Left ventricular end-diastolic diameter
LVEDP	Left ventricular end diastolic pressure; also called intracavitary LVEDP
LVESP	End-systolic left ventricular pressure
LVESV	End-systolic left ventricular volume
LV-H	Left ventricular hypertrophy
LVMI	Left ventricular muscle mass index
LVOT	Left ventricular outflow tract
LMWH	Low molecular weight heparin
MAP	Mean arterial (blood) pressure
mPAP	Mean pulmonary arterial pressure
MR	Mitral valve regurgitation

NA	Noradrenaline, also called norepinephrine (NE)
NHs	Neurohormonal systems
NO	Nitric oxide
NT-pro BNP	N-terminal pro b-type natriuretic peptide
PA	Pulmonary artery
PAH	Pulmonary arterial hypertension
PAP	Pulmonary artery pressure
mPAP	mean pulmonary artery pressure
PBV	Pulmonary blood volume
PCWP	Pulmonary capillary wedge pressure
PE	Pulmonary embolism
PEEP	Positive end-expiratory pressure
PH	Pulmonary hypertension
PKG	Proteinkinase G
PLR	Passive leg raising
PP	Pericardial pressure
PP-V	Pulse pressure variation
P-V relationship	Pressure-volume diagram of the ventricle cycle
PvH	Pulmonary venous hypertension
PvP	Pulmonary venous pressure
PVPI	Pulmonary venous permeability index
PVR	Pulmonary vascular resistance
RA	Right atrium
RAAS	Renin-angiotensin-aldosterone system
RA-P	Right atrial pressure
RBF	Renal blood flow
RCA	Right coronary artery
RHF	Right heart failure
ROS	Reactive oxygen species
RV	Right ventricle
RV-F	Right ventricular failure
RV-AMI	Acute myocardial infarction of the right ventricle
RV-D	Right ventricular dysfunction
RVEDD	Right ventricular end-diastolic diameter
RVEDP	Right ventricular end diastolic pressure
RVEDV	Right ventricular end diastolic volume
sBP	Systolic blood pressure
s.c.	subcutaneous (injection)
$ScvO_2$	Central venous oxygen saturation (central vein, i.e. vena cava inferior)
SIR	Systemic inflammatory response
SIRS	Systemic inflammatory response syndrome
SP-V	Systolic pressure variation
SV(I)	Stroke volume (index)
SvO_2	Mixed venous oxygen saturation (pulmonary artery)

SVR(I/i)	Systemic vascular resistance (index)
SV-V	Stroke volume variation
SW(I)	Stroke work (index)
TGF	Tubuloglomerular feedback
TNF_{α}	Tumor necrosis factor α
TPG	Transpulmonary pressure gradient
TPR	Total peripheral resistance (which is the same as SVR)
UO	Urinary output
v-a-coupling	Ventriculo-arterial coupling
VT	Ventricular tachycardia
WU	Wood unit (dyn s cm^{-2})

Cardiac Physiology and Acute Heart Failure Syndromes

1

1.1 Cardiac Performance

Cardiac performance depends on a wide variety of factors, of which preload, afterload, heart rate, and contractility are the best recognised (Fig. 1.1). However, other factors play important roles but are less acknowledged. The diastolic ventricular interaction (DVI) and its impact on preload, the preload recruitable stroke-work,

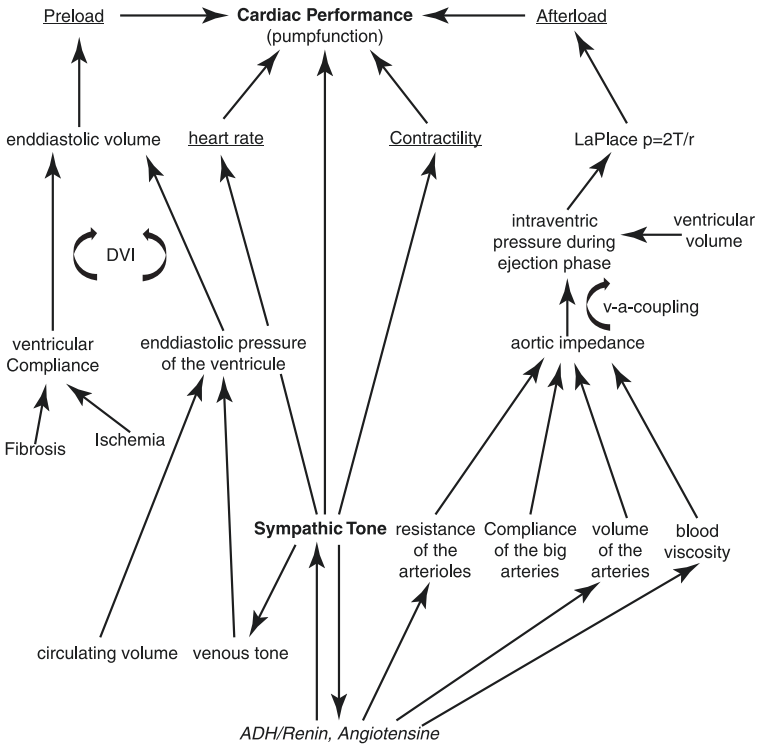

Fig. 1.1 The modified diagram by Gould and Reddy, "Vasodilator Therapy for Cardiac Disorders", Futura, Mount Kisco, New York, 1979, pp 1-6, illustrates the complex interplay of factors affecting cardiac performance. With permission

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ventriculo-arterial coupling and other vascular and ventricular properties, through their interaction at end-systole, all have significant influence on cardiac performance.

1.2 The Fundamental Equation of the Circulation

$$\mathrm{MAP}=\mathrm{CO}\times\mathrm{SVR}\left(\text{Pressure} = \text{Flow}\times\text{Resistance}\right)$$ [1, 2]

The fundamental equation of the circulatory system expresses the basic function of the heart: to generate flow and pressure in order to ensure appropriate perfusion of the body [3, 4].

The systemic peripheral resistance, difficult to determine directly in practice, can be calculated by using the measurable parameters of MAP and CO. However the SVR is not determined by them, **SVR and CO are independent, the MAP is the dependent variable** [5].

Poiseuille's law offers three ways to change blood pressure [6, 7]:

- alter flow,
- alter resistance,
- alter both.

Thus, increased blood flow and/or an increased ratio of resistance/blood flow (SVR/CO) can alter the MAP [8]. If CO and SVR change reciprocally and proportionately, only then will the MAP be unchanged. If CO increases but with a reduction of SVR due to peripheral vasodilatation, MAP will increase if the increase in CO is proportionately higher than the reduction of SVR. In the case of volume loading, increasing CO will lead to an increase in MAP if SVR remains unchanged [5].

Kumar showed that volume loading in **healthy hearts** increases contractility, stroke work, systolic blood pressure, **and MAP** [9]. However, in the heart with compromised contractility, blood pressure might not increase. Michard [10] showed that the increase in SV (flow) depends critically on the contractile abilities of the heart. Thus, if volume loading does not lead to an increase in SV, we should be suspicious of significant heart failure. Furthermore, we should keep in mind that, in heart failure syndromes, the **LV afterload** is the decisive determinant of cardiac performance [11–14]. Therefore, a reduction in afterload by vasodilators is the treatment of choice [15, 16].

As a rule, in **daily clinical practice** in acute heart failure when **lowering peripheral resistance**, the LV end-systolic wall stress will be reduced and the SV will increase, but the MAP will be maintained or will even increase [17–19]. If, under these conditions, the MAP does not increase or at least cannot be maintained, the following circumstances have to be considered:

- severe mitral regurgitation [20–22],
- inappropriate filling of the LV due to DVI [23–25],

- ventriculo-arterial coupling mismatch [26, 27],
- inadequate intravascular volume (relative hypovolaemia) [28, 29]—(seldom).

1.3 Preload

1.3.1 Definition

Preload is defined by Braunwald and Ross [30] as "**the force acting to stretch the left ventricular muscle fibres at the end of diastole and determining the resting length of the sarcomeres**".

Returning venous blood fills the ventricle, exerting force on the heart muscle, stretching the myofibrils [30] and is one of the main determinants of cardiac performance [31–33].

The end-diastolic ventricular volume, or preload, is well reflected by the end-diastolic wall stress (**preload ~ end-diastolic wall stress**) [34].

1.3.2 The Frank–Starling Mechanism

Transmural LVEDP accurately reflects the effective distending pressure responsible for the length of myocardial fibres [35].

Otto Frank [36] and Ernest Starling [37] obtained a relationship between the end-diastolic fibre length and the force of contraction:

With increasing fibre length the force of contraction increases and thus the **LV or RV stroke volume (SV)** [36, 37] **increases** or, more accurately, the stroke work (SW) increases:

$$\text{LV-SW} = \text{SV} \times \left(\text{LVESP} - \text{LVEDP}\right) \text{ [38, 39]}$$

The diastolic ventricular filling is limited by the acutely non-distensible pericardium constraining the filling ventricles and by the cytoskeleton [40–42], thus preventing the ventricles from fluid overload [43, 44] (physiological protective mechanism) as well as from pathological dilatation [41].

With an increase in resting fibre length the velocity of fibre muscle shortening increases as well [45].

Frank [36] established a linear relationship between the left ventricular **end-diastolic volume** (LVEDV) as a correlate of the fibre length and the **force of ventricular contraction** [30, 36, 37, 43].

LV-SV correlates well with LVEDV: **SV ~ LVEDV** [46]

Starling [37] reported an increase in the **contraction force** with increasing atrial **pressures**. Starling's result is similar to that described by Frank, as long as the increase in LVEDP rep-resents a **roportional** increase in LVEDV (linear relationship between LVEDP and LVEDV).This is true in most healthy persons as long as the LVEDP remains within normal ranges, but in the case of high LV

filling pressures and in certain pathological circumstances the rise in LVEDP is often disproportionately high in comparison to the increase in LVEDV [23, 24, 47–49].

The LVEDP may even rise without any increase in LV filling volume, producing no increase in preload, which is essential to recruit a higher SV [23, 39, 42]. Therefore, although the LVEDP rises, there may be no adequate increase in SV; in fact, there may even be a fall corresponding with the 'descending limb' of the Starling curve [35, 37, 39, 50]. This descending limb described by Starling is, however, an artefact of his experimental conditions.

When using the **effective distending pressure** rather than the intra-cavitary pressure the relation between fibre stretch and force of contraction is described adequately and corresponds to Frank's findings and the statement:

The effective distending pressure or **'transmural' LVEDP** is the intracavitary **LVEDP** (commonly just called LVEDP) **minus** the **surrounding** pressure(s) [35].

Katz, in 1965, already assumed that intracavitary and transmural end-diastolic left ventricular pressures were only equal when the pressure surrounding the left ventricular heart muscle was negligible [35]. Otherwise the external pressure must be subtracted from the intracavitary LVEDP to calculate the effective distending or transmural pressure.

Transmural LVEDP = LVEDP – surrounding pressure [35]

Usually, the surrounding pressure has contributions of one-third by the RVEDP and two-thirds by the pericardial pressure [51, 52]:

Transmural LVEDP = intracavitary LVEDP − (2/3 pericardial pressure + 1/3 RVEDP) Under normal conditions, RAP and pericardial pressure (PP) are nearly equal [53–55] and further changes in pericardial pressure are very closely reflected by RA pressure changes [53, 56, 57].

The close relation between changes in RA pressure and pericardial pressures allows us to give a reasonable estimate of transmural pressure by subtracting RAP from pulmonary capillary wedge pressure (PCWP) [23, 53, 56]:

Transmural LVEDP = PCWP – RAP ≈ PCWP – CVP

with CVP reflecting the 'surrounding pressure' [23, 53, 56, 58, 59].

There is substantial evidence that PCWP reflects LVEDP [60–62]. CVP is measured where the vena cava leads into the right atrium [58] and, as such, equals the RAP [58, 59]. Due to the very close relations between RAP and PP ($r = 0.95$, $p < 0.005$) [63] and RAP and changes in PP [53, 56, 57] respectively, CVP is a good estimate of PP [53–55, 58, 59, 63] in daily practice. Furthermore, both, CVP and RAP reflect the RVEDP [44, 59, 63]. Over a wide range, pericardial pressure, RAP and RVEDP are literally equal [64]. Tyberg [53] demonstrated that RVEDP well represents PP in ranges between 4 and 20 mmHg. However, in case of right

ventricular hypertrophy when the RV is stiffened [65] and in cor pulmonale or pulmonary hypertension, RAP and RVEDP are much higher than PP. **RV-failure always cause a rise in CVP** [58].

In healthy persons the surrounding pressure is low (nearly zero) and an increase in preload will increase the LVEDP more than the surrounding pressure [23, 41]. Hence, the transmural LVEDP will rise along with LVEDV [23, 43, 66], increasing the preload recruitable stroke volume (work) and thus SV, as described by Frank and Starling.

In conditions where the surrounding pressure rises substantially, external constraint increases more than LVEDP [23, 24, 47, 48, 67, 68]. Transmural LVEDP and intracavitary LVEDP will differ considerably and will change in opposite directions with a fall in transmural LVEDP, lowering the preload and, consequently, the preload recruitable stroke volume (work) will decrease.

The intraventricular pressures (intracavitary LVEDP and RVEDP) are influenced by:

- LV-compliance [69],
- alteration in lung anatomy and physiology-inducing changes in the intrathoracic pressure [47] and the pressures in the pulmonary circulation [70],
- intra-abdominal pressure [71].

The LV compliance describes the diastolic properties of the heart muscle and can be depicted by the relation between LVEDP and LVEDV [51, 72] (relation between pressure and volume).

With this in mind, the discrepancies between transmural LVEDP and intracavitary LVEDP can be related, at least partly, to the ventricular compliance [73].

The ventricular compliance varies almost continuously in the critically ill, producing changes in the intracavitary LVED**P** but without any corresponding change in LVED**V** [69, 74, 75]. Kumar [76], however, established evidence that continuous change in the ventricular compliance is a physiological phenomenon present in healthy persons as well as in those who are unwell.

In heart failure, the compliance of the LV is almost always reduced [50], hence, increases in filling volumes cause a higher rise in LVEDP compared to a healthy heart.

The compliance is determined by factors such as muscle mass, tissue composition, elastic properties, ventricular interactions and extramyocardial conditions including pericardial structure and intra-thoracic properties [77–80].

Raised intrathoracic pressure due to pneumonia, ARDS, pulmonary oedema, etc., as well as raised intra-abdominal pressure will increase constraint, in particular on the thin-walled RV, affecting the RVEDP and PP more than the LVEDP [47].

Furthermore, the higher the LVEDP the greater the amount of external force acting on the LV, thus impeding the LV-filling, the preload, and preload recruitable SV (SW) [24, 25].

Examples of situations which alter the surrounding pressures or produce significant external pericardial constraint are:

- increased lung water due to congestive HF [81],
- mechanical ventilation and PEEP: Both induce a rise in intrathoracic pressure (surroundingpressure) and an increase in RV-afterload [82]. The normally low RVEDP and PP will rise markedly in case of mechanical positive pressure ventilation and/or PEEP application, pneumonia, ARDS, etc., and so contribute essentially to an increase in the surrounding pressure [56];
- In heart failure patients we expect a marked external constraint to be present in the majority of patients, compromising LV-filling and becoming significant if LVEDP > 10(12)–15 mmHg [24, 25, 83]. Physiological external constraint, mainly due to PP, contributes up to 30–40% of the LVEDP [25]. In heart failure the contribution to LVEDP by the external constraint is as high as 50–80% [23];
- acute pulmonary embolism: ↑ RVEDP and thus ↑ in PP [47], hence a rise in the surrounding pressure inducing no change [47] or even ↓ in the transmural LVEDP [39].

In the case of external constraint, LVEDP markedly overestimates effective distending pressure [42].

Changes in opposite directions (transmural LVEDP ↓ and intracavitary LVEDP ↑) are explainable now, and **only** an increase in transmural LVEDP is consistent with an increase in LVEDV and vice versa [23, 39, 42].

Numerous publications have established that haemodynamic monitoring by PA-catheterisation measuring intracavitary (filling-) pressures fails to be an accurate guide of the preload because filling pressures do not adequately reflect the myocardial fibre length at end-diastole and, hence, the LVEDV [36, 84–86]. If the transmural pressure is used instead, then changes in the preload are accurately reflected [35].

However, the filling pressures are still one of the most important components in assessment and treatment decision-making processes in heart failure. The heart always tries to generate an adequate CO on the lowest possible LVEDP [73, 86, 87]. In heart failure patients, a therapeutic reduction of the LVEDP is correlated with improved outcome [15, 88]; hence, unloading the left ventricle and reducing the LVEDP is the therapeutic maxim that adheres to the physiology/pathophysiology of the situation [23, 24, 36, 37, 50] and improves outcome [13, 15, 24, 88]. Thus, we might do much better in our patients with severe heart failure and cardiogenic shock using the transmural LVEDP to make our therapeutic decisions.

There is, of course, a physiological optimum and maximum of fibre distension and concomitant force development (see Fig. 1.2) [89].

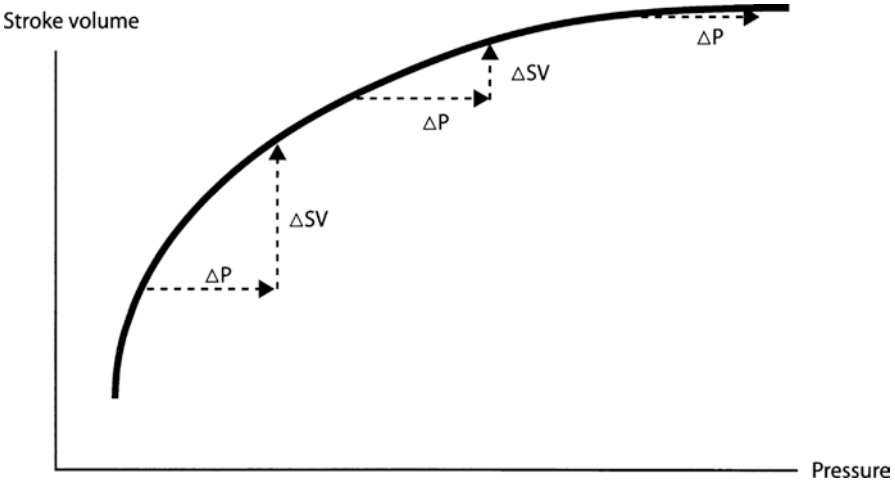

Fig. 1.2 Δp: Change in pressure; ΔSV: Change in SV; with increasing transmural pressure and thus preload, the recruited SV becomes less (modified from Michard [10], with permission)

Furthermore, in the situation of (acute) heart failure the Frank–Starling mechanism is markedly diminished [50] and thus, in the failing heart, an increase in fibre stretch (ventricular filling) is not accompanied by the same increase in the force of contraction as in healthy persons [90].

In the failing heart the SV depends substantially on the contractility [10, 75, 91, 92] and the afterload [3, 12, 46, 93, 94].

1.3.3 Venous Return and CVP in Daily Practice

SV is determined by venous return (responsible for the preload) and cardiac performance (con- tractility, afterload and heart rate) [31–33].

Guyton et al. [32] evaluated the relationship between total cardiac function (contractility and total peripheral resistance) and venous return:

"The actual cardiac output changes with changes in cardiac function (CF), but with changes in venous return as well".

Indeed, as increasing ventricular filling and (thus) ventricular stretch will lead to an increase in SV, is SV basically a function of end-diastolic filling volume [95], and as such (up to an upper limit—sarcomere length of 2.2 µm) in some aspects of the amount of venous return.

Guyton plotted the relationships (total cardiac function and venous return) on one graph (see Fig. 1.3) [32].

Under most physiological conditions, changes occur simultaneously in these relationships, although one effect will be dominant [31], for example:

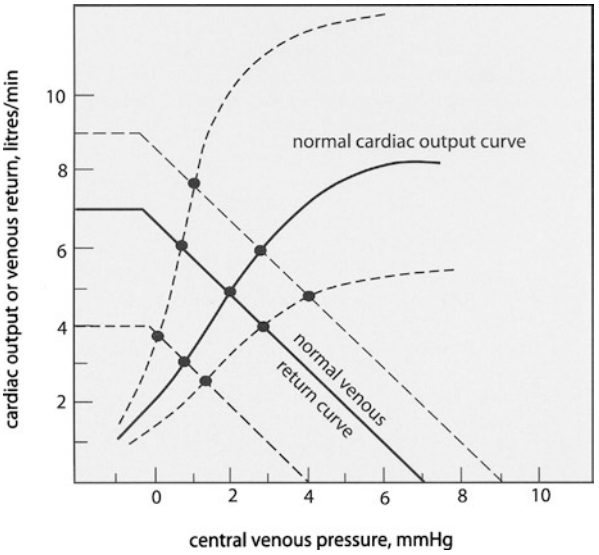

Fig. 1.3 The upper cardiac function curve depicts a supra-normal performance (i.e. ↑ sympathetic tone) while the lower curve represents the situation in H.F. Venous return: High – normal – low (adapted from Mohrman, DE and Heller, LJ *Cardiovascular Physiology*, 4th ed. McGraw-Hill Comp., 1997, chapter 9, p. 147), with permission

- If CO rises with a fall in right atrial pressure (central venous pressure), the dominant effect is improvement in cardiac function (increase in contractility and/or reduction in afterload);
- If CO rises with an increase in RAP the dominant effect is an increase in volume, and a decrease in venous compliance or venous capacity, resulting in a higher venous flow for any pressure in the right atrium.

As such, the special interrelationship between CVP and CO has to be considered when interpreting hemodynamic conditions: Both, CVP and CO are determined by the interaction of the two functions, the cardiac function and the venous return [32, 96, 97]. RAP/CVP is not an independent determinant ascertaining CO, and "depends on CO as much as it determines it" [98]. Accordingly, CVP can be **low** in a person with low blood volume and normal cardiac function, but it can also be low in cases of normal volume and good cardiac function [31]. CVP can be high in cases of normal filling with impaired cardiac function, but also in cases of normal function but with fluid overload [31].

Venous return depends on mean systemic filling pressure, right atrial pressure, and vascular resistance, particularly venous tone [98]. A rise in venus tone precipitates a progression in venous return. The pressure difference between the pressure in the periphery (systemic filling pressure which is largely represented by the pressure of the extrathoracic veins [99]) and the pressure within the right atrium (central venous pressure), is usually 7–10 mmHg whereupon RA-P is normally 0 mmHg, and determines the amount of venous return [100]. Spontaneous breathing, creating negative intra-thoracic pressures, increases this pressure gradient facilitating venous return [101]. On the other hand, increases in RAP and particulary elevated RAPs oppose venous return [98].

As the level of the right atrial pressure is decisively affected by extracardiac, intrathoracic conditions, any rise in pericardial pressure (displaying pericardial constraint, as found in case of pericardial effusion or tamponade, positive pressure

ventilation and pleural effusions via heart–lung interaction) will enhance RAP [102, 103]. This rise in RAP is not accompanied by, or due to, an increase in filling volume, however it will further blunt venous return [98]. Increases in ventricular afterload and myocardial ischemia affecting diastolic myocardial properties (diminishing myocardial compliance) subsequently alter ventricular filling pressures and hence RAP (LAP respectively) [95, 104]. Accordingly, no relationship exists between RAP and SV in case extracardiac, intrathoracic pressures are elevated [103, 105].

As such, the level of the right atrial pressure is determined by the pressure with which the blood distends the atrium and by the pressure effects of the pericardial, thoracic, and pulmonary adjacent structures [103, 105].

Anyway, a high CVP may be related to (a) elevated extracardiac/intrathoracic features, or may (b) indicate RV-dysfunction and/or RV outflow obstruction (namely pulmonary hypertension PH) with blood welling up in the RA, or reflects (c) both a and b. In any case, differential diagnostic considerations are implicitly required as different causes will inevitably entail different therapeutic measures [98].

While in the arterial system the pressure depends on, and is determined by, the flow and the arterial resistance (MAP = SV × SVR) [1], the venous blood flow is determined by considering volume and venous capacitance [106]:

$$\textbf{Total venous pressure}\left(\textbf{CVP}\right) = \textbf{volume} \times \left(\textbf{fluid/venous}\right)\textbf{capacitance}$$

It is the **venous capacitance which dominates the venous behaviour** and the central venous pressure is determined, essentially, by the venous capacity [107, 108]. It is not the venous return (as a flow), but the volume that predominantly controls basic RAP/CVP [106].

During exercise, sympathetic activity, stimulated by the reduced activity from arterial and atrial receptors, will increase venous tone and decrease venous capacitance [109]. This will increase the venous return to the heart [110] and, in case of a recruitable preload reserve (this depends on CF [10–12, 75, 91, 94]), SV will increase [36, 37]. The immediate effect of a decrease in venous capacitance is an increase in all pressures [106], including transmural RVEDP and thus RV filling, enabling the RV to increase its systolic performance [36, 37].

Fluid infusion leads to **an increase in venous capacitance**, lowering the central venous pressure [108, 110, 111]. A high CVP always has consequences and will limit the venous return [49].

In patients with septic shock, Stephan [112] found that, despite vasodilatation of both the arterial and venous systems [113, 114], volume loading increased the venous tone and thus the CVP significantly and to high values (>10 mmHg). This is due to a marked reduction in the compliance of the venous system secondary to stiffening of the vein walls by several sepsis-induced mechanisms [112]. Furthermore, drastic increases in CVP indicte that the ability to accommodate in case venous return has reached its limit and that blood is welling up [98].

CVP is normally **0 mm**Hg at rest and might increase to **2–4 mmHg during exercise** [115]. The **CVP is only elevated in disease states** [116, 117], a CVP > 10 mmHg often reflects an elevated RV-afterload [116].

In critically ill humans [4, 69, 93, 118, 119] as well as in healthy persons [76] we know that **no correlation at all exists between CVP and preload** or change in CVP and change in preload. The lack of a relationship is due to the fact that, in humans, the compliance of the atria and, in particular, of the ventricles is highly variable [76]. Furthermore, preload is not the same as fluid responsiveness [120, 121], and CVP and its change poorly (do not [122]) predict fluid responsiveness [10, 75, 123, 124].

Thus, in daily practice the absolute value of the CVP and even dynamic changes in its value are very difficult to interpret and cannot be used as a valid indicator of fluid management at all [117].

In general, a CVP ≥ 10–12 mmHg has to be considered high, and most patients within this range will not respond to volume administration [44]. Bafaqueeh [125] found that 40% of patients with a CVP < 6 mmHg did not respond to further fluid administration.

Pericardial constraint accounts for 96% of the RAP, if CVP > 10 mmHg [71]: A CVP ≥ 5 mmHg [126], and particularly when exceeding 9–10 mmHg, will exert substantial constraint on (left) ventricular filling [63, 127].

Thus, an **elevated CVP > 9–10 mm Hg is always pathological** [116, 117], signalling that fluid administration is unlikely to be successful [125], and that **diastolic ventricular interaction (DVI)** [63, 127] may be present or will occur if the CVP increases further (see part 8 of this chapter).

1.4 Hemodynamic Monitoring

1.4.1 Assessment and Monitoring of Fluid Status

Haemodynamic monitoring is a cornerstone in the management of critically ill patients [117]. It helps identify pathological states [13, 128] and complications of circulatory failure [13, 117] and aids restoration of normal haemodynamic parameters to prevent tissue and organ injury, to restore organ failure/dysfunction and hence to reduce mortality [117].

When faced with a compromised circulation, volume expansion is very frequently the **first therapeutic measure** used to improve haemodynamic status [129]. Unfortunately, only 40–70% of all patients with acute circulatory failure respond to fluid administration (SV/CO ↑) [75], which means that 30–60% of patients are not fluid responsive and volume administration may be harmful [117, 130–132]. Both, acute and chronic right heart failure [47] as well as acute left heart failure [23, 24] may deteriorate with volume loading.

Therefore a rational approach to fluid administration is needed, where the therapeutic decision is based on correctly assessed **effective intravascular volume** (preload) and the probable **response to increased volume** [117, 133]. However, the clinical tools available to evaluate the patient's fluid status and specifically the **intravascular/intraventricular filling (preload)**, such as jugular venous distension, crackles on auscultation, peripheral oedema, etc., are of minimal value and

very poor indicators of the volume status, particularly in the critically ill patient with (cardiogenic) shock: They cannot be validated as a useful tool or basis for treatment decisions [134–138]. The only relevant clinical sign which, although still non-specific, may indicate a possible volume deficit is the heart rate. Volume deficits are usually compensated by an increase in **heart rate** (>90 bpm) to maintain CO in case of low SV [92, 139, 140].

In acute heart failure patients a two-minute bedside assessment [88, 141, 142] is extremely helpful to allocate the patient to one specific haemodynamic profile (**wet or dry** *and* **cold or warm**) with corresponding treatment regimes [88, 142–144] (see detailed information in Chap. 2). This evaluation, however, does not provide any usable information about the patient's **actual intravascular fluid status** (to classify the patient as normo-, hypo-, or hypervolaemic) or whether a cold, and thus hypoperfused, patient will respond and benefit from fluids or not [28].

Hence, in addition to this useful bedside assessment, a proper assessment of the patient's intra-vascular volume status must be carried out to clarify whether a benefit (positive fluid responsiveness) can be expected from volume expansion before fluids are given. Blind administration of intravenous fluid may be harmful through an increase in LVEDP [130], as the elevation of the LVEDP predominantly causes the patient's symptoms to worsen [15] and, with increasing LVEDP, the patient's prognosis [15, 16, 88].

In case of central hypovolaemia, volume administration will induce a significant increase in SV (flow) **as long as a preload reserve can be recruited** [130, 131, 145]. Thus, it is important to predict in a haemodynamically unstable patient whether this patient will increase his/her systemic blood flow (SV) in response to volume expansion or not [131].

Kumar [9] showed that, in healthy individuals, volume loading increases the systolic BP/LVESV ratio and the LV-SW by:

- an increase in LV-SV due to a reduction in LVE**S**V while the LVE**D**V remains unchanged and
- an increase in contractility.

The contribution of the Frank–Starling mechanism is only mild to moderate, the contractility is the main component [9]. Kumar examined healthy volunteers and confirmed the findings of animal studies conducted in the 1960–70s [146–148]. Flow represented by SV is the original, central, and decisive parameter to be assessed when defining fluid responsiveness [75, 76, 121, 131, 145, 149].

Fluid loading must increase LV-SV if the heart is preload responsive [75, 131, 145]

In heart failure, although the LVEDV may be in the normal range, fluid administration can fail to increase the SV due to a significant reduction in contractility [10, 75, 91, 92]. Furthermore, we know that the Frank–Starling mechanism is impaired in heart failure [50, 90] and hence volume expansion may well be harmful and worsen the haemodynamic situation [117, 130–132].

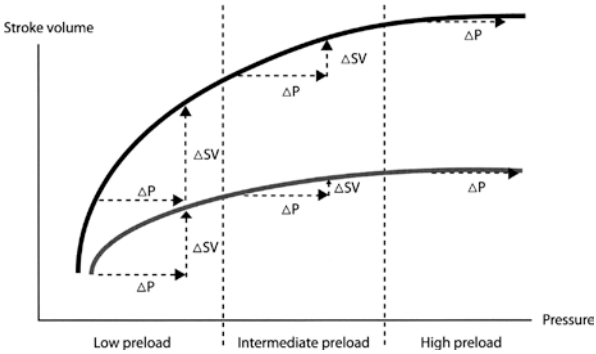

Fig. 1.4 Δp: Change in pressure; ΔSV: change in SV; upper curve: normal heart function, lower curve; impaired heart function (modified from Michard, F [10], with permission)

Braunwald [91], and recently Michard [10, 75] have established proof that **the increase in SV due to increased LVEDV depends on the contractility and pre-infusion preload** (initial end-diastolic fibre length in respect to the Frank–Starling mechanism), **particularly in the case of compromised cardiac function** [10, 75, 91] (see Fig. 1.4).

In those patients with intermediate pre-infusion preload (normovolemia), the effect of volume loading depends exclusively on the contractility and, in the case of a compromised heart function (lower curve) in 'intermediate preloaded' patients, the effect of volume loading in order to increase SV, and thus CO and/or BP, is minimal and clinically not relevant [10].

Nevertheless, even in cases of cardiogenic or other types of shock, fluid administration may initially be helpful. Up to 70% of all patients in shock show a positive response (increase of blood pressure, increasing the perfusion of vital organs) when fluids are administered [150]. In non-responders we most often find that RV-dysfunction/failure with sepsis is the main underlying reason [150].

The physiological and pathophysiological facts described above demonstrate and emphasize that preload and fluid responsiveness are not the same, and this has been stressed in many published studies [117, 120, 121, 130, 151]. Therefore, as prerequisites to a **positive response** to fluid administration, there must exist both a recruitable contractile reserve (**myocardial reserve**) and an absolute or relatively hypovolaemic **central vascular and cardiac system** to provide a filling reserve.

An increase in SV by ≥15% due to volume administration is the most accepted benchmark confirming a positive fluid response [123, 152–154], although others define a positive response if SV increases secondary to volume expansion by ≥10% [155–158].

1.4.2 Prediction of Fluid Responsiveness

1.4.2.1 Pressure Measurements

Cardiac filling pressures such as CVP and LVEDP/PCWP have **failed** to predict either preload or fluid responsiveness. The relationship (if there is any) between the intravascular/intraventricular volume and the CVP/PCWP is, as already mentioned,

very poor in both ill patients [4, 69, 118, 119, 159] and healthy volunteers [76]. Even in sedated and mechanically ventilated patients, CVP and PCWP have been shown to be unreliable parameters to reflect the preload or to predict fluid responsiveness [10, 75, 76, 124, 160]. Osman [122] states that, "fluid responsiveness is documented to be unrelated to CVP/RAP and PCWP/LVEDP, respectively".

1.4.2.2 Volumetric Measurements

Volumetric measurements (RVEDV, ITBV or GEDV) and **ventricular areas** (LVEDA or LVEDD) have been shown to **be useful in assessing the preload** and seem to be better than cardiac filling pressures in guiding volume therapy [75, 76, 161, 162] but, unfortunately, they are still not great at predicting **fluid responsiveness** [123, 163, 164].

In particular, it was hoped that GEDV(I), reflecting central blood volume [165, 166], and the direct measurement of the RVEDV would overcome the mentioned difficulties. However, the indirectly measured volumetric parameter GEDV **failed** to provide additional prediction in terms of the patient's response to volume expansion [9, 161, 162, 167]. The direct measurement of the absolute value of the RVEDV allows a definitive assessment of volume status, however unfortunately whilst SV increased with volume loading there was no change in the measured RVEDV [9].

Furthermore, Reuter found only a poor correlation between SV and LVEDA (from echocardiography) [156], and Slama showed that changes in LVEDD are also dependent on LV stiffness [168]. Several other authors followed by confirming the poor correlation between LVEDD and SV/CO [123, 153, 159].

Thus, filling pressures such as CVP/RAP, PCWP, or areas/geometric dimensions of the LV, such as LVEDA or LVEDD, are unable to predict fluid responsiveness [75, 117], nor can direct [9] or indirect measurements of end-diastolic volumes (overview by [75]) predict the patient's response to volume expansion [161, 162, 167].

Preload is simply not the same as preload responsiveness [121, 171, 130, 151].

Osman concludes that, in the assessment of preload responsiveness, parameters other than pressures and ventricular volumes need to be measured [122].

1.4.2.3 Dynamic Parameters

In contrast to the static parameters discussed above for assessing the filling pressures, filling volumes, and left ventricular areas, we have the **dynamic parameters**, which comprise stroke volume variation (SV-V), pulse pressure variation (PP-V), systolic blood pressure variation (SP-V) and aortic blood flow changes, which provide substantial information and are valuable tools in predicting fluid responsiveness [123, 140, 152, 153, 162, 169].

The dynamic parameters reflect changes in LV-SV due to heart-lung interactions induced by mechanical ventilation [123, 139, 167, 170, 171] and several studies have documented that variations in LV-SV associated with mechanical ventilation are highly predictive of preload responsiveness [152, 153, 156, 158, 168].

The alterations in cardiac preload, and hence variations in LV-SV associated with respiration, are referred as to SV-V and are defined by the maximum to minimum

SV values during a period of three breaths, or over a time interval of 20–30 s [153, 158, 168]. SV-V is validated in several studies for deeply sedated, mechanically ventilated patients with a tidal volume of 6 mL/kg without any spontaneous breathing effort. A SV-V ≥ 10% predicts an increase in CO of ≥15% for a 500 mL fluid bolus [157, 158, 168].

Positive pressure ventilation with its cyclic increases in intrathoracic pressure and lung volume [172, 173] induces intermittent variations in cardiac preload (heart–lung interaction) [156, 174–176]. This is predominantly due to a reduction in venous return secondary to the increase in RA pressure during mechanical inspiration [174, 177–179]; hence, the RV filling is reduced (↓ RVEDV) [174, 180–182]. In accordance with the Frank–Starling mechanism this produces a reduction in RV-SV [36, 37, 183]. An additional effect that is at least partly responsible for the reduction in RV-SV is exerted by the increase in RV-outflow impedance [184, 185] and thus a rise in RV-afterload with consecutive impaired RV ejection secondary to positive pressure ventilation [176, 186–188].

However, this inspiratory reduction in RV-SV affects the LV-filling after a few heart beats, producing a ↓ LVEDV [175, 189, 190]. Consequently, the LV-SV is reduced [175, 176, 189, 190] and this takes effect during expiration. Thus, ventilation-dependent variations in RV-filling will induce cyclic variations in LV-filling with a concomitant reduction in LV-SV, and thus arterial blood pressure, if both RV and LV are fluid responsive [117, 176, 183, 189].

Conversely, during inspiration the opposite occurs; increased LV-filling will result in a higher LVEDV and hence higher LV-SV and arterial pressure [117, 176, 189].

The influence of positive pressure ventilation on the cyclic haemodynamic changes is greater when central blood volume is low rather than when it is normal or high [75, 135, 153].

The dynamic parameters will lose their validity if tidal volumes vary from breath to breath, as with (assisted) spontaneous breathing [131, 155, 191] or in case of marked arrhythmias inducing variations in LV-SV [135]. Exaggerated values of SV-V were found with large tidal volumes, reduced chest wall compliance and air trapping [156]. Furthermore, a moderately elevated intra-abdominal pressure (up to 20 cm H_2O) affects cyclic circulatory changes by inducing a progressive increase in intrathoracic pressure enhancing the pleural pressure swings and thus may feign fluid responsiveness [192]; if the intra-abdominal pressure is higher than 20 cm H_2O, less influence is seen [192].

Nevertheless, the dynamic parameters have shown themselves to be far better than the static parameters in predicting fluid responsiveness and are currently the approach of choice in sedated and ventilated patients [117, 135, 152, 153, 155, 156].

The **dynamic swing** in LV-**SV** is the current gold standard [145, 152] in predicting response to fluid administration—but **SV-V**, although affected by preload, predominantly also seems to reflect the **myocardial response** to volume loading [156]. This is consistent with our knowledge that SV predominantly depends on LV-function (mainly the contractility [10, 75, 91, 92] and, in heart failure, on afterload as well [11, 12, 46, 94]) rather than on pre-infusion preload [10, 75, 91]. Kumar

[9] showed that, in healthy volunteers, the increase in SV due to volume loading is predominantly a result of an increase in contractility rather than an increase in filling volume, and thus a larger fibre stretch as described by Frank and Starling.

Besides the assessment of SV-V during positive pressure mechanical ventilation [191], surrogates of SV such as aortic flow [153, 157], systolic BP (SP-V) [189, 193], and pulse pressure (PP-V) [145, 183] have turned out to be reliable and valuable indices by which to check central blood volume and the response to fluid administration.

Descending Aortic Blood Flow as a Direct Correlate of SV/CO

Descending aortic blood flow represents the majority of CO [194, 195] and is accepted as a clinically realistic estimate of SV and or CO [196–198]. Aortic Doppler flow velocity measurements can determine the SV, calculated with the help of the product of the velocity-time interval in the ascending (estimated by echocardiography [151]) or descending aorta (oesophageal Doppler measurement) [197, 199, 200] and a measured [151] or estimated aortic diameter using the nomogram by Boulnois [195]. These flow velocity measurements have been reported to predict fluid responsiveness accurately [153, 168, 197].

Systolic Pressure Variation (SP-V)

Systolic pressure variation (SP-V) is probably the easiest way to assess fluid responsiveness and is defined as an 'increase or decrease in systolic arterial pressure with each mechanical breath relative to the systolic pressure during the short apnoea phase' [193, 201]. Numerous studies have shown its value as a sensitive parameter in predicting preload responsiveness in patients who are mechanically ventilated without any spontaneous breathing [123, 153, 156, 167, 169, 202]. The sensitivity of this method is not as high as that of PP-V because it does not quantify the varying diastolic arterial pressure components [183].

Pulse Pressure Variation (PP-V)

Pulse pressure variation (PP-V) may be the most robust and sensitive indirect indicator of volume status [75, 183]. The variation of the aortic pulse pressure (aortic pulse pressure ~ LV-SV [203, 204]) is established as an evidence-based index with which to assess and predict the response to fluid administration in mechanically ventilated patients [75]. A cyclic variation of the aortic pulse pressure due to varying LV-SV during a respiratory cycle of more than 13% ($r^2 = 0.85$, $p < 0.001$) [75] implies a very high likelihood (85%) that the patient will benefit from fluid administration with a significant increase in SV and thus in blood pressure (positive predictive value of 94%, negative predictive value of 96%) [75, 190, 205].

Calculation of PP-V during one respiratory cycle:

$$\begin{aligned}&\text{Ppmax: maximal systolic pressure} - \text{maximal diastolic pressure,}\\&\text{Ppmin: minimal systolic pressure} - \text{minimal diastolic pressure.}\\&\mathbf{PPV(\%) = \left[(Ppmax - Ppmin) / (Ppmax + Ppmin) / 2\right] \times 100.}\end{aligned}$$

Passive Leg Raising (PLR), An Autotransfusion of Fluids

Several studies recently published have given encouraging evidence that prediction of fluid response is feasible in spontaneously breathing as well as ventilated patients [130, 151].

Raising the legs to approximately 30 or 45° is called passive leg raising (PLR) and will increase the aortic flow **in case of a recruitable preload reserve** 15–60 s after the legs have been raised [131, 145, 149, 151] and this will persist for 30–90 s [206] (Pinsky [117] up to 3 min).

Clinical studies have proven that the volume of blood transferred to the heart by PLR is sufficient to increase the left ventricular filling volume [131, 145, 207, 208]. While the predictive value of the transient changes in SV is only fair if SV or its surrogates, SP-V and PP-V, are estimated from a **peripheral pulse pressure curve** [129, 131]—due to the influence of the arterial compliance and the vasomotor tone [145, 204]—high sensitivities were achieved when measuring **variations in SV centrally**, i.e. by oesophageal Doppler [131], echocardiography [151] or by femoral artery access, which is considered to be central [209, 210]: Monnet [131] found a sensitivity of 97% and a specificity of 94% to achieve an increase of ≥15% in aortic blood flow in response to volume administration if, during PLR, the aortic blood flow increased by ≥10%. Lamia [151] showed a similar specificity (100%) but with a slightly worse (but still good) sensitivity of 77%.

Thus, an increase in aortic blood flow (SV/CO) by ≥10% [131, 145] or 12.5% [151] during PLR is reliably predictive of central hypovolaemia and a positive response to volume expansion [130, 131, 145, 151] in either mechanically ventilated patients or those breathing spontaneously. In the **absence of central hypovolaemia** and/or in the presence of an **unresponsive RV and/or LV** (compromised function, mainly impaired contractility) SV/CO will not increase by the PLR manoeuvre [131, 145].

As no external fluids are administered, the hazards of unnecessary volume loading can be avoided [44, 87, 162, 211–213] and hence the measurement of **central blood flow** (aortic blood flow normally represented by SV or CO) in response to **PLR** is more robust and probably **superior** to PP-V when **evaluating the patients' fluid response**, even in spontaneously breathing patients [121, 130, 131, 151]. Furthermore, this approach is more independent of varying tidal volumes and arrhythmias than a peripheral one [130, 131, 151]. The central measurement of blood flow avoids the relevant influences of arterial compliance and vasomotor tone [204] and the complex changes in pulse wave propagation and reflection along the arterial vessel system [214], both of which may change during PLR with a concomitant change in SV.

1.4.2.4 Fluid Challenge

A fluid challenge is still advocated as a tool to evaluate the need for further fluid administration if strictly monitored and the response observed closely [133, 215], but the dynamic parameters described above are clearly superior and blind volume administration should be avoided if at all possible [130].

A fluid challenge does not mean fluid resuscitation; it merely identifies those patients who are likely to show a beneficial response to (further) fluid administration [216]. To minimise the amount of fluid needed to assess responsiveness, the fluid should be given quickly [44] and some authors require an increase in CVP of at least 2 mmHg [217, 218] to confirm that a sufficient amount of fluid has been given. Rapid bolus administration of 250 mL in 5–7 min or 500 mL in 10 min [44] of fluid or PLR is expected to show an appropriate haemodynamic response if beneficial for the patient [116, 217]. If a recruitable preload reserve is available, the SV must increase [217].

Although no definition as to what comprises an adequate fluid challenge is generally agreed upon, most studies do agree that a positive response is indicated by improving circulatory status as suggested by ↑ BP, heart rate unchanged or ↓, with accompanying SV ↑, and an improved effective blood flow documented by $ScvO_2$/SvO_2 ↑, and lactate ↓ [116].

It is always worth remembering that a fluid challenge should only be performed if an indication is obvious, i.e. within the context of hypoperfusion [219] and that there is only a very poor correlation between change in BP and CO [44]. If no positive effect is achieved, fluid administration is useless, potentially harmful, and must be stopped immediately [44, 87, 162, 211–213].

Despite uncertainty, even in life-threatening situations such as cardiogenic shock, the administration of moderate amounts of fluid (about 3 mL/kg, hence ~ 250–300 mL) as a fluid challenge under close monitoring is appropriate and may stabilize the acute situation **temporarily** [220].

Appropriate and immediate fluid resuscitation in critically ill patients, if adequate, will improve outcome [221]. McConachie [222] states that a fluid challenge is appropriate in virtually all critically ill patients in shock situations with blood pressure 'too' low and/or hypoperfusion due to low cardiac output, unless obviously suffering from gross congestive cardiac failure.

On the other hand, it must be emphasised that, although a patient responds to volume administration, this does not automatically mean that the patient requires volume, as healthy subjects will respond as well [44, 216].

Vincent and Weil have recently proposed the following algorithm as being the proper approach to performing a fluid challenge [133]. In hypotensive patients with circulatory compromise administer 250–500 mL colloidal fluid (~3–5 mL/kg) over 15–20 min in order to stabilize the patient haemodynamically (at least temporarily), to improve organ and tissue perfusion, and to 'test the system' as to whether or not they are likely to respond positively to further fluid administration.

Criteria suggestive of effective volume loading [10, 31, 133, 183, 219]:

- **increase in SV by ≥10% and/or increase in systolic blood pressure by ≥10%**,
- heart rate unchanged or reduced,
- **CVP increase** ≤ 2–5 mmHg (if >5, no further administration, be cautious already if increase >2),
- no clinical signs of fluid overload,
- additional parameters, if monitored:

- PCWP increase ≤ 3–7 mmHg; stop fluids if increase >7 mmHg,
- EVLWI prior and post fluids ≤ 7–10 mL/kg,
- ↓ lactate, positive result by OPS (see below),
- increase in urinary output.

Stop fluid challenge during or after infusion if [10, 31, 133, 183, 219]:

- **SV/blood pressure does not increase appropriately** (<10%) [92, 139, 140];
- **Hypoperfusion does not improve** (clinically, no ↑ UO, no ↓ lactate / no ↑ SaO_2, no change in capnography/OPS evidence of improved tissue perfusion);
- **CVP increase** > 5 mmHg due to volume administration, be cautious if increase > 2: ↑ risk for DVI;
- **High risk of DVI** if CVP > 9–10 mmHg [116, 117, 127, 223] and particularly if SV/BP falls during volume administration.
- Additional parameters, if monitored:
  - EVLWI > 10 mL/kg [200, 224–226],
  - PCWP-increase > 7 mmHg.

An International Consensus Conference [218] from 2006 suggested 'a rise in CVP of at least 2 mmHg either by 250 mL fluid administration within 10–15 min, or leg raising' as a sign of sufficient fluid administration—defining a positive response if cardiac function and tissue perfusion improve. However, bear in mind that this recommendation is non-specific and expert opinion only.

As we know, CVP does not reflect preload or changes in preload, either in healthy or critically ill patients [69, 76, 119, 144, 159]. Thus, CVP cannot be used as a predictor of RV-filling and cannot be used to assess the effect of volume loading. A change in the magnitude of the CVP of at least 2 mmHg is the minimum necessary for detection with confidence on most currently used monitors [44] and therefore seems to be an arbitrary figure. Remember, in patients with good cardiac function, the CVP may even fall despite the fluid challenge being successful [76] and, if using the PLR method, central monitoring is essential and peripheral monitoring is not adequate [129].

1.4.2.5 PiCCO-Monitoring (Pulse-Induced Continuous Cardiac Output)

PiCCO is a method of haemodynamic monitoring which combines transpulmonary thermodilution and continuous arterial pulse contour analysis (see overview by Pfeiffer [227]).

This method allows the measurement of volumes [34, 160, 228] such as intrathoracic blood volume (ITBV) representing the intra-vascular volume status, the global end-diastolic volume GEDV (of all four chambers) and, of most importance, the extra-vascular lung water (EVLW) [224, 229].

These **volumetric** measurements are performed semi-invasively and are superior to the common pressure measurements, CVP and PCWP, when assessing the patient's intravascular volume status and the cardiac preload [84, 85, 119, 230]. Unfortunately, these parameters (ITBV and GEDV) do not allow any prediction of

the response of the circulatory system to fluid administration [75, 161, 162] (see above). However, the PiCCO-method fulfils all the requirements to evaluate response from PLR [131, 151, 231].

EVLW is an extremely informative parameter, proven as being an accurate measurement of the real amount of fluid in the lung tissue [225, 229, 232], the EVLW value provides substantial information about patient prognosis [211, 224, 232]. Currently, it is the only method able to diagnose 'developing' pulmonary oedema earlier than all other available methods, including clinical examination, chest X-ray and pressure measurement via PA-catheter (PCWP) [119, 233–236]. Furthermore, it is able to guide investigation of the pathologically high lung water: cardiac or extra-cardiac causes [213, 229, 237].

Two-thirds of all HF patients with a mean PCWP of <18 mmHg (18 mmHg is the generally accepted upper limit in case of a failing heart, probably providing the maximum preload recruitable SV) show a significantly increased EVLW/EVLWI [238], although it is not detect- able by auscultation or on X-ray [239, 240]. On the other hand, the PCWP is measured to be normal (≤12 mmHg) in some cases of cardiogenic shock, particularly in previously healthy patients with acute myocardial infarction, but the EVLW is already elevated and thus pulmonary oedema is present [28, 241, 242]. An increased EVLW/EVLWI signals increased mortality [211, 232, 243] and in the case of an elevated EVLW, any fluid reduction will lead to an increase in CO [234] (Fig. 1.5).

EVLW is valuable in indicating fluid overload [225, 235, 236] and its value (normal range EVLWI 3–7 mL/kg) should influence your therapeutic decision. If the EVLWI exceeds 10 mL/kg, the mortality increases exponentially and further fluid administration is not advisable [212, 226, 232, 243].

The permeability index PVPI (PVPI = EVLW/pulmonary blood volume (PBV) with PBV = ITBV − GEDV) reflects, if elevated (>3), an increased capillary permeability (capillary leakage resulting in non-cardiogenic oedema) [213, 229, 237], while an index <3 in combination of elevated EVLW/I is suggestive for a cardiogenic oedema.

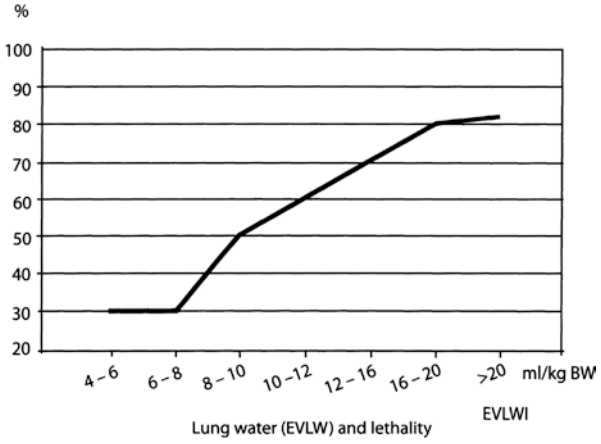

Fig. 1.5 This diagram shows the mortality rate depending on the amount of extravascular lung water. The graph is of special value because it is validated by post mortem analysis of lung water, confirming the accuracy of the clinical measurement (adapted from Sturm et al. [232]), with permission

1.4.2.6 Echocardiography

Echocardiography is essential to help diagnose the underlying pathology in circulatory failure and/or cardiac dysfunction [244, 245]. Heidenreich [246] successfully improved diagnostic accuracy by identifying a further 28% of the underlying aetiologies in unexplained hypotension when examining patients by transoesophageal echocardiography (TOE) in addition to the other obtained hemodynamic parameters. Thus, he showed that TOE adds significant information to invasively acquired haemodynamic data. Echocardiography has the ability to rapidly diagnose and aid decisive therapeutic decisions in cases of cardiac tamponade [247] and aortic dissection [248], confirming the clinically suggested diagnosis of endocarditis [249], to reveal evidence of haemodynamically significant pulmonary embolism [250], and is, of course, extremely helpful in assessing the heart's performance [251].

The assessment and evaluation of SV/CO, probably the main determinant of sufficient organ perfusion, is relatively easy to obtain by flow measurement in the descending aorta [200]. Laupland [199] gave proof that this is easy, quick to learn, and simply done in daily practice. However, this method does have some limitations. It is assumed that about 70% of the total CO will reach the descending aorta [195] and, furthermore, instead of measuring the diameter of the LVOT needed for the calculation of CO, a nomogram by Boulnois [195] is used. Thus, this method provides a rough estimate of the CO and the correlations with invasive measurements are weak when compared with PA-catheterisation or PiCCO [243, 252, 253]. If estimating the CO with PA catheterisation, as recommended by the ESC and AHA, advanced skills and training are necessary [254].

There have been 11 large studies evaluating the use of echocardiography as a continuous monitoring method in critically ill patients, most of them using the transoesophageal technique. No final conclusion can be made as to whether or not echocardiography should be recommended as equal to the established methods in continuous haemodynamic monitoring.

Echocardiography is time consuming, requires advanced physician training in acquisition and interpretation, and it is not realistic to establish this technology on a 24 h basis worldwide [176, 255, 256]. The usefulness of echocardiography lies in its diagnostic capacity and there is a consensus that an echocardiogram is absolutely essential in the initial assessment of all patients suffering from (cardiogenic) shock and should be performed as early as possible [244, 245, 257, 258]. Echocardiography (especially TOE) frequently depicts abnormalities overlooked by catheter-based invasive assessment tools such as LVOT obstruction, diastolic ventricular interaction, RV-dysfunction/failure, LV diastolic dysfunction, valve disease, cardiac compression, etc. [246, 259]. Furthermore, it has a great impact on therapeutic considerations, with 60% [260] of planned treatments altered following echocardiography [261–264].

Echocardiography can be a life saving tool; in cardiac failure patients, echocardiography is far easier and faster than PA-catheterisation and provides key haemodynamic information [265].

1.4.3 Arterial Blood Pressure

1.4.3.1 BP and Autoregulation

Adequate organ perfusion is essential to avoid the development of shock [266]. Although the mean arterial pressure (MAP) is the best estimate of organ perfusion pressure [116], there is no known threshold pressure defining adequate perfusion pressure amongst different organs, between patients, or in a patient over time [267]. The autoregulation of most organs maintains a constant organ-specific blood flow over a broad range of varying BPs and changes in metabolic rates, but hypotension is always pathological [116, 117].

Most authors define hypotension as systolic BP < 90 mmHg [268, 269], MAP ≤ 65 [267, 270] to 70 mmHg [271, 272], although in known hypertensive patients this may be altered to a MAP ≤ 85 mmHg and, in known hypotensive patients, ≤50–60 mmHg. In patients with IHD a MAP of ≤75–80 mmHg [267, 273–275] is commonly used.

Hypotension impairs autoregulated blood flow distribution [276, 277], and the MAP needed to maintain autoregulation varies from organ to organ and depends on clinical conditions (i.e. known arteriosclerotic disease or not).

Kidneys

A constant renal blood flow is maintained by autoregulation, which acts in a range of MAPs between 80–180 mmHg [278–280]. Iglesias [281] demands a MAP > 70 mmHg in order to prevent acute renal failure, or if acute kidney injury has already developed, in order to re-establish adequate renal perfusion. Esson [282] stresses that adequate renal perfusion pressure is a cornerstone of care in acute renal failure.

Brain

Autoregulation works within MAPs of 60–160 mmHg [283], the recommendations for an adequate cerebral perfusion pressure in critical illness vary from at least 60 mm Hg [284, 285] to ≥70 mmHg [283, 286–288].

$$\textbf{Cerebral perfusion pressure} = \textbf{MAP} - \left(\textbf{Intra-cerebral pressure} + \textbf{CVP}\right)$$

(In case of brain injury even higher pressures may be desirable).

Heart

A coronary perfusion pressure (CPP) is determined by:

$$\textbf{CPP} = \textbf{diastolic blood pressure} - \textbf{LVEDP} \quad [289]$$

Coronary autoregulation functions from (50 [273]) 60 mmHg up to 140 mmHg [273, 274]. This means that in the case of an elevated LVEDP (>15 mmHg), a **minimal diastolic pressure** of > 65 mmHg is essential. In coronary artery disease, even higher pressures are required in order to prevent further deterioration due to progressive ischaemia [267, 273–275].

Septic Shock

In septic shock, a MAP between ≥ 65 mmHg [260, 270, 275, 290] and 75 mmHg (in patients with known occlusive arterial disease, peripheral arteriosclerosis or long standing hypertension) [275] is recommended. A study by LeDoux showed that a MAP between 65 mmHg and 85 mmHg was not associated with significant differences in organ perfusion [267].

This was confirmed by Bourgoin [291] who showed that an increase in MAP from 65 mmHg to 85 mmHg with an infusion of noradrenaline did not improve **renal function**. The key point is that, as long as autoregulation is not substantially disturbed, a MAP of ≥65 mmHg is sufficient. But in case of a breakdown of autoregulation, however, higher MAPs are necessary to re-install it [270].

However, even a BP generally considered normal does not necessarily reflect haemodynamic stability and adequate organ perfusion [292]. Blood pressure is an inadequate indicator of incipient shock in a patient [293]. It is therefore essential to make an assessment of tissue perfusion.

1.4.3.2 Assessment of Tissue Perfusion

Organ perfusion essentially depends on blood flow and thus cardiac function [200]. Circulatory shock is known to cause tissue hypoperfusion [117] and inadequate tissue perfusion is associated with elevated morbidity and mortality [221, 294–298].

Compared to the difficult task of evaluating the vascular fluid status and the patient's likely response to volume expansion, tissue hypoperfusion can be assessed fairly well by clinical examination [257, 269, 299]. Clinical signs suggestive of tissue hypoperfusion are [129, 130, 151]:

- tachycardia,
- hypotension (sBP < 90 mmHg, MAP < 70 (60) mm Hg, or BP-drop > 40 mmHg),
- oligo-/anuria,
- clinical or biological signs of extracellular fluid depletion (ketoacidosis, vomiting, diarrhoea),
- delayed capillary refill,
- mottled skin,
- altered level of consciousness.

Menon [257] strongly recommends **a diagnosis** of cardiogenic shock (CS) in all patients exhibiting ***signs of inadequate tissue perfusion*** in the setting of severe cardiac dysfunction ***irrespective of the BP.***

SvO_2 (mixed venous oxygen saturation) reflects the balance between oxygen delivery and oxygen consumption [291, 300]. Pinsky [117] and Reinhart [301] state that a decrease in SvO_2 to <70% represents increased oxygen extraction by the tissues [117, 301] suggestive of hypoperfusion [302]. A persistent SvO_2 < 30% is associated with severe tissue ischaemia [303].

Plasma lactate levels, although non-specific, are still a reasonable surrogate for inadequate tissue perfusion [304, 305]. A reduction of an initially elevated value signals improvement of perfusion [306].

Thus, ↑ plasma lactate levels and ↓ SvO_2 [307, 308] coupled with a suggestive clinical examination may help support the **earlier** diagnosis of tissue hypoxia.

Ander [309] found that monitoring of $ScvO_2$ and lactate in patients with severe heart failure (patients with known cardiomyopathy being admitted with acute decompensation) is superior to assessment and monitoring clinical vital signs for the recognition of occult cardiogenic shock. If both parameters are abnormal (lactate > 2 mmol/L, $ScvO_2$ < 60%), occult/pre-cardiogenic shock requiring a special therapeutic approach could be clearly identified, whilst this was not possible from the vital signs [309].

Newer developments such as *sublingual capnography* [310], *orthogonal polarization spectral spectroscopy (OPS)* [311, 312] and *near-infrared spectroscopy* (*NIRS)* attempt to measure local tissue blood flow and oxygen utilization [287, 313] and evaluate any improvement due to therapeutic intervention.

Due to the fact that the use of 'the conventional global haemodynamic and oxygenation approach' may fail to provide adequate information on tissue perfusion, non-invasive monitoring of peripheral perfusion could become complementary in acting to warn of imminent global tissue hypoxia [314].

It must be remembered that the rationale for haemodynamic monitoring is to restore normal haemodynamic parameters in order to prevent organ injury and restore organ dysfunction [117], however this may not be valid in all cases. **Haemodynamic monitoring** usually **assesses** the **global circulatory** status, **not** organ function or **microcirculation** [288, 315–319], and does not address the mechanisms by which disease occurs [320, 321]. Therefore, we have to be careful in drawing therapeutic conclusions from the results of monitoring the macrocirculation, improvement of macrocirculation may compromise the microcirculation even further [322].

1.5 Afterload

1.5.1 Definition

The force opposing myocardial fibre shortening during ventricular ejection is called afterload [30, 323–325].

1.5.2 Vascular Properties, Effective Arterial Elastance, Wall Stress and the Law of LaPlace

Braunwald [30] states: "the load opposing LV ejection, in its simplest sense, is reflected by the systolic blood pressure". However, the physiology is much more complex and systolic blood pressure has turned out to be a very poor reflection of afterload. Indeed, the arterial system imposes a hydraulic load on the heart, and a higher arterial load requires higher energy to eject a given amount of blood. This vascular, hydraulic load, opposing ventricular ejection is most completely described

and reflected by aortic input impedance[1] (respectively pulmonary artery input impedance) [326–329].

The main parameters characterizing arterial input impedance are peripheral vascular resistance, total arterial compliance, and aortic characteristic impedance [326, 329, 331]. While peripheral vascular resistance specifies steady state conditions, the pulsatile load (pulsatile load is complex and time varying [332]) components are represented by:

1. The total arterial compliance, reflects, by quantifying the pressure-volume–relation, the overall structural behaviour of the arterial system as a whole [327, 333–335], but specifically represents properties related to pulse wave propagation and reflection [327, 336–338], which affects the loading conditions, as intensity and timing of the pressure wave reflections are influenced by inertial forces, and oppose LV ejection [339], and
2. Aortic characteristic impedance [326, 340], contributing up to 80% to the total compliance [341].

The characteristic impedance outlines physical properties, such as viscoelasticity and dimensions of the large central, proximal arterial vessels (aorta, respectively pulmonary artery), and thus the contribution of elastic vascular properties to total load [327, 328, 340, 342, 343]. "Pulsatile afterload" largely includes characteristic impedance and pulse wave reflections [326, 340, 344], directly opposing ventricular ejection.

In fact, special attention has to be paid to the impact of the pulsatile elements on the total vascular load, as the intensity and the timing of reflected pressure waves change according to the elastic vascular properties (largely proximal aorta), and thus may exert a substantial impact on the vascular load the ventricle is facing [338, 345, 346]. In case of arterial vascular stiffening, as occurring with (physiological) ageing [347–349] or in hypertensive individuals [317, 350, 351], the wave velocity increases, and reflected waves return and sum up with incident forward waves, augmenting net pressure [318] and reaching the ventricle (already) in late systole, after-loading the ventricle [319, 338]. Concomitantly, aortic input impedance considerably increases [317, 319, 352, 353]. Accordingly, reflected pressure waves are shown to exhibit a substantial impact on systolic load imposed on the heart [345], and arterial stiffening is recognized to afterload the ventricle [317, 319, 354], by elevating (late) systolic load, thereby increasing systolic ventricular elastance, compromising ventricular filling, and influencing diastolic properties with raising filling pressures [347, 355]. Indeed, it has to be emphasized, that diastolic cardiac function is affected if arterial compliance decreases as in arterial stiffening [356]. Therefore, central vascular stiffening and pulse wave reflections determine late systolic arterial loading [338, 346].

The impact of pulsatile load, particular wave reflections, is even more relevant in the pulmonary circulation [341, 357]: In contrast to systemic circulation, resistance

[1] The term impedance means to transfer and to apply physico-electrical and—mechanical concepts to biological issues, to explain how and under which conditions power is transmitted from one part of a system to another part, under varying circumstances [330].

and compliance of the pulmonary vasculature are inversely releated to each other, and are evenly distributed over the complete vessel tree [358, 359]. Accordingly, an elevated pulmonary capillary wedge pressure, by decreasing pulmonary vascular resistance, enhances net RV afterload, due to increasing pulsatile load relative to the resistive one [357].

However, it is hard to obtain aortic (pulmonary artery) input impedance, as a frequency domain analysis (by Fourier method) of simultaneously measured pressures and flows is required [328, 360, 361] in order to describe the relation between arterial pressure and flow within a vessel/vessel system [327]. This is a technical challenge [360, 361] and additionally, it would be quite complicated to apply the derived frequency domain factors to daily clinical concepts and routines [330]. Sunagawa [362] made vascular properties (evaluated in the frequency domain) comparable with ventricular properties (expressed in the time domain), by lumping principal elements of vascular load (peripheral vascular resistance and total arterial compliance, characteristic impedance, and systolic and diastolic time intervals) together in (effective) arterial elastance (Ea), and as such, constitutes a close approximation of arterial load [363]. Effective arterial elastance characterizes aortic input impedance, and thus arterial load that is imposed on the ventricle [362]. This "simple measure", which lumps together static and dynamic components of impedance, has been shown to perform well in experimental studies [362, 364]. Although dominated by the non-pulsatile load component (SVR), Ea is also altered by artery stiffening due to increased pulsatile load [365]. Ea is the most complete, and also reasonably applicable, delineation of aortic input impedance [330].

Operationally, Ea is numerically defined as the ratio of end-systolic ventricular pressure to stroke volume, and is directly related to heart rate and peripheral vascular resistance, and is inversely related to total arterial compliance (which is determined, in large parts, by the central elastic arteries) [366]:

$$\text{Ea} \sim \text{SVR}\left(\text{TPR}\right), \text{Ea} \sim \text{HR, and Ea} \sim 1/\text{arterial compliance}$$

[366, 367].

However, practically, Ea is derived from the pressure-volume relation, defined as the ratio of left ventricular end-systolic pressure (LVEDSP) to left ventricular stroke volume (LV-SV) [362, 363]:

$$\text{Ea} = \text{LVESP/LV - SV}.$$

This equation can be further simplified: If LVESP equals systolic arterial pressure (sBP), corrected by 0.9 [363], Ea may be calculated as: Ea = LVESP/LV-SV = sBP × 0.9/LV-SV.

Normal Ea values are around 2.0 mmHg/mL [347, 363, 368, 369].

Regarding the right ventricular—pulmonary vessel system interaction, Ea-Pulm is reported to be a reliable measure of the load faced by the RV during systole, and accounts for pulmonary vascular resistance, compliance, and impedance, thus including pulsatile components of arterial load [341, 370, 371].

However, the tension the ventricular wall sarcomeres must overcome during systole in order to shorten is related to:

(a) characteristics of the arterial system [331, 372, 373]
(b) LV cavity size/dimensions [331, 374]
(c) Pumping performance of the LV [331, 372]

Accordingly, aside from the vascular properties opposing and affecting ejection, there are specific cardiac properties contributing to, and participating in, afterload characterization. As such, myocardial wall stress during contraction represents "true" afterload, because wall stress reflects both central aortic and peripheral, vascular loading conditions and intrinsic heart muscle properties, such as LV geometry, LV size and intra-cavitary pressure [324, 375–377].

The relation between afterload and systolic ventricular wall stress can be formally defined by the law of Laplace [329, 378–381]: $\sigma = p \times r/2h$

at which the ratio r/h is a main determinant of wall stress [5, 329, 374].

(σ represents wall stress, p = ventricular pressure, r = LV or RV radius and h = wall thickness).

(The law of LaPlace applies to spherical figures, thus its transposition and application on the right ventricle with its varying regional internal radius may be problematic [380]).

Thus, directly applied:

$$\text{Wall stress (tension)} = \text{LV (RV) pressure} \times \text{LV (RV) diameter} / 2 \times \text{LV (RV) wall thickness} \quad [382]$$

Dilatation will induce an increase in LV(RV) diameter and generally in LV (RV) filling pressure, and as such leads to a rise in wall stress. An increase in wall thickness (in the case of hypertrophy) reduces the wall stress.

$$\text{LV dilatation} \rightarrow \text{increasing wall stress/tension} \quad [382, 383].$$

Determinants of the LV wall stress mediated by LaPlace's law are continuously changing during systole, producing varying measurements of LV wall stress depending on the phase of the cardiac cycle. Peak wall stress occurs within the first third of ejection, and wall stress then declines to its end-systolic value, which is less than 50% of the peak value. At the same time, the total systolic wall stress (estimated by the stress time integral), predicts myocardial oxygen consumption [384].

All measures show a significant difference and the choice of index depends on the question being asked [384]:

- total stress reflects myocardial oxygen consumption,
- peak stress correlates closely with the progress of hypertrophy, and
- end-systolic wall stress represents most accurately the afterload.

The very good correlation between end-systolic wall stress and myocardial fibre length at end-systole [69], as well as between end-systolic wall stress and

end-systolic ventricular volume (ESV) [385–387], underlines the fact that the end-systolic wall stress is literally the (after)load that limits the ejection [388, 389].

$$\text{Afterload} \sim \text{end}-\text{systolic wall stress and} \sim \text{end}-\text{systolic volume}\ [382, 385–387].$$

Furthermore, several authors have confirmed the excellent correlation between end-systolic wall stress and LV afterload in daily practice [323, 376, 386, 387, 390].

During systole, the LV-chamber size will decrease while the ventricle contracts, and thus the wall tension will fall. When the afterload increases, a greater rise in pressure is necessary for any given reduction in chamber size, and therefore, wall tension during systole is higher. The pressure increase has to be even greater, of course, in a primarily dilated LV [19].

By the way, there are two echocardiographic methods described by Reichek [378] (M-mode assessment, meridional wall stress) and Greim [391] (2D-assessment, circumferential wall stress), which directly assess the end-systolic wall stress. Both are time consuming, require advanced skills, and Greim [391] expresses concerns about the ability of the M-mode method to recognize acute changes in afterload in patients during cardiothoracic surgery.

To summarize, two alternative biophysical concepts may describe and characterize afterload [329]. Ross and co-workers [392] gave evidence, that the level of wall stress, rather than input resistance or pulsatile impedance, determine ventricular performance, favouring **wall stress** as the most exact feature **representing "true" afterload**. Furthermore, arterial input impedance specifically refers to vascular properties, while more or less neglecting cardiac properties. As such, while wall stress integrates the forces that oppose ventricular ejection, Ea is a measure of the hydraulic load faced by the ventricle [380, 393]. Wall stress is considered to be the most accurate feature to describe ventricular afterload [329]. However, while wall stress estimation has not gained any clinically feasible relevance in daily practice, Ea may be obtained with reasonable effort.

1.5.3 Afterload Mismatch and Acute Heart Failure Syndromes

In order to perform well, heart performance and afterload have to match, leading to the concept of afterload mismatch [329]: Basically, "a mismatch can be induced acutely in a normal heart if end-diastolic volume is not allowed to compensate for the increase in afterload" [394]. Subsequently, SV, EF and ventricular circumference will fall [329]. Examples include: volume depletion in the presence of rapid and substantial rise in systemic pressure, and increases in afterload in a ventricle already having utilized the maximal preload reserve with average sarcomere length exceeding 2.2 μm, indicating maximal stretch (limited by pericardial constraint, and as such explaining why there is no descending limb of the Starling curve). Imposing an extra load on such a ventricle will cause a sharp drop in SV, unless the contractility can be increased intrinsically or by applying inotropic agents [395].

1.5.4 Concluding Remarks

Afterload can be defined as the forces that oppose ventricular muscle fibre shortening [329, 396]. Features opposing comprise:

(a) load imposed by the vascular tree and the properties of the blood within those vessels [331, 358, 372, 373], and
(b) ventricular properties, which oppose contraction such as valves, and muscle fibre tension [372, 374, 396].

Systolic wall stress integrates the forces opposing ventricular ejection, accordingly, wall stress may be considered the most accurately feature characterizing the load faced by the ventricle during systole [324, 332, 375–377, 397].

However, the clinical feasibility to apply the one, or the other, method assessing the highly complex relationship between ventricular contraction, arterial system and blood flow at bedside is nearly impossible [329]. Furthermore, that one single parameter can fully encompass all aspects cannot be expected [329]. To simultaneously measure pressures, wall thickness and radius in a constantly changing system, in order to determine wall stress, is currently not feasible. Therefore, simplified derivations are necessary and as such, effective arterial elastance has gained high acceptance and is widely used, at least in medical research, to evaluate the discussed relationships, and thus get insights into pathophysiological and pathogenetic processes, interrelations, and sequences [329].

In daily clinical practice, the systemic (peripheral) vascular resistance (SVR) is the most common parameter used to describe the actual afterload, and often, SVR is used synonymously with after- load.

SVR however, only reflects the non-pulsatile component of the peripheral load under steady state conditions [398]. It does not comprise the impact of wave reflections, arterial impedance, or ventricular properties. Each of these phenomena affect LV-afterload independently of peripheral vascular resistance or arterial pressure [376]. Ageing, hypertension, and aortic stiffening contribute considerably to the pulsatile component of the afterload, and thus, this component becomes more prominent under those conditions [399, 400]. Lang [401] showed in his investigation that the measurement of SVR substantially underestimates the change in afterload when LV afterload alone was decreased, increased, or remained unchanged, but with a simultaneous increase in contractility. These findings are not surprising, because from the peripheral pressure-flow relationship, the systemic peripheral resistance is not seen by the LV [378]. Nevertheless, SVR accounts for 90% of the resistance to ejection (arterial resistance is the dominant component of impedance load [402]) [403] and thus is justified as being the most commonly used parameter to clinically estimate afterload [222]. Furthermore, SVR may be very helpful in clarifying the diagnosis [13, 128, 222], particularly in hypotensive patients, and in heart failure syndromes, as shown by Cotter [13].

The fundamental pathophysiological alteration in acute heart failure syndromes is a substantially and inappropriately elevated afterload, with a markedly elevated systemic resistance/markedly increased LV outflow impedance, exerting a high

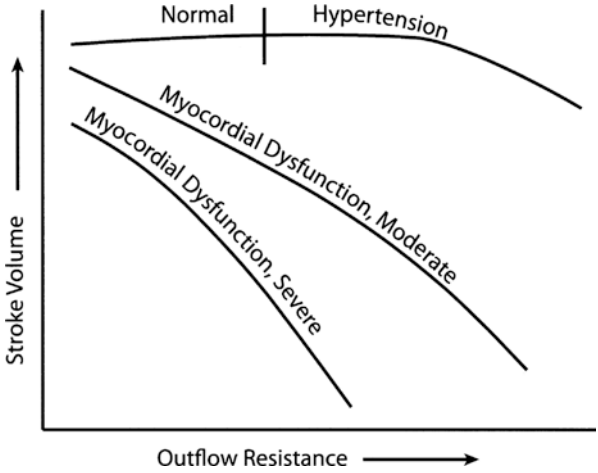

Fig. 1.6 Relation between SV (SW) and outflow resistance/impedance (adapted from Cohn, J. N. and Franciosa, J. A. [11], with permission)

(end-)systolic load on the LV during ventricular ejection [11, 19, 394]. This is referred to as afterload mismatch, defined by "a fall in SV due to inappropriately high afterload" [329, 394, 404]. In heart failure syndromes, the LV afterload becomes the decisive determinant of cardiac performance [11, 12, 14]. As early as 1977, Cohn and Franciosa published their impressive diagram showing the correlation between afterload and cardiac performance/cardiac output (SV) (see Fig. 1.6) [11].

SV depends decisively on the magnitude of the afterload [3, 46, 93]. Furthermore, an elevated (after)load causes an increase in the LV filling pressure [405], and thus affects the already compromised diastolic properties of the heart, resulting in a further reduction of the LV filling rate [406, 407]. Afterload is inversely proportional to the stroke volume, SV ~1/afterload [394], and therefore an increase in afterload should result in a fall in SV and ejection fraction (EF) [378, 408]. However, in healthy hearts, despite an increase in wall tension due to the increased afterload, normal fibre shortening is accomplished by a compensatory increase in contractility [9, 93]. In the case of impaired LV function the increase in afterload is not tolerated, fibre length shortening is impaired, and a decrease in EF results [19].

Finally, remember the following [382, 383]:

- afterload ↑ → LVEDP ↑ [355, 406, 407, 409],
- afterload ↑ → LVESV ↑ [410] and SV ↓ [410] (in healthy persons SV may be maintained due to an increase in contractility),
- afterload ↓ → LVEDP ↓ [17, 18, 411] and LVEDD ↓ [17, 18, 93, 410, 411]. Due to the law of LaPlace:
- afterload ↓ → LVEDP ↓ → diastolic wall stress ↓ → O_2–requirement ↓ [20, 410] → LVEDD ↓ [17, 18, 93, 411],
- LV dilatation → wall stress /tension ↑ → afterload ↑ [382, 383],
- ↓ LVEDP → ↓ afterload [91, 411] (implication is inevitable & in accord with the law of LaPlace),
- ↓ aortic impedance (ventricular afterload) → ↓ systolic wall stress, and vice versa [412]

1.6 Contractility

1.6.1 Definition

Contractility is defined as the **inherent capacity of the myocardium to contract independently of changes in pre- and afterload** [413]. This capacity of **Intrinsic Force** of contraction is called **Contractility or Inotropy** [414, 415].

Braunwald writes, "Changes in cardiac performance independent of alterations in pre- and afterload are caused by 'contractility'. It has to be separated from changes in the performance due to a change in loading conditions" [413].

The sympathetic tone plays an important role in the regulation of contractility. The positive inotropic effect of increased sympathetic tone enables the heart, without a change in diastolic filling (without a change in the preload), to eject a higher SV or to maintain SV in case of increased afterload or increased resistance to ejection [416]. Kumar [9] found in healthy volunteers that the increase in SV due to volume loading is predominantly caused by an increase in contractility and only in minor part by the Frank-Starling mechanism, hence confirming previous results [146, 147]. Due to the increase in 'intrinsic' contractility, the end-systolic volume will decrease [9].

1.6.2 Measurement and Quantification

It is very difficult to measure and to express contractility as a single, independent parameter. At the sarcomere level, contractility and load are interrelated; thus, they are not independent variables [417, 418]. Any parameter attempting to characterise 'true' contractility has to be independent of changes in pre- and afterload, LV-size and geometry and LV-pressure [419].

The rate of LV intraventricular pressure rise dp/dt, an index of the isovolumetric phase of the contraction [420], correlates well with the LV contractility [421]. The highest dp/dt, called dp/dtmax, throughout systole is expected to be proportional to the contractility [421]. Dp/dtmax, is sensitive of preload, but not of afterload because it is measured before the aortic valve opens [421].

Dp/dtmax shows reasonably good sensitivity to detect and express changes in the 'true' inotropic status (intrinsic contractility) [422, 423]. It is the most valuable parameter to measure and express inotropy [422–425] and is currently the gold standard in representing the 'true' (intrinsic) contractility [426].

The contractile conditions of the ventricle are influenced by intrinsic properties of the ventricle at end-systole, the chamber elastance (Ees). These contractile properties of the ventricle can be quantified by the relationship between end-systolic left ventricular pressure (LVESP) and the end-systolic left ventricular volume (LVESV) [388, 427].

The ventricular pressure-volume relationship at end-systole is linear (at least under physiological conditions [428]) and its slope, **Ees, quantifies the ventricular (systolic) contractile properties** [388, 428, 429] (read more in part 1.9.3 of this chapter) (Fig. 1.7).

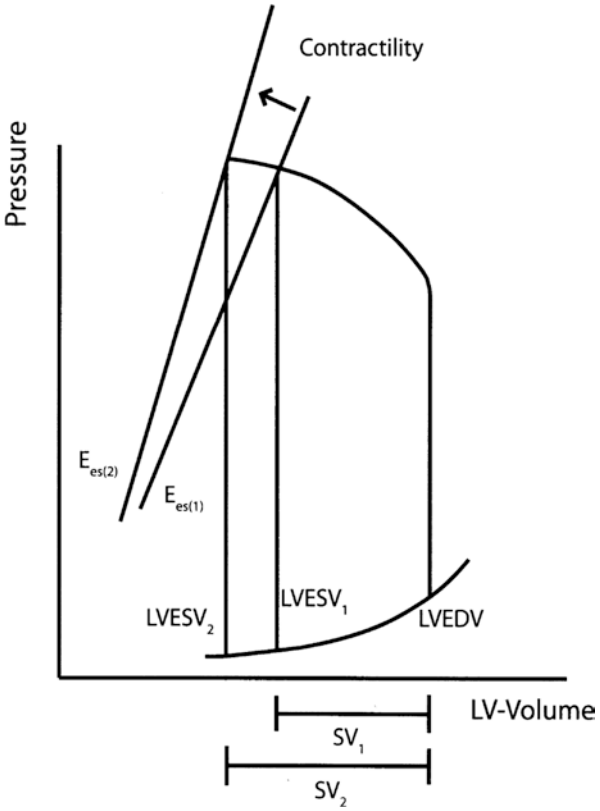

Fig. 1.7 The diagram depicts the effect of an increase in true contractility: The slope of E_{es} becomes steeper, SV increases (SV2) and LVESV gets smaller (LVESV2). Thus the improvement in contractility is reflected by a larger SV ejected, leading to a smaller LVESV while the LVEDV remains unchanged

E_{es} is defined as LVESP divided by LVESV, thus

$$\mathbf{Ees} = \mathbf{LVESP}/\mathbf{LVESV} = sBP \times 0.9/\mathrm{LVESV} \quad [430]$$

E_{es} is **roughly** load-independent [388], and Kass [431] found that over a wide range of load, E_{es} is a powerful index of true LV-contractility [432–435].

When describing the systolic properties of the heart, we must differentiate between indices referring to the 'true' contractility and to other parameters describing the systolic function of the heart muscle or the heart performance. The latter two are less independent than the other indices and haracterise the heart function in a more 'global' way. (For an overview see Baicu [368]).

LV systolic performance is characterised by the stroke work, taking into account that the heart has to generate pressure and flow (SV) [4, 93]:

$$\mathbf{LV-SW} = \mathbf{LV-SV} \times (\mathbf{LVESP} - \mathbf{LVEDP}) \times \mathbf{0.0136} = \mathbf{LV-SV} \times \mathbf{MAP} \times \mathbf{0.0136} \quad [39, 436]$$

Normal values: 58–104 $gm^{-1}\ m^2$ [437]

The systolic performance is influenced by load and ventricular configuration [438]; thus, it is not the same as contractility. Hence, abnormal performance may be present although contractility is normal (i.e. in case of high afterload) and vice versa, performance may be normal although the contractility is impaired (i.e. sepsis, MR) [438].

Whilst **cardiac work** describes the transferral of energy from the cardiac contraction to the de- velopment of blood flow [128], **cardiac power output (CPO)** describes the amount of energy generated by the heart that the whole systemic vasculature receives at the level of the aortic root [128]. Thus, it characterises the recruitable reserve still available in case of acute failure or shock in order to maintain the perfusion of the vital organs and hence reflects the severity of the patient's illness [132]. CPO has shown substantial prognostic power [128, 439] across the broad spectrum of acute heart failure syndromes and, in particular, in cardiogenic shock [128]. CPO is defined [128] as

$$\mathbf{CPO} = \mathbf{MAP} \times \mathbf{CO}/\mathbf{451}\left(\text{Watts}\right)$$

and follows the physical rules of fluids. Reflecting the essential task of the heart (to generate pressure and flow) [3, 4] CPO is a measure of cardiac pumping by coupling both pressure and flow domains [440].

Furthermore, CPO and its index, CPI, have shown superiority in determining the exact diagnosis of the actual heart failure syndrome compared to CI, BP, PCWP and their combination [13, 128]. Whilst the traditional haemodynamic measures and their presumed target values used in treatment protocols have been misleading [441], they have also failed to show any relevant effect when therapy was titrated upon reaching these values [442].

CPO appears to be a better parameter than CPI for predicting outcome. Adjustment of CPO for body size, yielding CPI, showed a weaker association with mortality [443, 444]. A CPO $\leq$ 0.53 most accurately predicts a high likelihood of in-hospital mortality [128, 439].

Conventionally SVI and SWI were used as powerful predictors of short term mortality in cardiogenic shock complicating AMI [445], but the use of CPO is now thought preferable.

The **LV systolic function** of the heart can be described in a number of ways but, **ejection fraction** (EF, %) is still the most frequently used parameter. EF is determined by the interaction of arterial and ventricular properties and is dependent on the afterload, and thus it is not exclusively governed by the LV [347, 368, 446].

$$\mathbf{EF\%} = \left[\left(\mathbf{LVEDV} - \mathbf{LVESV}\right) / \mathbf{LVEDV}\right] \times \mathbf{100};$$

$$\mathbf{EF\%} = \mathbf{SV} / \mathbf{LVEDV} \quad [447, 448].$$

However,

$$\mathbf{afterload} \uparrow \rightarrow \mathbf{EF} \downarrow \mathbf{and\ vice\ versa} \quad [378, 408].$$

As such, EF may, by all means, be considered as a good coupling parameter, describing fundamental aspects of ventriculo-arterial coupling [449, 450] rather than contractility.

EF is thus far from being an ideal parameter to assess contractility. EF depends on afterload as well as on preload and heart volume or mass [394, 423, 451, 452].

EF will fail to report:

- excess afterload (EF reduced although the contractility is normal) [453],
- in case of augmented preload (i.e. MR), EF will overestimate the systolic function, missing myocardial dysfunction [454, 455],
- in concentric LV-H, EF measurement signals normal systolic function, although substantial dysfunction may be present [456].

Normal values EF > 55% [447, 448, 457–461]; an EF > 40% is considered reasonable [457–462].

Despite its shortcomings, Braunwald [438] and Gillebert [463] state that EF is the best parameter to describe overall contractility in comparison to all others currently in use.

'True' LV-contractility is best expressed by:

- v dp/dt_{max} (mmHg/s), normal values 1400–2200 [398]
- E_{es} (mmHg/mL), normal value about 2.0 [347, 356].

E_{es} <1 mmHg/mL is found in dilated and failing hearts [464], in case of hypertrophy there will be a significant increase—up to 4 mmHg/mL [465].

It has to be stressed that CI is not an index of contractility, but rather a measure of cardiovascular flow: CI is affected by contractility, vascular stiffness and resistance, intravascular volume and filling pressures [128]. Furthermore, there is no normal CO/CI, since metabolic demands can vary widely [117].

1.6.3 Inotropic Medications

Medications able to increase the myocardial contractility are called **inotropes**. In recent years the administration of inotropic drugs has been overshadowed by clear and growing evidence of adverse events and increased mortality [143, 466–470], particularly when given in patients with reasonably preserved left ventricular function (EF > 40%) [471, 472]. Conners [473] and Sandham [474] found a **significantly increased mortality when clinically stable patients** were treated with conventional inotropic agents secondary to numerically low cardiac output. Only patients who absolutely require inotropic support secondary to low output as result of severely **impaired** contractility and who are **resistant** to other treatments should be treated by such drugs [462, 475].

The European Society of Cardiology (ESC) recommends inotropic agents in heart failure syndromes if the illness has deteriorated to become life-threatening and

the situation has become critically dependent on the haemodynamics: "Inotropic agents are indicated in the presence of peripheral hypoperfusion with or without congestion or pulmonary oedema refractory to diuretics and vasodilators at optimal dosages" [462].

1.7 Heart Rate and Contractility

At the end of the 19th century Bowditch published his observation that the force of heart con- traction increases—up to a limit—with an increase in heart rate [414].

The peak isometric force increases with increasing heart rate [414, 476]. This is due to the fact that calcium will accumulate within the myocytes when diastole shortens [477] (which happens with increasing heart rate). In the case of a compromised or failing heart this effect is attenuated, or even the opposite may happen—with increasing heart rate the force of contraction will decrease [476, 478]. When the tachycardia exceeds 130/min, the severity of myocardial impairment correlates with the extent of tachycardia [479]. Furthermore, tachycardia will always precede a fall in BP [293].

Thus, in the **case of tachycardia** in a compromised heart the reduction in heart rate will **increase the cardiac contraction and hence SV** (MAP and organ perfusion):

$$\text{Heart rate} \downarrow \rightarrow \uparrow \text{EF} \quad [480]$$

In heart failure patients developing or suffering from atrial fibrillation, a heart rate of 100–110/min is acceptable [481].

1.8 Diastolic Ventricular Interaction/Interdependence (DVI)

1.8.1 Definition

The right and the left ventricle are anatomically and functionally closely interrelated, since they share the interventricular septum (IVS), the pericardium, and (by their continuity) parts of myocardial fibres [482]. Ventricular interdependence characterizes the "response of one ventricle to the changes in pressure and volume of the other" state Elzinga et al. [483]. However, the interactions include even more features as they refer to the changes in size (volume), shape, pressure, and (concomitantly) compliance of one ventricle due to direct, predominant mechanical (independent of neurohormonal and circulatory effects), impact on the other [482], and further to a systolic contribution of the LV to RV contractile performance [393, 484]. Accordingly, *diastolic ventricular interaction* largely refers to the competition of the two ventricles for space within the non-distensible pericardial sack, namely when RV dilates, and *systolic ventricular interaction* applies to the contribution of LV to RV systolic performance (read more about this issue in Chap. 4) [393]. The impact may be even dramatic in case of acute changes in RV size and pressure [24, 41, 47, 485].

These diastolic interactions are mediated via the shared structures of the two ventricles, the interventricular septum and the pericardium. The pericardium has constraining effects on ventricular filling due to its poor distensibility and its pressure transmitting effects [47, 486]. The interaction mediated by the septum and the pericardium is called 'direct' interaction, compared to the so called 'series' interaction which refers simply to the physical relation between the two ventricles and their outputs: The two ventricles are coupled in a row, one after the other and thus their output necessarily has to be equal over time [31, 41].

1.8.2 Septum and Trans-septal Pressure

The shape of the septum, under physiological conditions, is concave when viewed from the LV side. There is no difference during systole and diastole, due to the fact that the LVEDP always remains higher than the RVEDP and increases proportionately during systole [41]. Kingma established proof that the position of the septum is determined by the end-diastolic pressure gradient between LV and RV [487]:

$$\text{Transseptal pressure gradient} = \text{LVEDP} - \text{RVEDP} \quad [487].$$

In disease, the position of the septum can change markedly due to changes in the pressure gradient, which will alter the end-diastolic volumes substantially [47, 48, 119, 487, 488]. In acute RV pressure or volume overload Kingma showed that the interventricular septum becomes flattened or even convex at end-diastole due to RV dilatation and raised RVEDP, diminishing the transseptal pressure gradient and pushing the septum towards the left ventricle [487]. Numerous publications confirm the change in the septum position in different diseases such as acute and chronic pulmonary hypertension [47, 48, 489], congestive heart failure [23, 24], and mechanical ventilation [119].

This leftward shift of the septum contributes significantly to the reduction in LV-filling; thus, total LV-volume and end-diastolic volume are reduced and the SV will fall as a consequence.

The very poorly distensible pericardium supports this process by exerting constraint, restricting the total heart volume from changing [478, 490].

1.8.3 Pericardium

All cardiac chambers (except the posterior part of the LA where the pulmonary veins enter) are enclosed by the pericardium. It works as a tight, unyielding band around the minor axis of the heart, fixing the cross sectional area of the heart and causing direct ventricular interaction [491].

Thus, an **increase in the cross-sectional area of one ventricle**, e.g. due to volume loading or enlargement, necessarily **reduces the area of the opposite ventricle** with less filling potential, **causing an increase in the pericardial pressure**, and **altering the transmural pressure** [23, 491]. The total cardiac volume remains **unchanged** [488, 490].

Increasing pressures in the pericardial space will exert a progressive restraining effect on ventricular filling, termed **pericardial constraint** [488]. When the pericardium becomes stretched due to enlargement of the ventricles, such as in chronic heart failure or due to volume loading, the filling—in particular the left ventricular filling—becomes significantly restrained [23, 127]. With further stretch the pericardium is even less distensible [486] and, **especially in cases of acute change**, the pericardium, with its constraining effect, plays a key role in loading conditions [85, 492–494]. Under those conditions the pericardial pressure (PP) will increase progressively and will significantly constrain the filling. PP rises in an exponential manner [491] and once the pericardium becomes 'overstretched', an exponential increase in LVEDP is seen [83, 495].

Raised intra-thoracic pressure, e.g. due to raised intra-abdominal pressure, chest infection, etc., will affect, secondary to an increased constraint on the thin walled RV, the RVED**P** more than the LVED**P** (rise in RVEDP > rise in LVEDP) [47, 48]. Hence, the transmural LVEDP (= LVEDP − RAP/CVP) will decrease with less LVEDV and less LV end-diastolic fibre stretch, and a reduced SV will result.

Ventricular interaction due to pericardial constraint is diminished as long as the PP is <5 mmHg [126]; when exceeding 9–10 mmHg the pericardium will exert a significant constraint on ventricular filling [63, 127]. Furthermore, when intraventricular LVEDP exceeds 10(12)–15 mmHg, the LVEDP-LVEDV relation becomes much steeper and the pericardium limits further increases in LV volume [83, 133, 495].

1.8.4 Pulmonary Hypertension and the Risk of DVI

In **pulmonary hypertension** fluid administration is shown to increase RVEDP more than LVEDP [47, 48]. The concomitant (along with RVEDP) increase in pericardial pressure will exceed the rise of the LVEDP (due to a higher increase of RVEDP compared with LVEDP), thus transmural LVEDP and therefore LV-preload will be reduced due to pericardial constraint [23, 51] (Fig. 1.8).

Fluid administration in pulmonary hypertension

$$\rightarrow \uparrow \text{RVEDP} > \uparrow \text{LVEDP}\left(\text{more constraint on RV}\right), \text{and}$$
$$\uparrow \text{PP} > \uparrow \text{intraventricular LVEDP}$$
$$\rightarrow \text{transmural LVEDP} \downarrow \text{and thus LVEDV} \downarrow \left[23, 39, 42\right] \text{with consecutive}$$
$$\downarrow \text{LV} - \text{SV} \quad \left[36, 37\right].$$

(An additional effect will be exerted by the leftward shift of the septum, reducing the LV-area and thus the LVEDV [47, 48, 489]).

1.8.5 Acutely Exacerbated Chronic Congestive (Left-Sided or Biventricular) Heart Failure

An acute exacerbation of chronic congestive heart failure is often crucial in the disease's course and may be the final point in a critical illness [496, 497]. In this

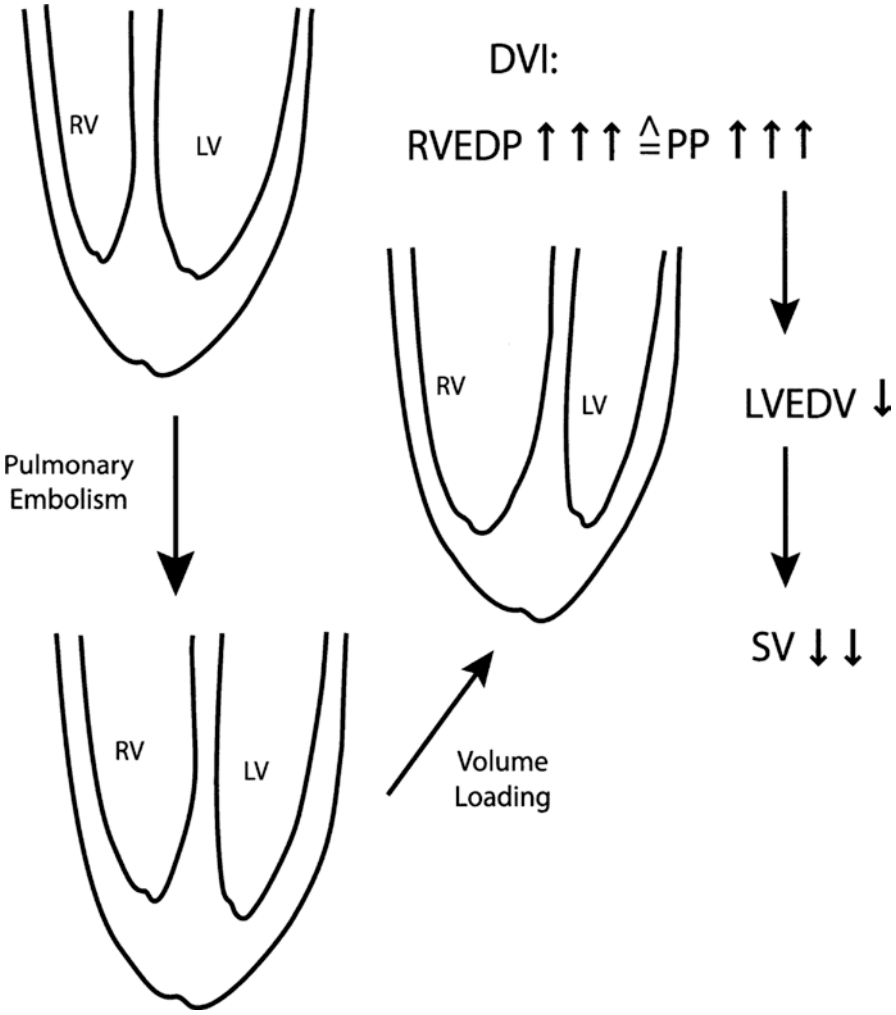

Fig. 1.8 Effect of DVI in pulmonary embolism and consecutive fluid loading. Modified from I. Belenkie [41, 47], with permission

situation, **DVI** may have a substantial impact on the haemodynamics and has to be taken into the therapeutic considerations [47, 48, 498, 499].

A sudden rise in RV-afterload/increase in RV-outflow impedance, e.g. pulmonary embolism, PE, and/or a loss in contractility, e.g. due to acute RV myocardial infarction [500, 501], will always induce RV dilatation [502, 503], a fall in RV-EF [502, 503] and a substantial increase in RVEDP [69, 382, 504]. This implies a considerable rise in PP and a leftward shift of the septum, which compromises LV filling [23, 39, 42, 44, 54, 56, 63, 487, 488, 490].

$$\textbf{Acute} \uparrow \textbf{RV-outflow impedance / RV-afterload}$$
$$\downarrow$$
$$\text{RV-dilatation}\left(\text{RVEDD} \uparrow\right), \uparrow \text{RVEDP, and} \downarrow \text{RV-EF}$$
$$\downarrow \textbf{DVI}\left[47, 48, 498, 499\right]$$
$$\downarrow \text{transmural LVEDP} \rightarrow \downarrow \text{LV-SV}\left(\text{LV-SW}\right)\left[23, 39, 42\right] / \downarrow \textbf{blood pressure}.$$

Atherton [24] showed that, in patients with **chronic congestive heart failure and high LVEDP** (causing pulmonary venous hypertension), LV-filling was markedly impeded due to direct diastolic ventricular interaction via the septum and from the stretched pericardium (pericardial constraint): Volume unloading resulted, as expected, in reduction of the RVEDV, but LVEDV "paradoxically" increased (see Fig. 1.9).

In nearly 50% of all patients suffering from congestive HF, pericardial constraint plays a marked role [24] and unloading leads to an improvement in cardiac performance. Even if there is less pericardial constraint present, as in the other 50% of patients studied by Atherton, the reduction in LVEDV secondary to volume unloading did not significantly compromise the haemodynamic situation.

These results are consistent with the findings by Dupuis, who showed that a reduction in PCWP in patients with congestive HF resulted in an increased SV and SW even though LVEDP fell [49]. Stevenson established in 1986 that volume unloading in patients with severe congestive heart failure and high filling pressures showed clear beneficial results, with an improvement in clinical short and long term outcome [67].

Moore explored the underlying pathophysiological mechanisms and established our current therapeutic approach [23]. In patients with congestive HF, and thus secondary pulmonary hypertension, direct diastolic ventricular interaction plays a substantial role in the LV-dysfunction responsible for the reduced LV-SV. The common approach of administering volume to a patient with low blood pressure will, in acutely decompensated chronic heart failure, worsen the haemodynamic and clinical situation [23]. Volume unloading will stabilise the situation (Fig. 1.9).

Pathophysiology of chronic congestive HF:

$$\text{LV is enlarged, LVEDP} \uparrow \left(\text{often high}\right) \rightarrow \text{RVEDP} \uparrow - \uparrow \uparrow$$
$$\rightarrow \text{RVEDV/RVEDD} \uparrow$$

The **elevation of the RVEDP** is due to **pericardial constraint** [23, 24] following the rule of total cardiac volume [488, 490] and/or due to (chronically) ↑ **RV-afterload** (pulmonary hypertension caused by ↑ LVEDP) [502, 505–507].

Furthermore, an elevated RV-afterload/elevated RV outflow impedance, as found in pulmonary hypertension due to a raised LVEDP, will always induce RV enlargement, hence ↑ RVEDD and ↑ RVEDV [502, 503, 505].

Thus: ↑ - ↑ ↑ ↑ in RVEDP, and the ↑-↑ ↑ ↑ in RVEDD and RVEDV → parallel ↑-↑ ↑ ↑ PP [44, 56, 57, 63].

However, as a result of the volume and pressure changes, the interventricular septum will take a position somewhere in the middle between the ventricles and thus more to left as physiologically.

If volume is given in this situation:

$$\text{Volume loading} \rightarrow \text{further} \uparrow \text{RVEDP}\left(\text{with} \uparrow \text{RVEDP} > \uparrow \text{LVEDP}\left[47, 48\right]\right) \rightarrow$$
$$\uparrow \text{in RVEDD due to} \uparrow \text{RVEDV and}\left(\text{further}\right) \uparrow \text{PP}$$
$$\downarrow$$

1. $\text{transseptal pressure gradient now} \downarrow [489], \text{and hence leftward shift of the septum} \rightarrow \text{reduced LV} - \text{filling}\left(\text{constant total cardiac volume}\left[490, 492\right]\right)$
$$\rightarrow \mathbf{LV - SV} \downarrow \left[36, 37\right].$$

2. due to a parallel rise of PP with RVEDP [44, 56, 57, 59, 63], the pericardial constraint will increasingly impede LV filling:
$\text{transmural} - \text{LVEDP} \downarrow \rightarrow \text{LVEDV} \downarrow \left[23, 35, 39, 42\right] \rightarrow \mathbf{LV - SV} \downarrow \left[36, 37\right]$

Unloading is the treatment of choice (GTN, diuretics):

$$\mathbf{Volume\ unloading} \rightarrow \quad \text{RVEDP} \downarrow, \text{RVEDV} \downarrow \text{and LVEDP} \downarrow \left[23, 24, 49\right]$$
$$\left(\mathbf{but}\ \text{LVEDP} \downarrow < \text{RVEDP} \downarrow \left[47, 48\right]\right),$$
$$\text{PP} \downarrow \left(\text{equal and parallel to RVEDP}\right)\left[44, 59, 63\right]$$
$$\downarrow$$

1. $\text{Transseptal pressure gradient} \uparrow [489], \text{hence septum shifts to the right} \rightarrow$
$\text{LV} - \text{area} \uparrow \left(\text{LVEDD} \uparrow\right) \rightarrow \text{LVEDV} \uparrow \rightarrow \mathbf{LV - SV} \uparrow \left[36, 37\right].$

2. $\text{Less pericardial constraint of the left ventricle due to} \downarrow \text{PP} \rightarrow$
$\text{transmural LVEDP} \uparrow \left[23,\ 24,\ 35,\ 49\right] \rightarrow \text{LVEDV} \uparrow \left[23,\ 24,\ 39,\ 42,\ 49\right]$
$$\rightarrow \mathbf{LV - SV} \uparrow \left[36,\ 37\right].$$

Although the heart is unloaded, the SV increases: This is often called the 'paradoxical ↑' in SV.

(As you can see, the term" **LV-SV ↑** [36; 37] "is always on the far right side and always one below the other)

A simplified summary of the unloading process [27]:

RV-preload ↓ → RVEDV ↓ → RVEDD ↓ → LVEDD ↑ → LVEDV ↑ → LV-SV ↑/BP ↑

It is important to remember that evidence of haemodynamically significant DVI was found in 50% of all patients with congestive HF, and even if a relevant DVI is not present, unloading reduced the LVEDV only marginally and did not compromise the haemodynamic situation (no fall in blood pressure) [23–25, 42, 49]. Hence, all patients with acutely decompensated chronic congestive heart failure should be treated by volume unloading.

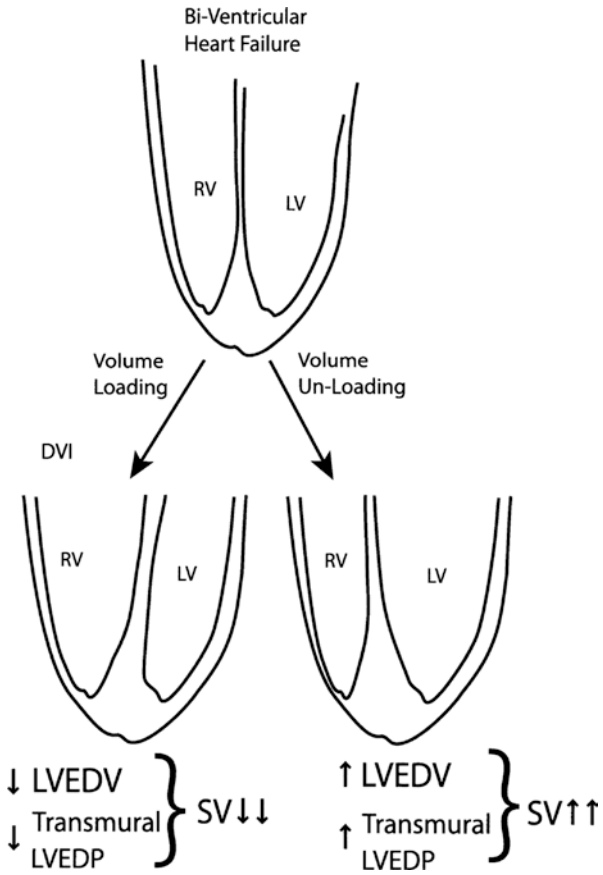

Fig. 1.9 Diagram to show the position of the interventricular septum in different loading conditions due to DVI effects in patients with bi-ventricular heart failure

1.8.6 Conclusions

Ventricular interaction has a considerable impact on the haemodynamic situation, particularly in critically ill patients with circulatory compromise [39, 47, 171, 508]. Circumstances **suggestive of significant DVI** are the **combination of pulmonary hypertension (PH) and elevated CVP**, especially in right-sided heart dysfunction/failure, which always implies increased PP [39].

Examples are:

- **acute pulmonary embolism** [47],
- **acute right HF** (RV-AMI, ARDS, sepsis) [42, 176, 506],
- **exacerbation of chronic RV-dysfunction** (COPD with acute exacerbation) [48],
- **acutely exacerbated chronic congestive HF** [23, 24, 49, 506, 507] **with enlarged LV, particularly in cases where the LVEDP is high** [23, 24, 49],
- **intubation and mechanical ventilation, in particular in patients with acute/chronic pulmonary hypertension** [48, 119],
- **PEEP** effects the heart in the same way as (cardiac) tamponade [177]; when PEEP >12 mm H_2O, an RV-pressure load (RVEDP ↑) and a septum shift was found [509],
- **other causes of a considerably increased intra-thoracic pressure** [70] such as severe chest infection, tension pneumothorax [56] and **increased intra-abdominal pressure** [71] as in severe abdominal infection, ascites or abdominal compartment syndrome.

All of the above will have an impact on the potential therapy and consideration of these should change our daily practice markedly [23, 25, 42, 47, 485, 510].

Volume loading can no longer be recommended in acute RV dysfunction/RV-failure [47, 83, 126, 496, 511, 512] and volume loading due to low blood pressure in acutely decompensated congestive heart failure carries a very high risk of worsening the situation and, as such, unloading is the approach of choice [23, 24, 42, 49, 143, 513, 514].

1.9 Ventriculo-Arterial Coupling

1.9.1 Definition

Ventricular-arterial coupling refers to as the interaction between ventricular and arterial system and describes the transmission of the ventricular performance to the systemic circulation [515]. V- a-coupling is a major determinant of net cardiovascular performance [342] and cardiac energetics [516].

Starling demands that the evaluation of the LV performance should only be done in the context of its interaction with the systemic arterial system [516]—a requirement proposed elsewhere as well [11, 13, 513, 517]. The systolic function can only be evaluated in light of the afterload which the ventricle faces during systole [13, 128, 368, 462].

The heart has to generate flow and pressure to ensure an adequate output [4, 93]. The net flow and pressure output developed by the heart as a pump depends upon [93]:

- intrinsic properties of the heart (end-diastolic and end-systolic chamber stiffness),
- properties of the blood—contribute to the arterial load,
- arterial properties (arterial load) comprising arterial compliance, characteristic aortic impedance, SVR, and the pulsatile component (in particular wave reflections) of the vessel system.

Vascular and ventricular properties have to match in order to achieve a maximal, efficient transfer of mechanical energy aiming for maximal SW [427, 516, 518–520].

Studies by Piene [521] and by Piene and Sund [223] have established that the work of the heart and the interaction of the ventricle with the arterial system can be calculated from the ventricular pressure-volume – time relationship and the load impedance [223, 521].

1.9.2 Arterial Elastance

The characterisation of the vascular load faced by the ventricle during systole is commonly described by the effective arterial elastance (Ea) [362, 363, 520]. It was Sunagawa [362] who 'distilled' the vascular impedance into the 'effective' arterial elastance (characterising the arterial pressure measured in the arterial system at any given ejected SV [402] which can easily be coupled with ventricular pressure-volume loops and relations [522]). The effective arterial elastance incorporates the principle elements of the vascular load [427] as:

- peripheral resistance,
- total lumped vascular compliance,
- characteristic impedance, and
- systolic and diastolic time intervals.

The assessment of the arterial load that opposes left ventricular ejection is performed by applying the Fourier method analyzing the aortic input impedance spectra derived from simultaneously measured aortic pressure and flow conditions [336]. Sunagawa [362] made it possible to compare vascular properties (evaluated in the frequency domain) with ventricular properties (expressed in the time domain) by lumping principal elements of vascular load (peripheral vascular resistance, and total arterial compliance, and characteristic impedance) in consideration of systolic and diastolic time intervals, together in arterial elastance, Ea, which can be easily compared with ventricular elastance, Ees. Ea is directly related to peripheral resistance and inversely to vascular compliance [366], the latter a stiffness component (change in pressure in relation to change in volume—which exactly is compliance) [450].

Hence, "Ea combines various aspects of the total arterial input impedance into effective stiffness" dominated by arterial resistance as the primary component of

impedance load [402]. The advantage of impedance as a descriptor of hydraulic load (vascular load) is that it characterizes the properties of the vessel bed **independently from cardiac output** [523, 524]. Furthermore, Ea has been shown to reflect aspects of the ventricular-arterial interaction [372, 523] and, insofar, is a coupling parameter as well [372].

1.9.3 Ventricular Elastance

The mechanical energy of ventricular contraction is transferred to the blood within the chamber, providing it with hydraulic energy [525, 526] to face the impedance of the vascular system (the arterial load) and enabling the heart to overcome those afterloaded forces [13, 327, 368].

The power of output and the stroke work generated depend on:

- preload (preload dependent recruitable SW/SV—described by the law of Frank [36] and Starling [37]),
- input impedance of the arterial system, Ea [327, 362, 519],
- **intrinsic properties of the ventricle at end-systole**, the so-called **chamber elastance (Ees)** [428, 429, 527].

The **intrinsic ventricular properties at end-systole** are scientifically depicted by the pressure- volume relation [388, 427]. The **slope of ventricular pressure-volume relationship at end- systole, Ees, quantifies the ventricular contractile properties** [388, 428, 429]. The ventricular compliance is the inverse of elastance [374].

Ees is widely regarded as a load-independent index of LV contractility [428, 528]. However, it is also influenced by the geometric and biochemical properties (including stiffness/compliance of myocytes, composition of muscle, fibrosis, collagen in the LV wall [529]) that underlie left ventricular end-systolic stiffness [365]. Still, is very likely that acute changes in Ees reflect acute alterations in LV contractility, whereas baseline values of Ees represent an index that integrates intrinsic LV contractility as well as the modulating effects of geometric, structural, and functional properties of the LV [402]. Accordingly, caution is advisable when interpreting Ees, as an increase may be due to changes in ventricular properties (stiffening) or may signalize an (ture) increase in contractility [529]. Particularly, if other parameters indicative for systolic function are unchanged and normal, the increase in Ees reflects changes in geometric or biochemical properties, e.g. ventricular stiffening, rather than an enhanced contractility [529].

An Ees (= LVESP/LVESV [430], normal value ~2.0 mmHg/ mL [347, 356]) of <1.0 mmHg/ mL is found in dilated and failing hearts [464] whereas an Ees > 3–4 mmHg/ mL is found in hypertrophied hearts [465].

Abnormal end-systolic ventricular stiffness is a **characteristic** finding in **diastolic dysfunction** [530–533] and **increased left ventricular stiffness** makes the patient **vulnerable to developing pulmonary oedema** [533].

1.9.4 Ventriculo-Arterial coupling

It is exactly ventriculo-arterial coupling which specifically refers to the relationship between ventricular contractility and afterload [534].

The Ea /Ees ratio describes the coupling of the ventricular and arterial system. Ea /Ees is a predictor of the efficiency of the energy transfer from the ventricle to the vascular system [535] and reflects the matching of cardiac systolic and arterial properties [464]. The Ea/Ees ratio is further a useful parameter in order to characterise the LV-pump function under varying loading and inotropic conditions [427, 516, 536]—**LV performance can only be assessed in the face of loading conditions** [11, 13, 513, 516, 517].

The Ea /Ees ratio provides information about:

- overall systolic LV-function,
- max. LV-SV (SW), and
- mechanical efficiency of the LV-pump [516, 537]

Transmission of power from one part to another part of the system is maximized when output impedance of the power producing part and the input impedance of the power receiving part of the same system are equal as we have learned from electrical and mechanical systems [330]. As such, maximal external ventricular work generation for a given load applies if Ea and Ees are exactely equal. However, the normal, physiological ratio of Ea /Ees in humans ranges between 0.6 and 1.2 [395, 538, 539]. This is owed to a better efficiency defined as the ratio between work generated by the heart during ejection and the heart's oxygen consumption [536, 540]. Certainly, maximal work generated does not match with maximal efficiency at a given loading condition [541]. The heart always intends to maximize efficiency—thus to cautiously handle oxygen and energy resources and to achieve optimal energetic efficiency [347, 348, 365, 537]. Thus, physiologically, Ees may be double as high as Ea indicative for optimized efficiency, and normal coupling allows for adequate flow output at the lowest energy cost [542]. In moderate heart failure, Ees and Ea may roughly equal affording maximal stroke work from a given load at the cost of efficiency [530, 543].

Uncoupling is an issue in acute heart failure [544], moreover, heart failure may be considered as a coupling malady since progressively blunted coupling is seen in heart failure patients [545].

As a rule, a decrease in Ea will lead to an increase in Ees [546] and vice versa [515]. Furthermore,

$$\mathbf{Ea/Ees \sim 1/EF} \quad [537]$$

(assuming the intercept volume (Vo) is zero or nearly zero, which is not the case in dilated hearts [372]).

An Ea/Ees ≥ 2 reflects, in general, a depressed LV inotropic state (Ees ↓) coupled with high vascular resistance (Ea ↑) [464, 530].

As such, E_a/E_{es} is an important determinant of net cardiac performance [342] and cardiac energetics [516]. Appropriate matching between LV and the arterial system

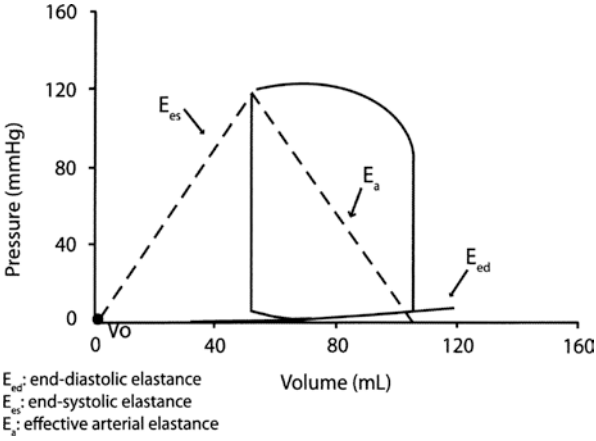

Fig. 1.10 This diagram depicts Ea and Ees in the PV-relationship of the venticle, modified from Kass [342] with permission

at rest results in an optimal transfer of blood from the LV to the periphery without excessive changes in pressure, an optimal or near-optimal stroke work and energetic efficiency [365].

E_a/E_{es} is inversely related to EF and the advantage of E_a/E_{es} over EF is that examining the components of E_a/E_{es} allows us to evaluate whether alterations in E_a/E_{es} are due to alterations in arterial properties, left ventricular properties, or both [345] (Fig. 1.10).

1.9.5 Deranged Coupling

With aging and in diseases such as hypertension, Ea increases [347, 356, 547, 548]. An increase in Ea is accompanied by an increase in Ees due to a rise in ventricular stiffness [347, 356, 549, 550]: The diastolic cardiac function is affected by the arterial compliance and an increase in vascular stiffness will lead to a concomitant reduction in ventricular compliance [356]. As described above, Ea and Ees have to match in order to achieve optimal energy transfer and mechanical efficiency, thus, the increase in Ees may be seen as a necessary adaption in order to match the vascular properties [347, 516, 530].

On the other hand, Ees is known to be pathologically high in diastolic dysfunction [356, 530–533, 551] and specific myocardial diseases such as amyloidosis [552].

However, these circumstances may lead to adverse or deranged **coupling,** where Ea and Ees do not match and the transfer of energy from myocardium to vasculature becomes inefficient. In the case of impaired LV compliance, as in diastolic dysfunction, adverse coupling may allow a rise in afterload (i.e. increasing blood pressure, increase in circulating volume) to cause a **disproportionate** increase in Ees and Ea (increase Ees > increase Ea) [347, 356]. Furthermore, LV stiffness in the presence of vascular stiffening is shown to amplify the impact of even small increases in LV-filling on cardiac workload and arterial pressure reflected by a disproportional increase in sBP for any

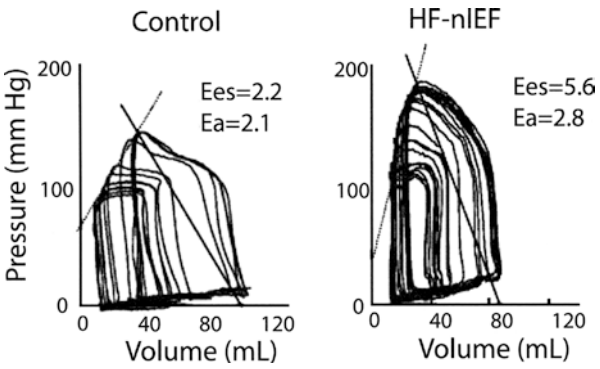

Fig. 1.11 Secondary to a rise in afterload (BP ↑), E_{es} of 5.6 measured in HFNEF increased by 145% (compared to normal controls) while the E_a increased by just 33% (adapted from Kawaguchi [356]) with permission

relative change in LVEDV [347, 427]. Severe consequences may result: Najjer [553] concluded that an acute rise in Ea, but with an otherwise normal arterial elastance, might induce a substantial increase in LVEDP in the elderly with higher Ees (age-related). Hundley showed that a reduced aortic distensibility (Ea ↑) can cause (acute) heart failure [547] and Kawaguchi [356] established further substantial evidence that arterial stiffening when combined with ventricular stiffness (attributed to age, hypertension and/or diastolic dysfunction) can lead to pulmonary oedema [538, 554] (see Fig. 1.11). This condition can occur when **deranged coupling** causes a marked rise in the systolic LV-load secondary to acutely altered afterload [356]. The increase in systolic load induces a prolongation of the diastolic LV-relaxation [355, 555] and **compromises LV-filling** [355], the latter both induce a substantial increase in LVEDP [355, 530] which may lead to decompensation and pulmonary oedema [538, 554].

Therefore, **acute changes in afterload** along with deranged ventriculo-arterial coupling producing a disproportionate transmission of vascular stiffening onto the ventricle [323] can increase the LVEDP markedly [311, 324, 513]. Hence, **flash pulmonary oedema** may be seen as a vascular, rather than a purely cardiac disorder [323, 513].

(This pathophysiology is quite different from that underlying pulmonary oedema in chronic congestive heart failure, where it usually develops relatively 'slowly' due to (severe) fluid overload [556]).

1.10 Myocardial and Chamber Stiffness

Myocardial stiffness describes the passive, diastolic elastic properties of the myocardial tissue (and as such provides insights into the specific cellular and tissue structure and composition (material properties)), but also reflects functional features such as elastic recoil, a passive mechanical force stored during contraction, of the myocardium as well [85, 557, 558].

Myocardial stiffness is derived by relating stress (which is measured in force per area) to strain (which is calculated as a percentage of distension) [85], raising muscle stretch implies increased stiffness [559]. While *myocardial stiffness* basically refers to "material properties", the so-called intrinsic properties (of the cardiomyocytes and of the extracellular matrix [560]), *chamber stiffness* delineates and integrates myocardial stiffness with ventricular geometric issues, as well as with "extrinsic", external forces (such as pleural pressure, right ventricular loading conditions, pericardial pressure, atrial contraction, coronary vascular volume all influencing the chamber characteristics) [25, 85, 557, 558].

Thus, **myocardial stiffness** and **chamber stiffness** need to be thoroughly **distinguished** [558].

Accordingly, *chamber stiffness* is determined by:

(a) **myocardial stiffness**,
(b) **external forces** (mechanical RV loading conditions / pulmonary-cardiac interaction, pneumo- pleural issues, especially pleural pressure, pericardial pressure, atrial contraction, diastolic suction, and coronary vascular volume), and
(c) **LV geometry** (chamber size, shape of heart, wall thickness, fibre orientation) [80, 85, 558].

Most impact can be expected from (a) diastolic relaxation and the associated diastolic suction in early diastole, and (b) the ventricular interdependence modulated by the pericardium in late diastole [80]. If diastolic suction (in healthy persons, LV effectively "pulls" blood to fill in early diastole, called diastolic suction [561, 562]) is blunted as in PH, left-sided filling pressures increase [561, 563–565].

LV diastolic chamber stiffness is the inverse of chamber compliance [557, 558].

The diastolic pressure-volume curve (PV-curve) reflects all three determinants, ventricular geometry, extrinsic features and the passive myocardial stiffness of the heart [85, 557]. "The slope of the tangent to this mono-exponential, curvilinear shaped function defines chamber stiffness at each level of filling pressure" [558].

As altered chamber stiffness can be attributed to changes in intrinsic, geometric and/or extrinsic features, or a combination, changes in the characteristics of the PV-curve may be helpful to distinguish between different reasons. Indeed, an increase in **intrinsic diastolic stiffness** will cause a steeper slope, with an increase in the curvature of the PV-relation at the same level of filling pressure, reflected by a **leftward and upward shift** of the PV-curve [533, 565–567] (see Fig. 1.12). Differently, **parallel upward shifts**, with **no change of the slope at the same pressure level**—denoting similar LV "intrinsic" diastolic properties (unchanged cardio-myocyte stiffness and extracellular matrix composition [568])—in general indicate "**extrinsic**" forces and altered "external" conditions, paticularly altered right ventricular loading

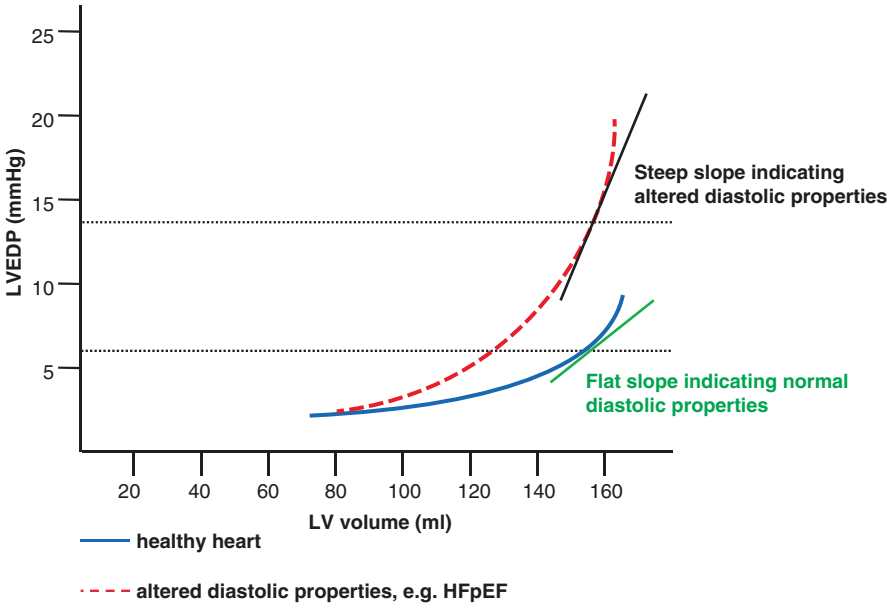

Fig. 1.12 Diastolic pressure–volume (P-V) relation—observe the different gradients of the slopes of the respective curves. Adapted from Borlaug BA. Circ Heart Fail 2014; 7: 2–4 [577], with permission

conditions, pneumo-pleural and pericardial effects [539] impacting the position of the PV-curve [85, 569] (see Fig. 1.13).

As such, Alderman and Glantz [85] demonstrated parallel PV-curve shifts, provoked by acute hemodynamic manipulations, without any change in diastolic stiffness. This was largely caused by the predominant influence of RVEDP and pericardial constraint (angiotensin exerts restrictive forces on the pericardium [495, 570]), associated with DVI, resulting in a parallel upward (angiotensin), or parallel downward (nitroprusside), shift of the relation and of the amount of LVEDP [85] (see Fig. 1.13).

Acute changes in chamber stiffness are largely caused by **external forces** and their associated effects [85], and are generally not able to alter intrinsic diastolic myocardial properties of normally oxygenated myocardium [85, 559].

As such, acute volume loading shows a sizable influence (mediated by pericardial constraint and associated DVI, as acute volume loading leads to an increase in RA-P and RVEDP, and thus, will exert stress on the pericardium) on the level of the LVEDP—a parallel upward shift of the PV-relation [571]. Even in healthy volunteers, transient noticeable, but significant increases in LV filling pressures, with parallel upward shifted PV-relations during rapid volume loading (attributed to RV loading and its interaction with the pericardium), have been demonstrated [572]. This pericardial impact on LV filling pressures is reported to become clearly active

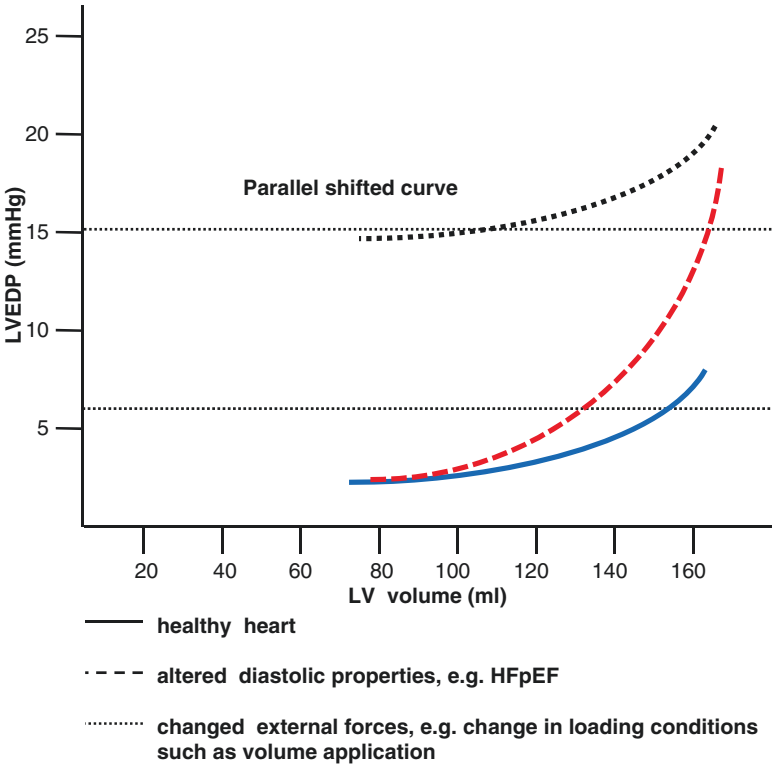

Fig. 1.13 Acute volume loading, but also acute increases in afterload, e.g. raised systolic blood pressure, may lead to a parallel upward shift of the p-v relation (the blue curve of a healthy person is shifted upward in parallel, dotted black curve) as they alter extrinsic conditions [85], while variations in the steepness of the slope represent true changes in intrinsic diastolic properties. Adapted from Borlaug BA. Circ Heart fail 2014; 7: 2–4 [577], with permission

at LV filling pressures above 10 mmHg as pericardial stiffness substantially increases at this level [493, 573–575].

Dauterman reported that extrinsic forces, primarily attributed to the filling of the right ventricle and the constraining effects of the pericardium, contribute 30–40% to the total diastolic filling pressures under physiological conditions [25].

Accordingly, acute increases in filling volumes result in higher filling pressures [85], shifting the PV-curve upward in parallel. Reductions in RV filling due to venous vasodilation, e.g. vasoactive agents such as GTN or nitroprusside, lowering RVEDP are shown to result in parallel downward shifts of the diastolic pressure volume curve [85, 576].

For our daily practice, a single measurement of the LVEDP can indeed show if the LVEDP is elevated or not. However, it cannot tell us if "the slope" has changed or not. To find this, several measurements with different conditions would be necessary to determine the PV-relation.

"Myocardial stiffness and relaxation largely determine ventricular diastolic function" [578], and therefore ventricular chamber stiffness [560]. Diastolic chamber stiffening is basically attributed to diastolic dysfunction caused by myocardial stiffness [365]. Altered myocardial properties include myocyte size, intra-sarcomeric protein composition, cytosolic distensibility, and/or extracellular matrix composition. However, functional abnormalities such as fibrillary cross-linking, elastic recoil, and particular compromised diastolic relaxation (as an active process being decisively dependent on adequate energy situation, specifically the phosphorylation state) are contributing as well [365, 557]). Nevertheless, in some clinical syndromes, ventricular chamber stiffness may be predominantly assigned to external features, e.g. in case of pulmonary hypertension [25, 539], denoting position and curvature of the diastolic PV-relationship [51].

The transition from compensated diastolic dysfunction to overt HFpEF is associated with worsening diastolic function, as Yamamoto and Masuyama have established, and is basically due to progressive myocardial stiffening, and not the progression of relaxation abnormalities [579, 580].

1.11 Evaluation and Assessment of the Cardiac Performance

As described previously the heart has to generate pressure and flow in order to pump the blood into the vasculature and hence ensure sufficient circulation [93, 581, 582]. Parameters currently used to measure cardiac (systolic) performance are the CPO and SW (see part 6 of this chapter) [128, 436, 437, 445]. Both parameters integrate the fundamental cardiac functions [4, 13, 93, 128, 445]. In comparison to SW, CPO characterises the recruitable reserve still available in cases of acute failure and in shock, which may be utilised to maintain the perfusion of the vital organs and hence reflects the severity of the patient's illness [128].

It should be noted that SV/SVI or even CO/CI do not reflect the cardiac pump function. They do not incorporate the pressure generation, nor are they an index of contractility. SVI/CI is affected by contractility, vascular stiffness and resistance, intravascular volume, and filling pressures [128]. CI is insufficient for accurate diagnosis and treatment titration in acute heart failure [220, 442, 583, 584]. Furthermore, there is no normal range for CO/CI, since metabolic demands can vary widely [119].

Flow represented by SV(CO) is dependent on afterload [3, 46]. In particular, in acutely compromised heart function (either due to impaired contractility and/or due to abnormal loading conditions) there is plenty of evidence that afterload is the most important determinate of pump function [11–14]. Cotter [13] established proof that the accurate diagnosis of the different heart failure syndromes can only be made when coupling both cardiac pumping abilities and afterload. He provided strong evidence that the cardiac pump ability can only be assessed correctly if related to the afterload present at the same moment as the pump function is measured [13].

Cotter's results have been validated and confirmed in several large studies covering a broad spectrum of primary cardiac diseases [128, 439]. Additionally, CPO (CPI) has substantial evidence supporting it as a powerful and robust prognostic parameter [13, 128, 439] (see part 6 of this chapter).

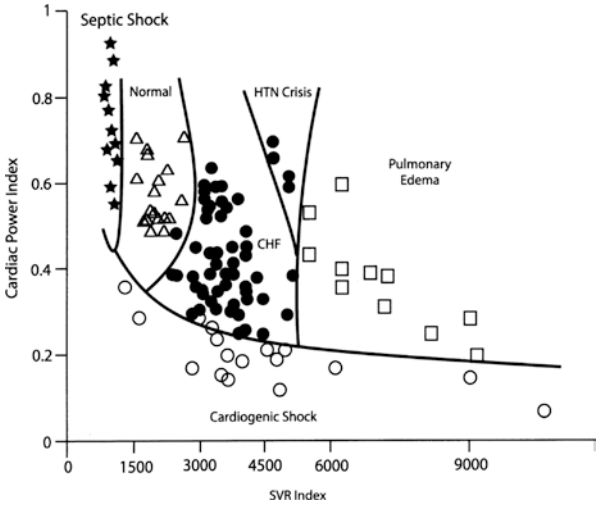

Fig. 1.14 Relationship between cardiac pump function and afterload in various clinical conditions. Abbreviations: *CHF* acute heart failure, *HTN crisis* hypertensive crisis, CPI cardiac power index. CPI = MAP × CI × 0.0022; *SVRI* systemic vascular resistance index; SVRI = (MAP-RA): CI); (adapted from Cotter [13]) with permission

The relationship between (simultaneously) measured/calculated CPI and afterload (represented by SVRI) has been shown to provide pivotal information about the actual haemodynamic situation (appropriate SVRI or inappropriately high/low [13]) and gives decisive information on the best management strategy [13, 128, 445].

In the special case of septic shock, an inverse correlation between cardiac performance and afterload has been demonstrated [585]. Furthermore, Müller-Werdan [586] demonstrated that septic cardiomyopathy is characterised by a significantly reduced cardiac performance which is relative to the effective afterload. Again, the actual cardiac pump function in relation to the afterload present provides strong prognostic information as well as clues on how to treat the patient (e.g. the timing of when inotropic support may be indicated) [587].

Although quite clearly having disadvantages and limitations in sensitivity and accuracy of reflecting the LV load at end-systole, the afterload [378, 401] is still well represented by the SVR/SVRI, which accounts for roughly 90% of the resistance to ejection (arterial resistance is the dominant component of impedance load) [402]. Furthermore, SVR may be very helpful in clarifying the diagnosis [13, 128], particularly in hypotensive patients [13, 128].

In summary, cardiac pump function can (and should) only be accurately and reliably evaluated in relation to the actual afterload [11–13, 128, 258, 271, 439, 586–589]. At the sarcomere level, contractility and load are interrelated and thus not independent variables [417, 418]. Furthermore, the consideration of the pump function in the light of the afterload will give substantial information about the severity of the patient's situation, the mortality, and the appropriate therapeutic approach [13, 128, 439, 586, 587]. Figure 1.14 depicts the fundamental relationship between cardiac pump function and afterload in various clinical conditions—a very practical approach to classify and diagnose patients as well as adding substantial information to the prognosis and therapy.

1.12 Summary Key Physiology and Pathophysiology

1.12.1 Frank-Starling-Mechanism

Frank [36] and Starling [37] established proof that, with increasing fibre length, the force of contraction will increase and so will the ventricular stroke volume. The pressure exerted on the myocardial fibres, the so-called effective distending pressure or 'transmural' LVEDP, is the intra-cavitary LVEDP (commonly shortened to LVEDP) minus the surrounding pressure(s) [35]:

Transmural LVEDP = LVEDP − surrounding pressure ≈ PCWP – RA = PCWP − CVP (with CVP reflecting the surrounding pressure [23, 53, 56, 58, 59]).

An increase in SV subsequent to an increase in preload (higher LVEDV) depends not only on the change in the left ventricular filling, but on the contractile capabilities (myocardial responsiveness) as well [9], particularly in the case of compromised cardiac function [10, 75, 91]. SV is determined by venous return and cardiac performance (afterload, heart rate and in particular contractility) [31–33].

Cardiac (pump) function, represented by CPO/CPI or SW, can only be evaluated in relation to afterload [12, 13, 128, 271, 439, 588] and the original diagram by Cotter [13] gives a good approach to diagnosis, therapy, and treatment in daily practice.

1.12.2 Afterload

The forces which oppose myocardial contraction (myocardial fibre shortening) during ventricular ejection are called afterload [30, 323–325]. Both, vascular and specific cardiac properties (LV size and dimension, contratile capability, LV pressure) determine these forces [329, 331, 372, 373].

Since myocardial wall stress reflects both, central aortic and peripheral vascular loading conditions (vascular features), as well intrinsic heart muscle properties, wall stress represents the "true" afterload [324, 373, 375, 376].

However, as the assignment of both, wall stress and arterial elastance (which is shown to properly reflect the arterial, hydraulic load as the main component of afterload [330, 362, 364]) are not feasible measures in daily practice, we still use the peripheral resistance as the best approximation of afterload [329]. SVR is not bad at all, since it is responsible for up to 90% of the total resistance to ejection [403].

The fundamental pathophysiological alteration of acute heart failure syndromes is an afterload mismatch with a markedly elevated resistance (SVR)/high input impedance (high end-systolic wall stress) during ventricular ejection [11, 19, 394]. In the failing heart, LV afterload becomes the decisive determinant of cardiac performance [11, 12, 14], and SV becomes dependent on the afterload [3, 46, 93], with SV ~ 1/afterload [30, 394]. Thus, cardiac performance can only be assessed in light of the actual afterload [13, 128], and afterload reduction is a fundamental therapeutic approach.

1.12.3 Systolic Function

EF, as an index of the global systolic function [388, 399], is the most frequently used parameter to estimate systolic performance, and gives an impression of contractility. However, afterload ↑ → EF ↓ and vice versa [369, 406]. Therefore, EF may be considered as a resilient coupling parameter rather than an index of myocardial contractility [449, 450]. However, the heart and vessel system have to be understood as a unit, and ventriculo-arterial coupling is a key determinant of cardiovascular performance [342, 516, 534]—insofar EF indeed well reflects the cardiovascular performance.

Note, EF may overestimate the systolic function in cases of excess afterload (EF reduced although the contractility is normal) [453] and augmented preload (i.e. MR). EF may miss myocardial dysfunction [454, 455] in concentric LV-hypertrophy as EF may signal normal systolic function, although substantial dysfunction may be present [456].

1.12.4 Volume Status

It is crucial to evaluate the actual fluid status of the central cardiovascular system and the most likely response to volume expansion. An assessment of the dynamic indices such as LV stroke volume variation (SV-V) [10, 183], peripherally or centrally, systolic BP-variation (SP-V) [193], or pulse pressure variation (PP-V) [183], is highly advisable [123, 140, 152, 153, 162, 168, 169]. The dynamic parameters reflect changes in LV-SV due to heart-lung interactions induced by mechanical ventilation [139, 170, 171, 183].

Blind volume administration [130], with its potential risk of fluid overload, may increase patient mortality [211, 212, 232, 243]. However, in life-threatening situations with severe hypotension and tissue hypoperfusion, even without basic monitoring or central blood flow measurements, a fluid challenge as described by Vincent and Weil [133] is justifiable [220].

Use the CVP as:

- an index of PP [53, 56–59] and indicator of possible DVI [39], particularly when CVP is > 9–10 mmHg [44, 63, 126] or if it increases by >5 mmHg due to volume loading [133],
- a marker of cardiovascular dysfunction if elevated (>7–8 mmHg) [117], especially as an indicator of right heart dysfunction/failure [116], if clinically suspected and CVP ≥ 9–10 mmHg [39].

Use EVLW(I) as:

- an index of fluid overload [225, 235, 236] and to guide fluid therapy [224–226],
- an indicator of (early) cardiogenic (hydrostatic) pulmonary oedema [225, 239, 240],
- a very strong prognostic index indicating, as a rule, absolute fluid restriction if elevated (EVLWI > 10 mL/kg) [211, 224, 232, 243].

The derived PVPI is a very helpful tool to differentiate non-cardiogenic pulmonary oedema (PVPI ≥ 3 [213]) from cardiogenic pulmonary oedema (PVPI 1–3) [211, 229] and/or to identify a significant capillary leakage (PVPI = EVLW/PBV) [213, 229, 237].

1.12.5 Ventriculo-Arterial Coupling

Ventricular-arterial coupling is recognized as being a key determinant of cardiovascular performance [516, 590]. Proper v-a-coupling, achieved by matched left (right) ventricular and aortic-vascular (pulmonary-vascular) features, is essential for the circulation: Circulatory adequacy and stability can only be guaranteed and maintained by matched ventricular and vascular properties, allowing for efficient cardiac work and efficacious energy transfer and thus appropriate blood flow and circulation [345, 365].

Acute changes in afterload, along with deranged ventriculo-arterial coupling, may produce a disproportionate transmission of vascular stiffening onto the ventricle [356], which can increase the LVEDP markedly [347, 355, 551]. Consecutively, flash pulmonary oedema may occur despite normal systolic function [356, 547, 551] and may be regarded as a vascular, rather than a (purely) cardiac disorder displaying AHF [13, 591].

1.12.6 DVI

DVI has a considerable impact on the haemodynamics. Significant DVI is suggested by a combination of PH and elevated CVP, especially in case of RV-dysfunction/failure [42, 47–49, 70, 71, 177]. In acute exacerbations of chronic congestive heart failure, in particular if LVEDP is elevated, due to DVI, volume unloading will lead to a ‘paradoxial’ increase in LV-SV and is thus the treatment of choice [23, 24, 49, 67]. Even if the patient is not fluid overloaded, there will be no haemodynamic compromise when unloading in this setting as Atherton showed [24].

1.12.7 Myocardial and Chamber Stiffness

While myocardial stiffness basically refers to the intrinsic, “material” properties (cardiomyocytes and ECM) of the heart muscle [560], the chamber stiffness characterizes the “overall” compliance of the ventricle by integrating the intrinsic myocardial properties, the chamber geometry, and extrinsic features contributing to ventricular stiffness [25, 85, 557, 558].

Diastolic function is largely determined by myocardial stiffness and diastolic relaxation [578]. While changes in myocardial stiffness altering diastolic function (causing diastolic dysfunction) are largely attributed to cardiomyocyte stiffening [592, 593],

the chamber stiffness may also change due to modified extrinsic features like acute volume loading [571, 572] or other hemodynamic variations like altered afterload [85, 495, 570]. Acute changes in chamber stiffness are, in any case, in the vast majority of circumstances related to **acutely altered extrinsic** conditions [85], in which pericardial constraint and DVI affect ventricular interdependence [85, 495, 570].

Changes in chamber stiffness due to extrinsic issues are reflected by parallel upward shifts of the P-V-relationship [85, 539, 569], while alterations in myocardial properties lead to an upward and leftward shifted curve, indicating modified intrinsic diastolic properties [533, 565].

1.12.8 Cardiac Power Output/Index

As the heart has to generate both, pressure and flow [4, 594], the CPO/CPI may be, compared to CO/CI, the more appropriate parameter in the assessment of cardiac performance as it integrates both, power generation (BP), and flow (CO).

Moreover, together with its relation to SVR, this index has substantiated its diagnostic value in daily practice [13].

1.12.9 Echocardiography

An early (immediate) assessment by echocardiogram may be pivotal due to the superior functional and diagnostic capability of this method [244–249, 259, 588].

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Acute Heart Failure Syndromes

2

2.1 Definition

As yet, no definition of heart failure is universally accepted, however, heart failure may be defined as "the inability of the heart to supply the bodies' tissues sufficiently and suitably with blood meeting their metabolic demand or do so only at the cost of elevated filling pressures" [1–3].

The European Society of Cardiology (ESC) defined acute heart failure in 2005 as "the rapid onset of symptoms and signs secondary to abnormal cardiac function. It may be occur with and without previous cardiac disease" [4]. In their 2012 guidelines, the ESC modifies and states heart failure to be subject to "an abnormality of cardiac structure or function leading to failure of the heart to deliver oxygen at a rate commensurate with the requirements of the metabolizing tissues, despite normal filling pressures (or only at the expense of increased filling pressures)" [5], confirming a definition developed by a joint expert group consisting of the ESC Heart Failure Working Group and the European Society of Intensive Care Medicine (ESICM) [6].

The ACCF/AHA Practice Guideline from 2013 defines, "heart failure is a complex clinical syndrome that results from any structural or functional impairment of ventricular filling or ejection of blood" [7].

However, elevated left-ventricular end-diastolic pressures (LVEDPs) are characteristic and essentially a general finding in all heart failure patients [2, 8–10].

2.2 Classification of Acute Heart Failure Syndromes (AHFS)

Acute heart failure may occur as an acute de novo event without previously known cardiac malfunction or as an acute decompensation of chronic heart failure [4].

The ESC Task Force Group has classified acute heart failure into six distinct pictures. This is based on the clinical condition at presentation and the hemodynamic characteristics described by Forrester [11], Killipp [12] and more recently by Cotter [13], along with a report and explanation by Adams [14] and in accordance with a publication by Gheorghiade [15]. This, in 2005 introduced classification, is

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still widely used [16–20], although some authors replaced high output failure, ESC-5 (due to its imprecise specification with the various underlying entities, ahead of all septic shock), by acute heart failure complicating acute coronary syndrome (ACS) which requires a especial treatment (immediate coronary angiography and intervention) [19, 21].

Classification based on Nieminen [4] and Gheorghiade [15], modified and replenished by Joseph [16].

- ESC-1: Acute Decompensated Heart Failure (AD-HF)
  De novo or decompensated chronic HF.
  Signs and symptoms of acute HF are generally mild and do not fullfil criteria for cardiogenic shock (CS), pulmonary oedema, or hypertensive crisis (HTN).The onset is gradual, peripheral edema often significant, while pulmonary congestion may be really discrete.
- ESC-2: Hypertensive Acute Heart Failure (hypertensive AHF)
  Characteristic signs and symptoms of HF are accompanied by high blood pressure (BP) and a chest radiograph which is consistent with acute pulmonary congestion, while left-ventricular systolic function is relatively preserved or even normal. Often rapid onset, marked dyspnea, altered mental status, and oliguria/anuria are possible (Table 2.1).
- ESC-3: Pulmonary oedema
  Symptoms and signs compatible with pulmonary oedema, normally accompanied by severe respiratory distress with SaO_2 usually <90% on room air prior to treatment, and a chest X-ray showing pulmonary oedema.
- ESC-4: Cardiogenic Shock (CS)
  The patient exhibits evidence of tissue hypoperfusion induced by HF although pre-load is appropriate or has been properly corrected. There is no clear definition

Table 2.1 Hemodynamic profiles

	ESC-1	ESC-2	ESC-3	ESC-4	ESC-5	ESC-6
Heart rate	=	↑	↑	↑	↑	↓/↑
Systolic BP	N/↑/↓	↑/↑ ↑ ↑	Low N/↑	N/↓–↓ ↓ ↓	N/↓/↑	↓/↓ ↓
Cardiac index [l/min/m²]	Low N/↓/↑	N/↑/↓	↓	<1.8–2.2–↓ ↓ ↓	↓↓/N	<2.2/↓↓
PCWP [mmHg]	↑, ≥12–16	↑, >18	↑, >16	↑↑, >16–18	N/↑↑	↓, <12
Congestion	+/+ +	+/+ + +	+ + +	+/+ +	−/++	None
Urine output	−/+	−/+	+	Low/None	+/−	Low/None
End organ hypoperfusion	−/+	−/+	−/+	+ +/+ + +	−/+ +	−/+
Forrester [4, 11, 15, 16]	II	II–III	II/IV	III/IV	I–II	I–III

of hemodynamic parameters, but CS is usually characterized by reduced BP (systolic BP < 90 mmHg or a drop of mean arterial pressure of >30 mmHg), and/or low urine output (<0.5 mL/kg/h) with a pulse rate of >60/min, with or without evidence of organ congestion.
There is a continuum from low cardiac output syndrome (hypoperfusion, oliguria, and hemodynamically a low normal sBP, a CI < 2.2 L/min/m^2, and a PCWP >16–18 mmHg) to CS (marked hypoperfusion, oliguria/anuria, hemodynamically a sBP < 90 mmHg, a CI < 1.8 L/min/m^2, and a PCWP > 18 mmHg).

- ESC-5: AHF complicating acute coronary syndrome (ACS) (has replaced high output failure)
  May clinically impress with pulmonary edema (ESC-3), pre-shock or manifest shock or as a cold and dry type (ESC-6). Life saving measure is immediate angiography and revascularization (evidence level A, class I recommendation) [22–26].
- ESC-6: Right Heart Failure (RV-HF)
  Characterized as low output syndrome with ↑ jugular venous pressure, increased liver size, and hypotension, often poor perfusion, but clear lungs.

2.3 Aetiology and Epidemiology [4, 14, 27–30]

The main causes of acute heart failure syndromes are:

- Coronary (ischaemic) heart disease/ischemic cardiomyopathy;
- Valvular heart disease;
- Dilated cardiomyopathy;
- Hypertension/hypertensive crisis and hypertrophic cardiomyopathy;
- Acute arrhythmias;
- Acute endocarditis;
- Restrictive cardiomyopathy;
- Acute pericarditis/cardiac tamponade;
- Acute (peri) myocarditis;
- Aortic dissection;
- Extracardiac diseases:
  - Broncho-pulmonary diseases, particularly those producing hypoxic states, e.g., acute exacerbation of COPD or severe pneumonia;
  - Anaemia;
  - Hyper/hypothyroidism, and other endocrine diseases;
  - Fluid overload;
  - Drug-induced heart failure;
  - Metabolic/toxic reasons;
  - Infectious diseases (particularly sepsis as high output heart failure);
  - Neuromuscular diseases such as the myopathies;
  - Trauma.

Coronary artery disease (CAD) is the underlying cause of heart failure syndromes in the majority of cases [16, 26, 31]. Rudiger [12] conducted a European survey showing that CAD was the underlying disease in 62% of cases. Other studies have confirmed this result showing CAD as the main aetiology of acute heart failure in 60–70% of all cases [28, 29, 31, 32]. Valvular heart disease is reported in up to 44% (seems very high!), dilated cardiomyopathy is prevalent in 25% [33].

Up to 70% of all heart failure patients admitted, suffer from arterial hypertension [14, 28], diabetes mellitus is found in 40%, and impaired kidney function was present in 20–30% [16, 31]. Atrial fibrillation/atrial flutter is seen in 30–40% of patients [16, 31].

The vast majority of all patients admitted with acute heart failure (approximately 75% [14, 16]) suffer from an acute decompensation of chronic heart failure, often decompensated due to systemic infection, treatment with cardio-depressive drugs, reduction of the patient's cardio-specific medication, pulmonary embolism, or inappropriate physical stress [14, 28]. About 50% of all AHFS suffer from HFpEF [14, 34–36].

The main reason for acute HF in patients with 'preserved systolic' function, HFpEF, (EF > 50%) [37–39]) is an acute increase in systolic blood pressure [40, 41], but new onset of atrial fibrillation (AF) is a frequent reason as well [42].

Less than 10% have advanced heart failure [16].

Acute heart failure is the discharge diagnosis in about one million patients of all ages each year [43]. The overall in-hospital mortality is as high as 5% [44], the 30-day one is 10–12% [45]. 33% will die within the first year following their first admission [46]. The 5-year mortality rate remains high, around 50% [47, 48].

The prognosis may be even worse as a recently published survey by Zinnad [49] revealed: In contrary to other surveys, this French survey included not only patients suffering from acute heart failure admitted to general and cardiology wards, but also severely ill patients requiring CCU or ITU admission. The number of patients with pulmonary oedema (82%) and cardiogenic shock (29%) was substantially higher than reported in previous studies [28–30]. The mortality in this study was as high as 27% at 4 weeks and 62.5% after 1 year.

2.4 Pathophysiology

2.4.1 General Remarks

Since the majority of patients admitted to an emergency department with heart failure display *acutely worsened* heart failure symptoms, acute heart failure (AHF) has recently been referred to as "an increase in the severity of chronic heart failure symptoms that requires an escalation of therapy and hospitalization" [50].

Both, acutely decompensated chronic heart failure and newly arisen, "de novo" cases without prior history are perceived as AHF, respectively known as acute decompensated heart failure (ADHF) or acute heart failure syndromes (AHFS) [6, 51, 52].

The pathogenesis of acute heart failure syndromes is complex and of multifactorial origin, however it is basically attributed to the interplay and interconnection between **essentially cardiac disorders** (e.g. altered diastolic and/or systolic features including ischemic or hypertrophic cardiomyopathies) **with systemic afflictions**, mainly *altered vascular properties affecting loading conditions* (as arising in hypertension, inflammation and infections, metabolic maladies, and as a consequence of modifications of adaptive measures in neuro-endocrine activity (NH)) [5, 7, 17, 50, 53, 54].

Changes in total body fluid content (fluid retention and accumulation) and fluid shifts within the body's compartments (central fluid redistribution) [53, 54], impacting LV and RV preload, are essential elements of the pathogenetic processes [53, 54]. Furthermore, typical comorbidities frequently seen in heart failure patients including pulmonary maladies like COPD, sleep-distorted breathing disorders, and renal dysfunction/worsening renal function, directly influencing cardiac and myocardial characteristics and likewise afterloading conditions [53], are well embedded in the pathobiology [5, 7, 17, 53, 54].

Typical, classic **features precipitating acute decompensations** and being responsible for the AHF incidence in more than 80% of all cases include:

- Ischemia/acute coronary syndromes;
- Systemic infections, notably respiratory tractus infections;
- Poorly controlled co-morbidities, such as exacerbated COPD with and without pneumonia;
- Uncontrolled hypertension/acute hypertensive dysregulations;
- Arrhythmias (atrial/ventricular arrhythmias);
- Nonadherence to medication;
- Renal failure/worsening renal function;
- Nonadherence to diet/inappropriate salt intake;
- Inappropriate physical stress

[14, 28, 55–60].

Some special notes:

Ischemia: Ischemic injury diminishes LV compliance, hence causes an increase in ventricular stiffness [61], subsequently LVEDP rises [62, 63]. Backward transmission of the elevated filling pressures puts the lung at risk for congestion or even pulmonary edema [64–67].

Furthermore, any rise in filling pressures bears the risk for (further) ischemia, as elevated intra-cavitary pressures may compromise endocardial perfusion, particularly in cases of coronary artery disease and already poor perfusion pressure as in hypotensive states [66, 68].

Around 60% of patients with ADHF definitely suffer from coronary artery disease [69], while myocardial ischemic events are more common in de novo AHF [26, 33].

Comorbidities such as obesity, diabetes, hypertension and COPD promote inflammation, moreover they may be seen as low grade inflammatory maladies [70, 71]. Increased levels of inflammation are independently associated with asymptomatic

diastolic dysfunction [72], and all these maladies have been verified to be independently associated with early development of diastolic LV dysfunction [73–75]. Moreover, systemic inflammatory conditions are predictive of incident HFpEF [70]. As such, by affecting diastolic function leading to increases in filling pressures [41, 76–79], these comorbidities are acknowledged to decisively contribute to or even cause heart failure [80]. Acute worsening of diastolic properties are well recognized to precipitate AHF [81, 82]. Read more on this issue in Chap. 5, HFpEF !

Arrhythmias: Atrial fibrillation or flutter (AF) is prevalent in 30–45% of patients admitted with ADHF [83–85]. AF in the presence of AHF is associated with a worsened prognosis and an increased rate of mortality [86, 87]. Both, systolic and diastolic dysfunction are associated with the risk for incipient AF [88]. Atrial fibrillation/flutter and heart failure interact in a deleterious way and fast heart rates due to AF may initiate de novo AHF, or may substantially worsen chronic heart failure [89, 90]. AF affects relevantly hemodynamics and left ventricular function [91] due to the loss of both atrial contraction, which is essential for sufficient ventricular filling, and the tachycardia itself [92]. Thus, diastolic filling is limited due to the high heart rate and the loss of atrial contraction, and that, in the presence of an already compromised cardiac performance, is one of the mechanisms able to cause ADHF [93]. Furthermore, the tachycardic heart rate may display tachycardia-induced cardiomyopathic effects [94]. Accompanying further activation/accentuation of the already stimulated (as in chronic heart failure) NH contributes to the detrimental events [95]. Patients with diastolic dysfunction and HFpEF are especially affected due to their subjection on a proper atrial contraction to assure a suitable LV filling [94].

Renal dysfunction/worsening renal function: A cross-talk between the heart and the kidneys, affecting function and performance of each other, is well established [96–98]. In the setting of heart failure, venous congestion, neurohormonal activity, inflammation as well as endothelial dysfunction are the main trigger and contributors to baseline renal dysfunction, by altering intrarenal and intraglomerular hemodynamics [97, 99, 100]. However, in contrast to traditional views, venous congestion rather than compromised cardiac output decisively contributes to worsening renal function (WRF) in most cases [101, 102].

Elevated filling pressures, enhanced peripheral resistance (more precisely increased aortic input impedance which best reflects and represents systemic afterload to cardiac pump as a whole [103]), diminished natriuresis, and often (generally in case of HFrEF), but by far not always, a reduced CO are the **hemodynamic hallmarks** of heart failure [5, 6, 104, 105].

However, the **clinical picture** presented by patients suffering from AHF always look very alike and is characterized by signs and symptoms related to pulmonary and peripheral congestion, regardless whether suffering from HFrEF or HFpEF [5, 17, 50, 106]. Bedside physical examination, lab-tests, and X-ray are not able to distinguish between both entities [106, 107]. However, history and response to therapy provide considerable clues as to which type is probably underlying: HFpEF patients are generally older, are significantly more likely to be obese and have a

high(er) BMI, moreover, 85% suffer from the metabolic syndrome, hypertension and AF are considerably more often seen in HFpEF than in HFrEF, and HFpEF patients less often have a history of coronary and valvular heart disease [47, 108, 109]. Iron deficiency is more often found in HFpEF [109]. BNP levels are generally significantly elevated and higher in decompensated HFrEF compared to those demonstrated in HFpEF, moreover, 1/3 of HFpEF patients do not show noteworthy elevated BNP levels at all, although acutely decompensated [110, 111]. This circumstance is explained by the lower end-diastolic wall stress triggering production and release of BNP, emerging in HFpEF due to remodelling processes, e.g. hypertrophy [110].

Since patients with HFpEF are considerably sensitive to changes in BP, their pressure may significantly fall in case of application of diuretics or vasodilators [112, 113], a phenomenon not found in HFrEF patients who generally benefit symptomatically from administering vasodilators or diuretics as long as a sufficient BP (systolic ≥100–120 mmHg) is measured before these are given [112].

2.4.2 Special Pathophysiological Issues

2.4.2.1 LVEDP and Congestion

The main factor and source causing AHF symptoms is congestion rather than low CO [14, 28, 114, 115]. Only a minority of patients (clearly less than 10%) admitted with AHF feature signs and symptoms of clinically relevant, significantly compromised peripheral circulation, hypoperfusion, and/or clinically meaningful hypotension [116–118]. As such, both entities (HFpEF and HFrEF) share one of the main **pathophysiological** issues indicating and promoting acute heart failure: **acutely and substantially elevated left, and generally subsequent right** [15, 119–121], **ventricular filling pressures,** which are associated with pulmonary and systemic venous congestion (with and without low CO) [14, 15, 122–124]. Left- and right-sided filling pressure is largely determined by (a) the amount of blood flow (venous return) to the heart and (b) by the diastolic cardiac properties, e.g. chamber and myocardial stiffness [125]. Accordingly, a considerable high blood volume flow to the heart (preload) alone may precipitate pulmonary edema as seen in completely normal hearts of patients suffering from acute glomerulonephritis, causing acute, oligo/anuric kidney disease [125]. On the other hand, worsening diastolic dysfunction (DD) is shown to provoke pulmonary edema even in the absence of relevant volume retention [113, 126, 127].

Backward transmission of the elevated left-sided filling pressures, causing pulmonary venous hypertension augmenting RV afterload [4, 128–130] and diastolic ventricular interaction [131, 132], decisively affect and, in turn, lead to marked increases in RVEDPs consecutively displaying systemic (peripheral) congestion [133, 134]. As such, congestion attributed to high LVEDP is responsible for and causes the foremost clinical symptoms, dyspnoea (acute dyspnoea at rest, orthopnoea or paroxysmal nocturnal dyspnoea, breathlessness on exertion), and signs and symptoms associated with peripheral edema development, like swollen legs,

ascites, renal dysfunction and gut discomfort [17, 30, 49, 50, 69]. Considerable evidence indicates that elevated, high LVEDPs causally underlie the development and presence of congestion [123]. Moreover, every relevant **acute** rise in LVEDP may precipitate pulmonary congestion or even flash pulmonary edema [67, 135]. Patients suffering from diastolic dysfunction are particularly at risk to develop pulmonary congestion or edema as any (additional) pathological effect affecting the heart muscle potentially worsens diastolic stiffness [126]. Typical conditions are acute ischemic episodes [136] and abrupt increases in BP [4, 113, 127, 137]. Ischemia causes (further) ventricular diastolic stiffening [138, 139] as acute myocardial ischemia slows ventricular relaxation and increases myocardial wall stiffness [140–142], consequently LVEDP increases [62, 63, 142]. Rising BP is, in any case, associated with elevated sympathetic tone, augmented afterload, increases in LVEDP, and may result in fluid redistribution and further neurohormonal activation [15, 143, 144]. Increases in afterload generally cause a rise in LVEDP [113, 127, 145, 146]. As such, HFpEF patients, found to be highly sensitive to changes in loading conditions (volume and pressure load) [113, 147, 148], are especially predisposed to develop pulmonary congestion or actually flash pulmonary edema [67, 113, 127, 149]. This is even true in the case of only mild, acute increases in BP [67, 113, 127, 149] or yet undetectable volume expansions [148]. In a rigid heart chamber, which is unable to properly accommodate to increasing blood flows and intracardiac volumes [150], already small increases in end-diastolic filling volume are accompanied by substantial, exponential (the diastolic pressure-volume relationship follows an exponential equation) increases in LVEDP [150]. Indeed, rising and elevated BPs or increasing LV filling volumes may lead, in the setting of combined ventriculo-arterial stiffening, to further increases in ventricular stiffness [113, 148, 151], thereby worsen diastolic dysfunction [152] which will result in disproportionate rises in LVEDP [113, 148]. Worsening diastolic function due to hypertensive dysregulations, uncontrolled hypertension, and myocardial ischemia, but hyperglycemia as well, are predominant causes for AHF development in HFpEF patients and in diabetic patients with diabetic cardiomyopathy [40, 41, 152]. However, new onset of atrial fibrillation (AF) is, as well, a frequent trigger [42]. As a result of the loss of atrial function, a compensatory increase in LVEDP in order to maintain end-diastolic filling volume and thus CO (via Frank-Starling mechanism) is reported. Subsequently the neurohormonal systems will be activated [152]. Both, reduced diastolic filling and abnormal left atrial function, may result in neurohormonal stimulation [152]. Increases in LVEDP are demonstrated to happen more rapidly in HFpEF than in HFrEF, attributed to the blunted diastolic distensibility, a typical property of HFpEF (in contrary, HFrEF patients show an increased diastolic distensibility) [123].

Accordingly, elevated LVEDPs causing central, pulmonary and systemic congestion are in the vast majority of AHFS the critical underlying pathology and the reason for presentation [5, 122, 153, 154]. Remarkably, central and peripheral congestion usually arise concurrently [155, 156].

Enhanced levels of left ventricular filling pressures unfortunately display a range of adverse effects, including enhanced myocardial oxygen demand,

compromised coronary perfusion with concomitant risk of angina, global and subendocardial ischemia [157–159], progressive mitral [15] and often tricuspid regurgitation, activation of the adrenergic and the renin-angiotensin-aldosterone system, thus activating the neurohormonal systems (NHs), and stimulate the cytokine system [160]. As such, high LVEDPs may evoke and contribute to disease progression [104, 161–164]. Indeed, features typically associated with and characteristic of AHF are neurohormonal activation [165–168], stimulated inflammation [169–172] and activated endothelial function, commonly termed endothelial dysfunction (ED) [173, 174]. Inflammation and ED generally accompany each other as they are closely interrelated and interconnected [175–177] and go along with enhanced levels of oxidative stress (ROS) [178, 179].

It should be noted that acute severe left heat failure may occasionally, in individual cases, not be accompanied by high filling pressures (markedly dilated ventricles, often with severely impaired systolic function) featuring a normal or even low LVEDP and no pulmonary edema, although they do suffer from severe acute left heart failure [180–182]—this is the so-called ! "forward failure" as described by the ESC [4].

2.4.2.2 Neurohormonal Systems, Endothelial Dysfunction and Inflammation

The neurohormonal systems, NHs, perform necessary and pivotal control and modulating functions and exert a substantial integrative impact on cardio-circulatory physiology [183–185]. Neuro-hormones carry hemodynamic and biological effects on the heart and the vascular system [186]: Augmented sympathetic discharge is not only exerting vasoconstrictive, positive inotropic and chronotropic effects, but is going along with blunted parasympathetic drive causing abnormal cardiopulmonary reflex control, including attenuated baroreflex and boosted peripheral and central chemoreflexes [168]. As such, autonomic imbalance (excess sympathetic discharge and coexisting withdrawal of parasympathetic tone) is a characteristic feature in heart failure [187]. Stimulated renin-angiotensin-aldosterone system [165] and augmented non-osmotic release of arginine-vasopressin, promote other than systemic and local vasoconstrictive effects, especially renal functional changes, namely declined ultrafiltration and retained sodium and H_2O, thus facilitate fluid accumulation [166, 186]. Endothelin-1 causes marked vasoconstriction (enhancing vascular tone) [188], while elevated concentrations of natriuretic peptides especially **counteract** the vasoconstrictive (show venodilative and peripheral arterial resistance lowering effects) and the fluid retaining effects of the NH mediators and hormones [167, 189–191]. However, their ameliorating effects on the sympathetic and RAAS discharge appear to be clinically of minor potency in acute heart failure [164, 192], and their clinical importance is attached to their diagnostic and prognostic power [193–195]. Of special note, elevated A II and aldosterone levels contribute (aside from their well-known and characteristic vasoconstrictive effects, which directly augment the systemic vascular resistance and as such the afterload [196], and their sodium and water retaining impact [197–199]), through endothelial activation and

enhanced ROS generation,[1] to the considerably diminished NO bioavailability [202–206], typically emerging in AHF [174, 206]. As such, A II promotes endothelial dysfunction and augmented ROS generation, and thereby a markedly diminished NO bioavailability ensues [161, 202, 206]. This results in significantly impaired endothelial NO dependent vasodilatation causing increased vascular tone (vasoconstriction) and disturbed regulation of ventricular function: "NO dependent regulation of ventricular function and vascular tone determines hemodynamics in AHF" [174]. The important NO-cGMP-PKG signalling pathway (NO is a pivotal paracrine and autocrine signalling molecule [207]), is a universal cascade of cellular communication regulating, via protein phosphorylation, gene expressions [208–210]. This signalling pathway will be affected resulting in (a) altered smooth muscle cell relaxation which concomitantly impacts local and systemic blood flows and blood pressure [211], causing vascular dysfunction, and (b), related to an afflicted cardiac endothelium, disturbed titin phosphorylation within the cardiomyocytes [208–210]. Titin hypophosphorylation leads to cardiomyocyte stiffening and thus precipitates diastolic dysfunction [78, 112, 210, 212]. Hence, vascular compliance (namely of the central larger vessels) is diminished (vasoconstriction in arteriolar vessels reduces arterial compliance [213]) causing increased vascular stiffness and subsequently enhanced LV (RV)-afterload thereby also facilitating diastolic dysfunction [147, 148, 174, 214–216]. Furthermore, a rise in systolic ventricular elastance is induced and as such augmented ventricular (end-)systolic stiffness [214, 217] impairing systolic performance/reducing systolic reserve capacity [199, 218]. Indeed, augmented arterial stiffness is associated with both, systolic and diastolic dysfunction [219–221], and moreover, considerably impaired NO bioavailability and worsening endothelial dysfunction are even suggested to propagate the development and/or progression of heart failure [175, 222, 223].

Without doubt, in the early phase of AHF, enhanced neurohormonal activity allows stabilization of the compromised hemodynamic conditions and disrupted homeostasis jeopardizing suitable tissue and organ nutrient and oxygen supply [224]. Ventricular filling pressures increase with increasing sympathetic tone [225] and thereby may assure appropriate ventricular filling volume in order to maintain CO in the failing heart. On the other hand, they may contribute and provoke pulmonary congestion or edema [226]. Over time, the effects of the NHs, if persistent and chronically activated, are considered and appraised to be maladaptive, deleterious for the circulation, and leading to disease progression [54, 118, 164, 192, 224, 227].

Moreover, very recent publications suggest that the stimulated neuro-endocrine hormonal systems are even "over-activated" and are overwhelming the counter-regulatory cascades, decisively contributing to, mediating, and maybe even precipitating **acute** heart failure [60, 162–164, 183, 186, 227, 228] as they considerably modulate myocardio-mechanical properties [229].

[1] Reactive oxygen species (ROS) are subsequently associated with "functional" NO deficiency: Due to a chemical reaction between NO and ROS in case of augmented levels of ROS, NO is utilized. Furthermore, peroxynitrate is formed, a toxic reactive molecule [200], which is also involved in cardiovascular pathology [201].

Endothelial activation (EA)/dysfunction (ED) being present in AHF is evidenced by elevated levels of biomarkers indicative for EA including vascular adhesion molecules (VCAM-1) and intercellular adhesion molecules ICAM-1 [230–232], cytokines such as IL-6 and IL-1β, and tumor necrosis factor TNFα [233–235]. ED is meanwhile acknowledged taking a central and crucial role in the pathophysiology and pathogenesis of acute and chronic heart failure [175, 223]. Endothelial factors and mediators, whereupon endothelial relaxing factor (NO) activity represents a hallmark of endothelial function [236], contribute via para-, auto- and endocrine pathways to organize pivotal homeostasis and co-modulate cardiac and renal assignments and vascular properties in order to assure appropriate blood volume, cardiac output, perfusion pressure and blood distribution to the tissues and organs meeting cellular and tissue metabolic demands [192, 236].

Altered endothelial function, endothelial dysfunction ("should more appropriately considered as endothelial activation" [237]), implies a disturbed NO bioavailability, among other issues (ED displays pro-inflammatory, pro-coagulatory, and vasoconstrictive conditions [238]), as probably its most relevant pathobiological consequence. A disturbed NO bioavailability critically contributes to an imbalance of local (and potentially systemic as the endothelium is present in the whole body) vasoactive substances [239–241], precipitating significantly increased vascular tone, resulting in deranged (local) blood flow distribution and autoregulation [242]. The restricted bioavailability of NO is not only associated with vasoconstriction but causes increased stiffness in the systemic and pulmonary circulation and hence augments LV and RV systolic load [174]. Shortage of NO availability further favours ET-1 related vasoconstriction [243], increases sympathetic discharge including raised release of catecholamines [244], and contributes to diminished sodium excretion [245]. Dysfunctional cardiac microvascular endothelium may affect, via paracrine paths, diastolic LV properties [206] whereupon the already mentioned NO signalling pathway, considerably affected by ED, precipitates compromised endothelial cross-talk and disrupted phosphorylation paths [246, 247], including the cardiomyocyte NO-cGMP-PKG pathway leading to titin hypophosphorylation and thus acute cardiomyocyte stiffening [210, 218]. Accordingly, the effects of ED relevantly contribute to the clinical-hemodynamic profile characteristic in heart failure [248]. Moreover, ED is related to heart failure initiation and thus AHF [249]. ED is associated with adverse outcome in acute and chronic heart failure [250–252], correspondingly improvement of endothelial function is affiliated with a better outcome [253]. The worse ED the more severe the heart failure stage present and the more severe the functional limitation [254, 255]. ED independently predicts mortality risk [249, 251, 256] and major cardiovascular events [252]. Hence, there is no doubt that ED has a major and crucial role in heart failure malady in both acute and chronic conditions, integrates the multifacet signals arising [176], triggers, modulates and even perpetuates the cascades activated [257–259]. Indeed it orchestrates the adaptive and potentially morbid processes, and unquestionably causally contributes to initiate and to display acute heart failure [174, 260]. Notably, dysfunctional vascular endothelium is a recognized hallmark of human diseases in general [261].

Inflammation as evidenced by elevated serum levels of TNFα, IL-1, IL-6, and ST-2, an activated complement system and adhesion molecules verified in AHFS is part of the pathobiology [170, 171]. Inflammation per se is a protective response to injury of any kind, ensues and applies by interactions between cell surfaces, extracellular matrix, and pro-inflammatory mediators [262], and may **basically be regarded as a vascular response to any threat or injury** [263–265]. As such, vascular stretch as present in acute and chronic pressure or volume load exerts biomechanical stress on the mechanoreceptors of the endothelial cells, and thus initiates an at least mild inflammatory response [266–268]. Even physiological adaptions in vascular tone and tension are principally regulated and mediated by the same molecules, agents, and hormones involved in inflammatory processes [17] and in endothelial functions and effects. The endothelium is substantially involved in the innate [269–271] and adaptive [272]) immune response to injury, processes associated with inflammation, and as such is surely a fundamental feature in cardiovascular disease processes and may be considered as "linking" inflammation and cardiovascular diseases [174, 175, 206]. Indeed, a distinct correlation between inflammation and endothelial dysfunction is well established [273], confirming that inflammation and endothelial cells are closely intertwined and interconnected [273, 274]. Furthermore, since being characterized and accompanied by an increase in inflammatory markers including CRP, cytokines, adhesion molecules, and acute phase proteins, a more substantial and chronic inflammation has to be considered as a systemic process rather than "purely" a local reaction [275]. Accordingly, inflammation is recognized as taking a central position in the pathophysiology of cardiovascular diseases and hypertension [276]. As such, inflammation may, by causing endothelial dysfunction [277, 278], promote hypertension due to impaired endothelium-dependent vasodilation favouring vasoconstriction following an imbalance between vasoconstrictor and vasodilator mediator production and release [279], namely an impaired NO bioavailability [280, 281].

Especially remarkable and important to understand is that systemic inflammation such as severe infections, especially sepsis, may cause acute cardiac decompensations: The set of cardio-vascular responses associated with inflammatory activation may include a dissociated reply with enhanced peripheral vasodilation (due to reduced peripheral vascular resistance caused by vasodilative mediators). Although occurring in the presence of limited NO bioavailability, which implicates impaired NO-related vasodilation, and coexisting with enhanced arterial stiffness, which consecutively causes increased afterload [282, 283], the net result is a potential drop in blood pressure (largely determined by the resistance vessels), LV afterload is augmented [174, 219, 284, 285] and systolic LV-function is blunted [174, 219, 286].

To resume this issue, beside the tight and intertwined relation between ED and inflammation [273, 274], a close interrelation and interaction between the NHs, namely the autonomic nervous system and the AII effects, and endothelial function/dysfunction is quite evident [287–289], whereupon NO constitutes the decisive link [272]. Enhanced sympathetic drive induces shear stress on the vessel walls [290], even in case of minor discharge [291]. Shear stress is associated with ED [292–294]. On the other hand, (activated) endothelial cells may trigger NHs

[287, 295]: Physiological and pathological (as e.g. in case of venous congestion) biomechanical forces affect the endothelial mechanoreceptors and subsequently stimulate endothelial cells and consecutively activate NHs [201, 261, 296]. Endothelial stretch (activating endothelial cells) [201, 261, 297], and as such even increasing ventricular filling pressures and myocardial stretch [160], directly evoke activation of the NHs, in case of SNS by altered autonomic reflexes [297]. Actually, elevated filling pressures and myocardial stretch are acknowledged as being among the most powerful impulses activating NHs [160]. Accordingly, NHs activation and endothelial dysfunction may be considered being a common path of the causative features contributing to incipient heart failure [186]. Furthermore, the tight interrelations and interconnections of the features and systems inevitably hold the risk to end up and to constitute a vicious cycle, potentially amplifying and perpetuating each other and as such facilitating disease progression [60, 104, 259, 297, 298].

2.4.2.3 Vascular Properties, AV-Coupling, Afterload Mismatch and the Dual Pathway Concept by Cotter

Vascular properties and "function play a central role in the development and progression of heart failure" [174]. Albeit the elevated left-sided (and mostly right-sided as well) filling pressures, which are associated with central pulmonary and peripheral congestion [14, 15, 122, 123, 153], coin the clinical picture and give rise for hospital admission in the vast majority of acute heart failure cases [17, 30, 49, 50, 69], **acute marked alterations in vascular tone, vasoconstrictions** (affecting LV and RV loading conditions) are actually **often the direct cause of incipient AHF** [13, 113, 127, 137]. Indeed, AHF may be considered as a disorder of "pathologic vasoconstriction" [299]. **AHF** is **almost always associated with** both, **elevated LVEDPs and generally** (in cardiogenic shock as the most severe form of AHF, the SVR may be even abased - read more about this phenomenon in Chap. 3) **substantially increased afterload,** in daily practice usually indicated by augmented peripheral vascular resistance (**SVR**), whereupon CI/CO is indefinite [300].

The often considerable increase in afterload (respectively SVR as part of total afterload) in the presence of deficient systolic and/or diastolic myocardial properties [300] cannot be compensated, as the cardiac properties are neither capable of allowing compensation by increasing preload (at least not at the cost of still reasonable increases in filling pressures below the threshold of pulmonary congestion/edema formation) and consecutively applied Frank-Starling-mechanism nor by subsequent sufficient increase in contractility following and adapting to the rapid increase in aortic pressure (afterload), known and referred to as Anrep's effect [301, 302]): This condition (a substantial rise in afterload in the presence of compromised systolic and/or diastolic capabilities) is referred to as **afterload mismatch** [303, 304]. Afterload mismatch causes a vicious cycle with secondary mitral regurgitation, reduced SV and increasing and elevated LVEDPs, and as the latter are being transmitted backward, pulmonary congestion/edema ensues [67, 305]. Notably, as a matter of fact, **veno**constriction is part of the "generalized "vasoconstrictive transaction [60, 306, 307].

Cotter demonstrated that almost always systemic vascular resistance is enhanced in acute heart failure syndromes (AHFS) [13, 137] and argues that most episodes of

AHF (about 70%) are attributed to increased aortic input impedance [308], which denotes enhanced afterload, with consecutively increased end-systolic LV-stiffness and reduced diastolic compliance [151], resulting in a noticeable rise in LVEDP [113, 127, 145, 146]. This opinion is agreed by Metra and co-workers [160] and supported by several facts, particularly:

(1) Relatively high systolic BPs are frequently seen in AHF patients [15, 69], at least 50% of all patients admitted with AHF are "hypertensive"—systolic BP > 140 mmHg [69, 309]. However, patients with systolic BPs of 140 mmHg or less may very well suffer from augmented afterload as in the setting of systemic inflammation/infection with increased **central aortic stiffness** and thus increased systolic LV-load [13, 282].

(2) Furthermore, AHF often develops rapidly, typically within hours [17] and without much previous complaints [4, 137], and as such is associated with acute alterations in arterial loading conditions directly affecting cardiac properties and function [160, 308]: " LV performance is influenced by arterial load [284] (since systolic wall stress reflects afterload as defined by the law of LaPlace [310, 311]), and arterial properties are, in turn, influenced by LV performance" [284, 312]. Consequently, vascular properties (specifically vascular tone) play an essential role in the development and progression of HF [174]. Moreover, (worsening) vascular failure is considered to be a precipitant for AHF [313].

As evident from the above depicted setting, altered vascular properties are decisively causally responsible for incipient AHF, accordingly, this type of AHF is referred to as "vascular failure" or "vascular type of AHF" in contrast to "cardiac failure" [308]. The latter, in which predominantly the **cardiac performance a**nd/or the myocardial efficiency is/are **considerably compromised,** may further deteriorate (e.g. due to ischemia with hibernating or stunning myocardium and thus (further) afflicted contractile properties [314], a common reason in de novo AHFS [26, 33]), and consecutively provoke AHF [308]. Of prominent concern are elevated troponin levels indicating myocardial damage, found in about 50% of all patients admitted with AHFS [315]. These elevations are suggested to be largely attributed to improper and disproportionate myocardial perfusion provoking ischemia (subendocardial ischemia due to high filling pressures, dysregulated cardiac/myocardial autoregulation (altered microcirculation), metabolic imbalances, hypotension, application of vasodilatory substances treating AHF, etc.) [26, 66, 68, 316–318], and will, in any case, (further) weaken myocardial performance [319]. Characteristic for the cardiac pathway (cardiac failure) is a marked de novo fluid accumulation, developed often over weeks, and relevantly involved cardio-renal features [17, 54, 164, 308, 320].

The concept by Cotter takes into account that (A) the heart and the vessel system have to be acknowledged as a functional unit, an absolutely essential view for understanding and interpreting the basic physiological and pathophysiological features, affecting each other and are together responsible for sufficient cardio-vascular performance [147, 312, 321–325], and that (B) both, an afflicted heart and altered vascular properties are present in acute heart failure. However, while one part of the unit may predominantly malfunction in the acute condition, the unit as a whole precipitates the

failure [326]. Metra emphasizes, it is even "essential for understanding and treatment of heart failure" to distinguish between both pathways, although they may be disrupted concomitantly and thus contribute equally at the same time to acute decompensation [160]. Further details of this new fundamental concept on AHFS by Cotter, meanwhile recognized and even endorsed by the ESC [5] are depicted in Fig. 2.1.

The vascular pathway is related to increased vascular stiffness/resistance with acute afterload mismatch and exacerbated filling pressures in the setting of activated NHs, resulting in (further) impaired systolic performance and redistribution of fluids from systemic (predominantly splanchnic veins, see below) to pulmonary circulation, rather than from general fluid accumulation. The cardiac pathway implies largely myocardial issues (due to acute ischemia, acute myocardial infarction, or acute myocarditis, but also due to sepsis and other threats affecting myocardium) in the setting of stimulated NHs (further) blunting and deteriorating systolic performance, to primarily responsible for the AHFS and is essentially associated with de novo fluid accumulation and cardiorenal dysfunction [104, 126, 154, 308].

Characteristic for the "vascular profile" of AHF development are rapid onset of clinical symptons and central fluid redistribution causing pulmonary congestion or edema rather than fluid accumulation, thus no or only marginal weight gain prior to AHF is seen, furthermore, most patients have preserved EF, suffer from diastolic dysfunction, and present with normal (sBP 100–140 mmHg) or elevated (sBP > 140 mmHg) blood pressure [17, 308]. Of course, especially affected are in

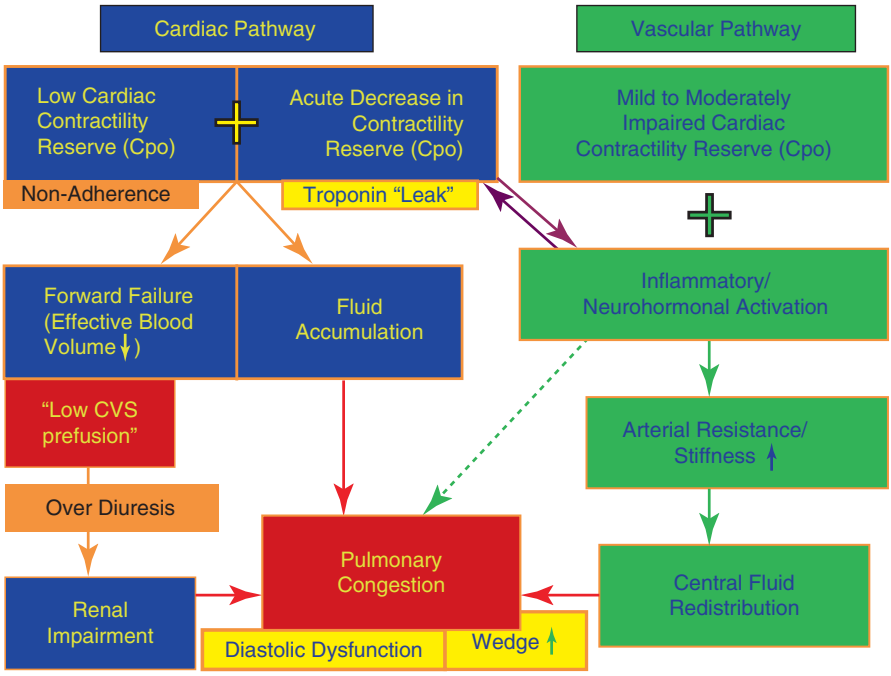

Fig. 2.1 Adapted from Cotter, G et al. Am Heart J. 2008; 155: 9–18 [308] (with permission)

general patients with pre-existing combined v-a stiffening, demonstrating amplified changes for any alteration in loading conditions [147], and ADHF arises due to temporary exacerbated/worsened diastolic dysfunction [127]. As such, acute increases in afterload (e.g. due to an increase in vascular resistance and / or in vascular stiffness) have a markedly unique impact on blood pressure and consecutively on filling pressures [145, 146] since blood pressure feeds back into (further) impairment of diastolic properties [151], potentially inducing pulmonary congestion [112, 327, 328]. Petrie established an inverse relationship between diastolic relaxation and afterload in hypertensive and non-hypertensive humans indicating cross-talk between arterial afterload and diastolic LV function [329]. Clinical pulmonary congestion (compared to hemodynamic congestion which is reflected by elevated LVEDPs but without clinical symptoms [153]) or even edema may apply in case of acutely increased LVEDPs already at relative low filling pressures, and consecutively, relatively lower pulmonary pressures than found in chronically elevated LVEDPs, as pulmonary lymphatics drain excess lung fluids in case of chronic overfilling more rapidly and efficient than in case of abruptly enhanced fluid onset [192, 330].

However, in conclusion, the classical vascular pathway relates to acutely altered vascular arterial impedance (due to increased vascular stiffness and/or resistance) associated with an acute afterload mismatch as the change in loading conditions cannot be compensated by adjusting cardiac performance, the latter in general due to compromised systolic cardiac performance or limited systolic reserve, further affecting systolic properties, and is accompanied by fluid redistribution (due to neurohormonal drive, read below) rather than by fluid retention [117, 154, 308, 331].

2.4.2.4 Fluid Redistribution, Splanchnic Veins and the Venocentric Input

Highly remarkable, very recent study results provide evidence that even subtly altered hemodynamic conditions may provoke AHF from vascular type in predisposed subjects with abnormal cardio-vascular function, whereupon acute sympathetic discharge mediates acute changes in vascular properties with subsequently modified loading conditions thereby leading to acute heart failure [60, 123, 126, 332]. The neurohormonal systems are, as described above, decisively controlling and modulating cardiocirculatory function [183, 184], and may acutely affect cardiovascular conditions and function [164, 186]. Particularly the sympathetic nervous system (SNS) is reported to be able to instantaneously affect cardiopulmonary and arterial baroreflexes [333, 334], and to acutely release vasoactive agents such as noradrenaline into the circulation and thus mediate and induce rapidly changes in vascular arterial and venous resistance and compliance [60, 335]. As such, abruptly enhanced sympathetic drive is demonstrated to critically influence the pathogenesis and onset of AHFS [60, 126, 165, 224, 226]: Study results and considerations by Fallick and colleagues address sympathetically-mediated central fluid redistributions from the splanchnic venous blood reservoir, caused by acutely elevated sympathetic discharge resulting in ADHF [60]. More than 70% of total body blood volume is mainly residing in the veins and not involved in effective circulation, since the venous system is substantially more compliant (about 30 times) than the arteries [335]. Of which, the splanchnic veins are even more

compliant than the other veins and are furthermore particularly densely equipped with α_1 and α_2 receptors [335]. These anatomic facilities translate into physiological consequences, displaying better storage abilities (reservoir veins) than other veins and a significant stronger degree of vasomotor response in case of sympathetic activation [336], which predominantly reduces venous compliance and as such diminishes the vessels' capacitance [60]. Hence, even minor sympathetic discharges prevailing, translate into constriction of the splanchnic veins while there is no, or only a negligible, effect to be seen in the other veins and hardly any in the arteries. Furthermore, the amount of fluids shifted in case of constriction of the splanchnic veins is comparatively greater as with an equal strong constriction in other venous areas.

Moreover, while the capacitance of the peripheral veins is reported to be normal in heart failure patients [337], it is suggested that splanchnic veins behave dysfunctional in that patient group unable to properly buffer changes in effective circulating volume [60]: The inhibitory control mechanisms, in particular reflex control, attenuate and modulate SNS discharge and cause its effects to not properly apply [338–341]. Adamson provided evidence that imbalanced autonomic activities prefer sympathetic over parasympathetic activity [342], and as such result in sustained sympathetic influence and activism.

Accordingly, sympathetically-mediated and initiated reduction in splanchnic venous capacitance may provoke relevant fluid shifts from the venous reservoir into the effective circulating blood stream, subsequently increasing preload and consecutively enhancing LVEDPs: Indeed, pulmonary diastolic pressures are demonstrated to fluctuate markedly during the day, apparently attributed to sympathetic discharges in response to in principal physiologic matters like upright posture and exercise [332]. While many of these sympathetic discharges are uncritical, some may initiate a vicious cycle ending up in acute heart failure in susceptible persons [60]. Patients suffering from chronic heart failure show chronic endothelial dysfunction and low grade inflammation [80, 175, 261, 343, 344] and as such are predisposed to decompensate—the vast majority (about 75%) of patients with AHFS are acute decompensations of chronic heart failure [345, 346]—in case of a further threat/threats (e.g. temporary ischemia—cardiac pathway) or even minor alterations in loading conditions (vascular pathway) [297]. Accordingly, Fallick and co-authors suppose that acute (and maybe even "physiological") sympathetic discharge, at least in the setting of dysfunctional splanchnic veins as found in (chronic) cardiac/cardiovascular dysfunction, alone has the potential to provoke AHF [60]. The concept is well consistent with other study results: Autonomic imbalance and elevated filling pressures become evident already days and weeks before acute decompensations turn into a clinically overt malady (display clinical congestion) [123, 342]. Furthermore, elevated pulmonary pressures are suspected to promote sympathetic excitation through pulmonary afferents [347], thereby amplifying sympathetic drive and thus may intensify venoconstriction and consecutively a fluid shift. The results from the COMPASS-HF study suggest, providing clinical evidence, that fluid shifts from the extracellular space into the effective circulation (expanding effective circulating volume) may underlie the development of AHF [348]. Moreover, the authors' concept also explains very well why patients without weight gain (weight gain is acknowledged to indicate

fluid accumulation in heart failure patients, although this is a relatively insensitive (and nonspecific) marker of fluid agglomeration with several limitation and restricted accuracy [160, 349–352]) may well develop AHFS without typical precipitants due to minor, elusory or even not comprehensible occasions initiating incipient acute heart [60, 126]. This pathogenesis explicates that the majority of patients presenting with AHF do not suffer from clinically comprehensible fluid accumulation and weight gain (inducing acute decompensations and AHF [123, 134, 353]), rather, fluid redistribution from peripheral, namely splanchnic venous, to central circulation is definitely an established pathway in AHF pathobiology [60, 126, 160, 308].

Furthermore, this approach broadens Cotter's concept who attributed fluid redistribution to increased vascular resistance and stiffness, thereby referring vascular failure to altered **arterial** properties. Obviously, changes in **venous tone** and hence venous capacitance (namely in the compliance of the **splanchnic veins** reducing their capacitance due to acutely increased sympathetic drive) foremost apply, and are able to shift within seconds up to 800 mL of blood into the circulation [335], thereby augmenting effective circulating blood volume and concomitantly increasing preload, and thus cause acute heart failure [60, 126]. In summary, sympathetically–mediated **veno-**constriction, predominantly affecting the splanchnic veins, with subsequent considerable blood shift into the effective circulation and hence increased preload causing (further) elevations in filling and concomitantly pulmonary pressures, inducing pulmonary venous congestion, has to be considered primarily as a vascular pathway with fluid redistribution following Cotter's concept.

2.4.2.5 Fluid Accumulation, Venous Congestion and the Link Between Cardiac and Vascular Pathway

Expansions, even very mild ones, of the effective circulating blood volume, inevitably increasing the preload, are in the setting of heart failure in any case accompanied by appreciable increases in filling pressures, actually even exponentially increases may be seen [354]. This condition is referred to as hemodynamic congestion [153]. As such, acute increases in venous return, due to reduced venous capacitance of the venous reservoir following sympathetic activation, are able to provoke (occasionally substantial) enhancements in LVEDP and RVEDP [60]. If the increase in cardiac filling and intravenous pressures (elevated left-sided pressures are usually responsible for increased systemic venous pressures [124, 355, 356]) become clinically obvious by precipitating acute pulmonary congestion/edema [60, 226] and systemic peripheral edema (the latter traditionally known and referred to as venous congestion [134, 139]), clinical congestion applies [153]. "Central (pulmonary and intrathoracic) and peripheral (venous) congestion usually exist together" [126, 155, 156]: Pulmonary and systemic congestion caused by elevated left- and right-heart filling pressures is almost a universal finding in AHFS [15].

Congestion is almost always associated with excess extracellular fluid and blood volume [60], whereupon most of the excess fluid will be located in the venous system [335]. However, increased intravascular fluid volume does not always reflect fluid accumulation or retention rather may be due to altered fluid distribution,

redistribution, as described by Fallick and coworkers [60] and as conceptualized for AHFS by Cotter [308]. Indeed, elevations in filling pressures following fluid shifts from the venous reservoir may result in a failing heart in hemodynamic or even clinical congestion without any relevant (at least for us recognizable) supplementary retention of salt and water [357]. Consistent, weeks before overt AHF ensues, autonomic imbalance and elevated filling pressures are demonstrated [123, 342]. As such, inappropriate autonomic regulation of the vascular, namely of the venous tone, and the physiological fluctuations in SNS drive, may induce (repetitively) some degree of fluid shift especially from the splanchnic reservoir to the effective circulation thereby potentially provoking incipient AHF [297, 357].

Accordingly, although in the majority of AHFSs (acute) central fluid redistribution, rather than fluid accumulation, is the recognized flash point leading to acute clinically relevant and overt malady [126, 160, 308], at least some degree of fluid excess, often beyond clinical comprehensibleness, is universally present in all AHF patients [35, 126, 358, 359] and a "basic and fundamental mechanism of decompensation" [160]: (1) Sympathetic excitation is reported to facilitate sodium retention and as such may contribute to decompensation [60]—enhanced sympathetic drive is an acknowledged issue in heart failure [227]. (2) Diminished natriuresis is a hallmark of heart failure and thus fluid retention has to be anticipated in heart failure patients [104, 105]. Threats, often minor ones, or even intense physiological fluctuations in the concentrations of (circulating) neurohormones are demonstrated to promote fluid retention in patients suffering from chronic heart failure [55, 59], and may launch acute decompensations—remember, the vast majority (75% and more) are acute decompensations of chronic heart failure cases [346]. (3) Arginine- vasopressin- mediated reabsorption of free water is reported to be present in heart failure [224, 349]. (4) Not only Silva Androne could verify that intravascular volume indeed is elevated in patients with "stabile" chronic heart failure [360]. (5) Furthermore, renal dysfunction is common in heart failure resulting in salt and water retention [224, 349] and may contribute to fluid overload. Actually, in a large majority of heart failure patients, a shortened kidney function has to be recognized [35, 353, 361]. The complex pathophysiology of kidney dysfunction associated with heart failure, the cardio-renal-syndrome (CRS), is largely attributed to a decrease in renal perfusion pressure, altered intrarenal hemodynamics, and elevated renal venous pressures [362], basically a result of the effect of activated neurohormonal systems (SNS and AII !) and associated fluid retention [199, 363], and deficient/overwhelmed counter-regulatory systems and effects [186, 224]. Furthermore the signalling pathways of the natriuretic hormones must be affected in heart failure, since in case of increased natriuretic levels, physiologically an accelerated natriuresis applies [364]. Thus, in heart failure, salt excretion in general is disturbed [126]. (6) Moreover, in the setting of an increased vascular tone which is accompanied by a diminished (foremost splanchnic) venous capacitance [60, 335], the hemodynamic effect of sodium and (consecutively) water retention may be amplified [365, 366]. (7) Especially to be noted, "fluid redistribution can only happen on the basis of an existing elevated blood volume" [126]. Thus some degree of fluid accumulation is necessary for the concepts of Fallick and Cotter to work, explaining very well the pathophysiology in absolute consistency with the clinical findings and presentations.

Nonetheless, fluid accumulation as the typical, classical feature characterizing the **cardiac pathway** of AHFS following the concept by Cotter [308], applies predominantly in case of relevantly compromised **cardiac** function [308]. In the setting of markedly impaired, prevailing cardiac performance, progressive **fluid accumulation occurs as the result** of cardiac failure. The ensuing, often persisting and thereby maladaptive, compensatory mechanisms, including activated neurohormonal cascades and endothelial—inflammatory programs, affect salt and water balance and renal function, clinically manifesting in a more gradual increase in total body volume, with concomitant enhanced body weight and in the front peripheral edema, jugular venous congestion, hepatomegaly, and gut discomfort [5, 17, 50, 308]. As the renal dysfunction and the modified fluid—salt balance component are relevantly involved [124], some authors talk about a **cardio-renal pathway** (instead of cardiac pathway) [54, 164, 297]. This "slow" decompensation over days and often weeks [134, 342] has been traditionally attributed to non-adherence in diet (improper high salt and fluid intake) and medication, as well decreasing contractility due to ongoing myocardial injury (mainly ischemia) [17, 55, 308]. This pathway is related to largely altered systolic, myocardial properties while changes in, and the impact of, the vascular conditions are seen in these circumstances in the background [308, 311].

Increased intravascular, thus particularly intravenous fluid content exerts biomechanical stress on the vessel walls [259, 367, 368]: Biomechanical forces including shear and circumferential wall stress as well as increased intravascular fluid content precipitating hydrostatic pressure display endothelial stretch, sensed by the mechanoreceptors located on the surface of the endothelial cells [296, 369–371]. Consecutively, the endothelial cells will be activated and hence switch phenotypically, altering their synthetic profile, and as such, physiologically deploy a signalling cascade resulting in a minor degree of vasoconstrictive, pro-coagulatory and pro-inflammatory condition [296, 369–371]. The reaction may be somewhat more pronounced in case of already enhanced vascular tone as typically present in "compensated" chronic heart failure [183, 184, 227]. Moreover, excessive and sustained activation is in any case crucial for disease progression [183]. As such, environmental cues may cause apparent or subtle, unrecognizable biomechanical stress which is associated with endothelial and neurohormonal activation and concomitant generation of oxidative stress. Oxidative degradation of the ROS's quenches NO (the key molecule of vasodilatation) activity despite elevated NO production and thus results in blunted NO bioavailability. This then affects vascular tone, causing (and amplifying) vasoconstriction [201, 261]. The vasoconstriction may be more distinct and amplified by other neurohormones modulated and released following vascular stretch, notably the renin-angiotensin-aldosterone—system with angiotensin II [259, 297] as its biologically most active representative, which, in turn, directly and indirectly promotes vasoconstriction [372]. Especially to be recognized, peripheral rather than central, cardio-pulmonary triggers are reported to be the decisive source of activating endothelial cells to generate and release vaso- and bioactive mediators [307, 373]. However, that is not surprising and absolutely consistent with the natural physiological conditions as most of the accumulated or retained excess fluids are

"stored" within the venous system [335]. Accordingly, systemic, particularly local **venous hemodynamic and finally clinical congestion** (venous congestion, mainly a result of the activated compensatory mechanisms and cascades, is associated with circumferential stretch [259]) causally accompanies and potentially facilitates acute heart failure evolution [54, 164, 174, 186, 192], as congestion is considered to play a crucial role in provoking endothelial and neurohormonal activation [374, 375]: "Systemic venous congestion is sufficient to cause endothelial and neurohormonal activation" [297]. However, as Hayashi [307] could demonstrate in a human study model of patients with systolic heart failure (HFrEF), **local** venous congestion is also, by all means, able to "promote endothelial and neurohormonal activation, even **exerting systemic effects**, as evidenced by an increase in plasma ET-1, IL-6, and VCAM-1 in this patient population" [297]. The special input from venous congestion in the acute and chronic heart failure pathobiology is further supported by the fact that venous congestion commences, and can be observed, days and even weeks before clinically overt heart failure ensues [133]. Hence, venous congestion has to be considered as being itself a primary contributor and hemodynamic, pro-oxidative, and pro-inflammatory stimulator of acute decompensation, rather than an epiphenomenon and merely a consequence of poor cardiac performance [133, 297]. Accordingly, there is substantial evidence that venous endothelial stretch, associated with and caused by local (and systemic) venous congestion following fluid retention and accumulation [259, 297, 307], is able to activate particularly the local, peripheral venous endothelial cells to subsequently produce and release, in a paracrine/endocrine manner, a number of vaso- and bioactive mediators and substances including vasoactive and inflammatory neurohormones and cytokines [259, 297, 374, 375] in a composition compatible with results typically demonstrated in AHFSs [374, 376]: "The peripheral release of vasoactive and pro-inflammatory neurohormones and substances from stretched endothelial cells and perivascular congested tissues may offset the physiologic adaptive state and may promote further fluid retention (fluid accumulation) inducing a vicious cycle resulting in overt decompensation" [375].

Thus, in consequence of the extended and elevated intravascular, namely intravenous, fluid amount, a rise in filling pressures of both the right and the left ventricle ensues. Subsequently **progressive** central pulmonary and **peripheral local and systemic venous congestion** will be displayed [104, 117, 126, 377]. Pulmonary (left-sided) and systemic venous (right-sided) congestion are related to elevated left- respectively right- sided filling pressures [15], whereupon the elevated LVEDP is the characteristic consequence of the systolic and/or diastolic cardiac dysfunction causally present in heart failure syndromes [378]. Elevated right-sided filling pressures are the result of (a) the elevated LVEDP being transmitted backward to the pulmonary vessel network, causing pulmonary venous hypertension, consecutively increasing RV-afterload [379, 380], (b) the increased RV preload and (c) of diastolic ventricular interaction applying in the presence of (acute) heart failure and typically if intravascular fluids distinctly accumulate as in cardiac malfunction [131, 132]: In circumstances with relatively preserved RV function, the failing left ventricle, unable to properly accommodate with any accessory fluid without a rise in LVEDP

[354], responds with a further (often inappropriate high) increase in LVEDP, even if the fluid amount offered by the RV is small [117, 125, 354] affecting markedly RV afterload and filling characteristics [380]. Accordingly, besides the enhanced right ventricular filling "inherently" promoting an increase in RVEDP [381, 382], and the backward transmission of elevated LVEDP first and foremost contributing to an enhancement of RVEDP [67, 383, 384], DVI will contribute to a recognizable, sometimes marked increase in RVEDP [132, 385, 386]. In case RV function is also altered, the increase in REVDP will be accentuated [385–387] and is typically higher than the rise in LVEDP [385, 386], as notably diastolic ventricular interdependence will decisively influence the filling pressures [131, 388, 389]. Accordingly, in most cases (≫80%), the increase in LVEDP is accompanied by a noticeably substantially elevated RV-filling pressure [121]. Indeed, Gheorghiade found that nearly all patients suffering from acute heart failure present with both, systemic and pulmonary congestion [153]. Anyhow, subsequently RV function [390, 391] as well as diastolic [392] and systolic [393–395]) LV properties will be further compromised.

Hence, a considerable increase in LVEDP following enhanced intravascular volume arises, potentially causing **clinical** pulmonary congestion or even provoking pulmonary edema [125, 396–399]. Pulmonary congestion is associated with reduced oxygen saturation and myocardial ischemia potentially arises if oxygen saturation is less than 90%, furthermore circulatory insufficiency results in metabolic acidosis which jeopardizes the heart [137].

In addition, venous congestion (which is affected by the amount of intravenous fluid volume, changes in venous tone and sympathetic activation [60, 400]) is demonstrated to impair cardiac function [125, 126, 401] (another hint that venous congestion is a contributor rather than simply an epiphenomenon of AHF), and increases in LV end-diastolic filling themselves inherently augment ventricular stiffness (and thus afterload) and decrease EF [126].

Hemodynamic congestion may be seen as fluid retention and occurs early in the course but is clinically imminent [153]. However, local peripheral venous distension and local tissue edema, both attributed to enhanced fluid content, result in **venoconstriction, since** endothelial stretch initiates local (but accompanied by systemic) neurohormonal and endothelial activation, where particularly A II, ET-1 and sympathetic discharge are responsible for the local venous venoconstriction [174, 261, 297, 402, 403]. This will precipitate further fluid influx, preferentially from the splanchnic veins, enhancing effective circulating blood volume [60] and promoting a further increase in venous return and thus preload, but as well amplifying venous congestion. As a matter of fact, there will arise a somewhat worsened/affected arterial stiffness due to the inflammatory effects displayed [282]. Both effects, venoconstriction with associated fluid shift and the (more) stiffened arteries (further) alter loading conditions and effect systolic and diastolic ventricular properties translating in a further increase in LVEDP (RVEDP respectively) and compromised LV and RV function [15, 60, 134, 153, 284, 285, 297, 354].

Very remarkable, these considerations are not only indicative for a vicious cycle being established and applied leading to acute decompensations and

disease progression, but are rather well suggestive of a link between fluid accumulation and vasoconstriction, notably venoconstriction, the latter affiliated with fluid redistribution. Hence a link between the vascular and the cardio-renal pathway [297]: **Venoconstriction** due to neurohormonal, namely sympathetic discharge by reducing the venous capacitance [60, 335, 404], induces a fluid shift, preferentially from the splanchnic venous reservoir, into the effective blood circulation, hence central fluid redistribution applies. Subsequently a rise in preload and inevitably an, often marked, increase in filling pressures ensues, *facilitating further venous congestion through* **fluid accumulation** [60, 153, 297, 374]. On the other hand, **fluid accumulation,** primarily due to impaired (and during the course progressively worsening) cardiac performance, leads to (further) endothelial and neurohormonal activation, ending up in a pro-inflammatory, pro-coagulative and *vasoconstrictive milieu,* fostering vaso-, especially splanchnic venous, constriction. The splanchnic veins are shown to be exceptionally sensitive to even discrete sympathetic discharge, and as such shift and **redistribute** blood from the venous reservoir into the effective circulating stream. Augmented preload and concomitantly filling pressures result [60, 133, 297] (Fig. 2.2).

With these remarks it becomes obvious, that even mild, primarily natural and reasonable modifications, adaptations (e.g. to upright position) within the physiological range may offset ("just") compensated conditions initiating a vicious cycle in which (further) sympathetic discharge and other regulatory cascades lead to and provoke acute heart failure [126, 297]. Furthermore, Fallick's [60] and Colombo's [297] considerations add a new aspect to the existing views and concepts, namely a special venocentric approach (in addition to cardiocentric, nephrocentric and arteriocentric): Venous congestion contributes (via triggering local and systemic endothelial-inflammatory response and compensatory mechanisms) to the heart failure

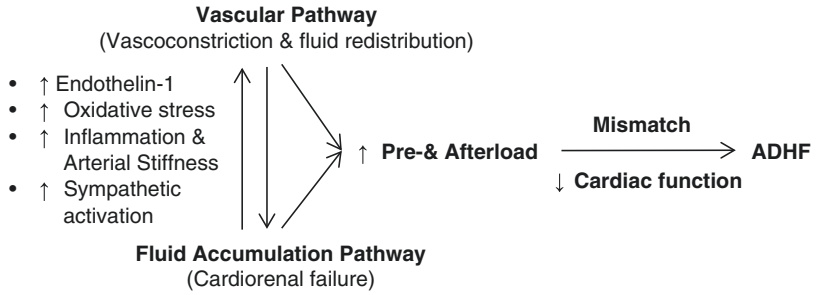

Fig. 2.2 Adapted from Colombo PC (Curr Heart Fail Rep 2015; 12: 215–222) [297], with permission. Depicted is the suggested link between fluid redistribution and fluid accumulation, both effective in acute heart failure pathobiology, independent of the threat primarily launching the decompensation. The pathways are linked and affect each other. The finding that venous constriction may also precipitate central fluid redistribution broadens Cotter's concept [308], and explains well that even minor (repetitive) sympathetic discharges may lead to acute decompensations—and that without noticeable fluid accumulation

pathobiology by promoting (further) increases in effective circulation blood volume with consecutively increased preload, filling pressures, aggravated congestion and additional fluid accumulation.

2.4.2.6 (Self)-Amplification and Vicious Cycles

Furthermore, as exemplarily demonstrated by the link between the vascular (vasoconstriction and fluid redistribution) and cardiac/cardiorenal (fluid accumulation and venous congestion) pathway, and as demonstrated by the interconnections of the neurohormonal and endothelial-inflammatory features and systems involved, this condition bears a considerable potential of self-amplification and perpetuation of a vicious cycle driving the heart failure malady [186, 297]. As such, elevated, high LVEDPs and myocardial stretch, typically present in acute (and chronic) heart failure, are known to be very powerful biomechanical incentives. They cause neurohormonal activation including the adrenergic and cytokine pathways and the RAAS, [104, 160, 405], provoke subendocardial ischemia (further affecting the cardiac properties) [66, 68] and reduce coronary perfusion (potentially causing ischemia) [160], not at least facilitate changes in LV-shape and thus functional mitral regurgitation (affecting hemodynamics) [36, 406, 407]. Furthermore, simply ordinary stress may induce an increase in LAP/LVEDP causing further distress in predisposed patients with neurohormonal activation, and in consequence facilitate congestion [297]. Moreover, in the setting of an increased vascular tone which is accompanied by a diminished venous, foremost splanchnic, capacitance [60, 335, 404], the hemodynamic effect of sodium and (consecutively) water retention may be amplified [365, 366].

2.4.3 Summary

"The syndrome of heart failure is the result of complex interactions among molecular, endocrine, and biodynamic systems" [408]. The intricate pathophysiology is of multifactorial and multi-facet nature, however appears to be largely related to the complex interplay between neurohormonal activation and adaptive remodelling efforts with the mechanical-hemodynamic disorders [288, 409]. Typically characteristic for ADHF is "a mismatch between loading (pre- and/or afterload) conditions and the afflicted, impaired cardiac function" [160, 297, 308]. Indeed, the communication, the cross-talk, between vascular and cardiac properties considerably determines the circulatory conditions [53, 54, 410, 411] of this systemic disease [412–414], which may affect over time several organs, preferentially the kidneys [98, 400, 415].

Two mainstream pathophysiological pathways applying and leading to AHF were recently introduced by Cotter allowing for integration and harmonization of the clinical pictures with the pathophysiological concepts [308]: **Vascular failure** precipitating and ending up in AHF describes alterations in vascular properties modifying systolic and/or diastolic loading conditions, evoking an acute mismatch as the systolic and/or diastolic cardiac capacities and capabilities are primarily

impaired or limited and thus not able to properly meet the altered conditions [60, 126, 153, 297, 308, 357]. This path is associated with central, pulmonary fluid redistribution rather than with fluid accumulation and has been originally related to predominantly (acutely) increased arterial vascular stiffness/resistance causing an acute afterload mismatch [117, 160, 308]. As such, it applies particularly to patients with diastolic dysfunction and HFpEF [112, 113, 127, 148, 214, 322]. However, this vascular failure path has been broadened and modified as even subtle hemodynamic changes, often affecting primarily preload conditions, may already precipitate AHF [126]: Sympathetically-mediated vasoconstrictions, preferably due to the anatomic circumstances, may be exclusive to the splanchnic veins (and thus a vascular path), and are shown to shift relevant amounts of the their stored blood into the effective circulation, subsequently increasing cardiac preload [60]. As the compromised left (and often right) ventricle cannot accommodate any increase in filling volume without often marked rises in filling pressures [354], consecutively clinical pulmonary and venous congestion arise and overt acute heart failure ensues [67, 104, 117, 126, 135, 153]. In predisposed patients (patients with chronic heart failure and chronically augmented NHs drive) minor sympathetic discharges, even physiological ones due to mild exercise or posture, upright positioning [332] may, particularly if repetitive with repeated blood volume shifts into the effective circulation [123], (ultimately) provoke AHF—this scenario, which may also apply in case of decompensations without evidence for classical precipitants, explains well that the majority of patients with AHF do not show any or only marginal weight gain prior to decompensation [60, 126, 357].

The **cardiac or cardiorenal pathway** represents the classical pathomechanism of AHF [308]. Related to considerably impaired cardiac performance (and thus systolic dysfunction, HFrEF), the hemodynamic alterations and associated, the activated, basically compensatory systems, lead to substantial fluid accumulation [5, 17, 50, 308], often developing slowly and gradually [123, 342]. Fluid accumulation, is, at least to some degree (including in the predominantly vascular failure path), in general part of the heart failure pathology [35, 126, 358, 359], although definitely quite often not obvious for us, as it is not measurable by methods applicable in daily practice (as it may be without relevant weight gain) [160, 349–352]. However, increasing intravascular fluid volume precipitates an increase in preload and venous congestion, the latter meanwhile verified to be an active contributor to heart failure pathobiology [133, 297], and furthermore challenges even more the neurohormonal (namely sympathetic and A II discharge) and the endothelial-inflammatory paths [297]. Again, the increase in filling volume, preload, and consecutively pulmonary and systemic pressures lead to overt clinical heart failure [104, 117, 124, 126, 135, 153, 355, 356]—an increase in LVEDP may be due to fluid redistribution and/or due to fluid accumulation [117]. Furthermore, venous congestion is demonstrated to (further) impair cardiac function [125, 126, 404] and to foster (further) fluid accumulation [60, 153, 298, 377].

Accordingly, both pathways are linked and interrelated [297], moreover their interaction "may promote a vicious cycle as fluid accumulation causes vasoconstriction", more precisely predominantly **veno**constriction, "while vasoconstriction causes an increase in filling pressures" (via increased preload due to blood shift

from the splanchnic veins) "and thus promotes (further) venous congestion through (further) fluid accumulation" [297].

The described modifications, adaptions, reactions, and altered conditions are partly due to, but in any case largely mediated, coordinated and integrated by the activated NHs and endothelial—inflammatory paths [165–169, 173, 174, 416], both with substantial impact on the cardio-circulatory system [183, 186], and with the endothelium playing a central role in the pathobiology of acute and chronic heart failure, "orchestrating" the processes [173, 175, 223, 416] .

The central feature related to the underlying primary pathologies and the incorporated multifactorial patho-biological processes, markedly elevated left- and generally right-sided filling pressures, which are affiliated and associated with pulmonary and systemic venous congestion (independent whether CO is low or not) [14, 15, 122–124, 153], are displayed [14, 122, 153, 154, 214, 378]. These elevated pressures may be the pivotal position in the pathophysiology and are decisively determining and coining the clinical picture [5, 17, 50, 106].

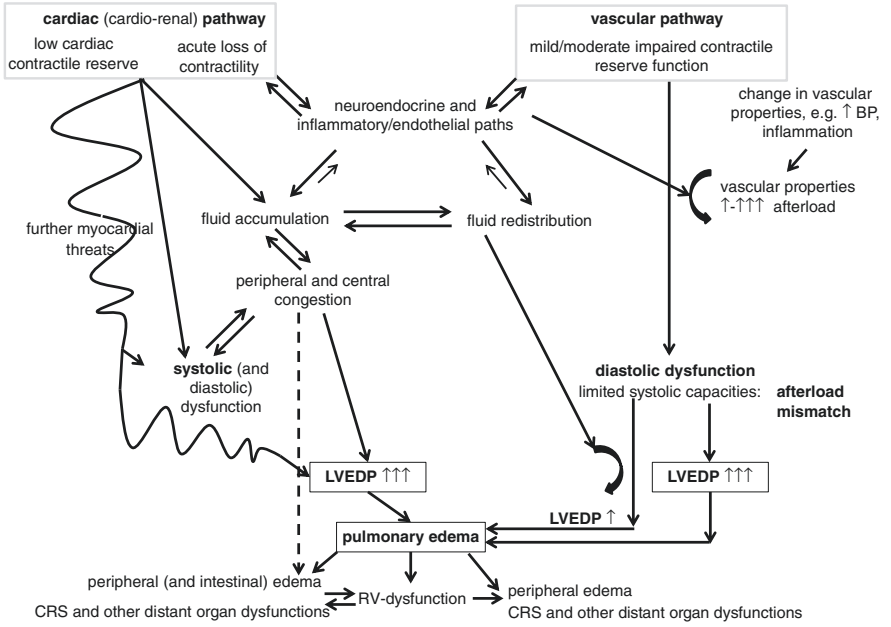

Fig. 2.3 Fig. 2.3 summarizes the central pathobiology of acute heart failure syndromes. It is mainly based on the publications by Cotter [308], Paulus [37], Fallick [60], Metra [147], Borlaug [147], and Colombo [297]. Modifying Cotter`s fundamental concept, it integrates the most recent pathophysiological findings contributing to and co-determing acute heart failure. It depicts that indeed one of the basic malfunctions/insults (altered loading conditions or impaired systolic performance) predominantly activates and launches certain pathobiological processes, but highlights the close interactions between the two paths and their potential to amplify each other, and thus facilitate the evolution of AHF

2.5 Diagnosis, Symptoms, Presentation, Important Clinical and Prognostic Data

2.5.1 Symptoms and Diagnosis

The diagnosis of acute heart failure is generally based on clinical symptoms (dyspnoea, orthopnoea, shortness of breath on) and signs (crackles on pulmonary auscultation, peripheral edema) suggestive for heart failure [14, 417] in the context of clinical history, physical examination and other findings [6, 418, 419]. Dyspnoea is the most common symptom, however it is non-specific. On presentation [14, 28, 44, 49]:

up to 89%	Suffer from	Any dyspnoea
up to 34%		Dyspnoea at rest
up to 32%		Fatigue
up to 68%		Rales on examination
up to 66%		Peripheral oedema
up to 75% (60–90% [49])		X-ray congestion

Symptoms and signs like paroxysmal nocturnal dyspnoea attacks, jugular venous distension, and third heart sound S 3 are quite frequently seen as having a specificity of 70–90%, but a really low sensitivity 11–55% [420].

Thus, symptoms are dominated by those related to pulmonary congestion, reflecting the elevated LVEDP [14, 69].

Insofar the pulmonary affliction attributed to the left heart disease may contribute to the patient's symptoms and the clinical picture: The pulmonary mechanics are affected leading to a reduction in lung volume and a diminished lung compliance, thus displaying a restrictive lung physiology [421, 422]. Furthermore, gas exchange is hindered [421, 422]. While fluid removal improves lung mechanics, a dysfunction of the alveolar membrane diffusion capacity will persist in the first instance [423, 424].

Blood pressure on admission both provides information on prognosis, and smooths the way of therapeutic measures [5, 35, 425].

Blood pressure ranges on admission are distributed as follows [14, 28, 33, 44, 69]:

sBP > 140 mmHg	50% of all admissions (approximately 25% have a sBP > 160 mmHg)
sBP 90–140 mmHg	45% of all admissions
sBP < 90 mmHg	5% of all admissions[a]

[a]Taking other study results into account, we see 5–8% of AHF admissions who present hypotensively, to be in general defined as a sBP <90 mmHg [426, 427]

However, high BP on admission may be due to sympathetic stimulation rather than established hypertension [69].

- Dominant clinical conditions on admission to hospital in the Euro Heart Survey [28] (see ESC classification [4]):
  - 66% presented with the picture of acute decompensated/exacerbated chronic HF;
  - 17% showed pulmonary oedema as the dominating clinical condition;
  - 10% were admitted due to HF and arterial hypertension;
  - 4% with cardiogenic shock;
  - 3% were admitted due to an acute right heart problem.

As mentioned, the French survey [49] published in 2006 included the very sickest patients as well and recognised pulmonary oedema in 82% and cardiogenic shock in 29%.

2.5.2 Prognostic Indicators

The main predictors of prognosis signalizing high mortality are low systolic blood pressure (sBP) and elevated BUN at admission [35, 49, 425].

- Blood pressure:
  An analysis from the Optimize-Study by Gheorghiade [69] is shown in Table 2.2.
  - In the analysis of the ADHERE study data, a cut-off level of systolic 125 mmHg indicating a significantly worse prognosis was identified [35];
  - In the French survey [49], a sBP > 120 mmHg promised a better short term (4 weeks) prognosis [49].

Thus, a systolic blood pressure (sBP) ≤ 120–125 mmHg should give cause for concern, and admission to a coronary care unit or high dependency unit should be considered.

Only 9.5% of all patients in the Optimize-HF study had a sBP < 104 mmHg on admission [69]

Table 2.2 Optimize-study by Gheorghiade [69]

sBP at admission (mmHg)	In-hospital mortality (%)	60–90 days mortality (%)
≤119	7.2	14.0
120–139	3.6	8.4
140–160	2.5	6.0
≥161	1.7	5.4

- Blood urea nitrogen:
  BUN blood concentration >37 mg/dL [35] (urea > 13.2 mmol/L), > 43 mg/dL [425] (urea > 15.35 mmol/L) is the other strong predictor of significantly increased mortality.
- Other factors of concern but with less impact on the mortality are [35]:
  - Low serum sodium concentration;
  - Elevated serum creatinine;
  - Advanced age;
  - Dyspnoea at rest;
  - Chronic β-blocker use;
  - congestion at admission [428].

2.5.3 Initial Clinical Assessment, Diagnostic Measures and Considerations

The cornerstones in making the diagnosis are the patient's history and the clinical examination, read above [4, 6, 419, 429–431].

Patients admitted with symptoms generally suggestive for heart failure and a typical history should be subject to a 2-min bedside clinical-hemodynamic examination [158, 431, 432] (see Fig. 2.4). Furthermore, potential conditions triggering acute cardiovascular decompensations have to be identified whenever feasible [431].

2.5.3.1 Hemodynamic Profiles on Admission

A clinical-hemodynamic, widely used in daily practice, and easy to perform assessment tool for patients with acute heart failure syndromes, allowing for a meaningful and crucial distinction of those patients [224], has been introduced by Nohria and Stevenson [158, 426] (see Fig. 2.4). It takes into consideration the most prominent clinical features and basic pathophysiological issues characterizing the nature of AHF, gives a clue about the severity of the actual situation and possible complications the physician may be faced with, like potentially ensuing shock, and provides hints to select therapeutic measures [16, 17, 433, 434].

Accordingly, most patients can be classified during that 2-min bedside assessment [158, 432, 435] into a hemodynamic profile with a corresponding treatment regimen [158]. The main hemodynamic abnormalities are related to filling pressure and peripheral perfusion. In the presence of elevated filling pressures the patient is said to be 'wet', in their absence 'dry'; if the perfusion of the peripheries is adequate, the patient is 'warm', if critically reduced 'cold'. Note that the assessment concerning a 'cold' patient due to hypoperfusion should be made by assessing the legs and forearms rather than the feet and the hands [435] (Fig. 2.4).

Haemodynamic profiles are:

- Profile 1: Warm and dry → will not be seen in emergency admission unit. Requires therapy along standard chronic heart failure guidelines.
- Profile 2: Warm and wet (67% of all patients [436]) → main step is the application of diuretics (or the increase the dosage of their diuretic medication), but

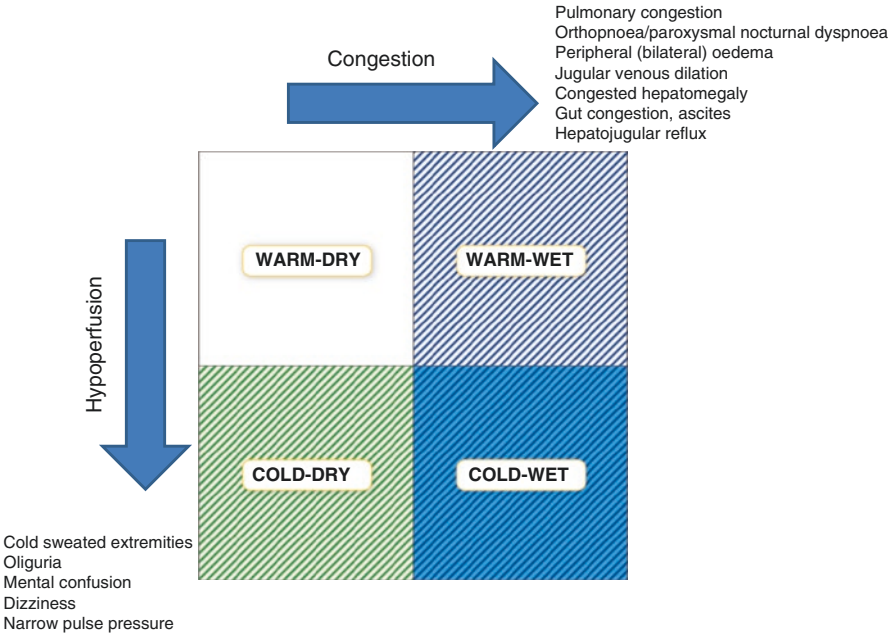

Fig. 2.4 The 2-min bedside assessment by Nohria and Stevenson [158, 426, 432] allows for a clinical—hemodynamic assessment and classification of AHF patients and furthermore provides therapeutic and prognostic hints. This figure is adopted from the ESC guideline [431]. Depicted are the four different profiles most patients can be assigned to. On the *right upper* (wet and warm), the patient is predominantly wet and signs and symptoms associated with increased filling pressures and congestion are dominating. Beyond, *right lower* (cold and wet), hypoperfusion is the dominating clinical impression indicated by the features described

initially nitroglycerin sublingual may make sense as well as long as sBP is >100–110 mmHg [5, 7, 35].

- Profile 3: Wet and cold (28% of all patients [436]) → warm the patient by either using vasodilators (nitroglycerin or nitroprusside) in case of sufficient blood pressure and signs of vasoconstriction, otherwise inotropes and/or vasopressors are required; when this is achieved, dry them with the aid of diuretics.
- Profile 4: Cold and dry → they seem often surprisingly stable, but may collapse unexpectedly; therapeutic measures depend on the underlying reasons and conditions and may include diuretics in case of predominant or isolated right heart failure (with DVI) as long as BP is sufficient, or inotropes and/or vasopressors; but sometimes just fluid may be needed.

Clinical symptoms and signs of congestion (wet) include: Pulmonary congestion (crackles and rales), jugular venous distension, peripheral oedema, hepatomegaly, orthopnoea, paroxysmal nocturnal dyspnea, gut congestion and ascites, hepatojugular reflux [4, 30].

Clinical signs of hypoperfusion/shock (cold) comprise the following [158, 437, 438]: Altered level of consciousness (confused, quiet, apathetic, dizzy), cold peripheries (forearms, lower leg), moist and clammy skin, mottled extremities, ↓ toe tip temperature, oliguria (renal dysfunction), narrow pulse pressure, ↓ MAP, hepatic dysfunction, low serum sodium.

Patients classified into profile 3 are reported to have a 6-month mortality rate up to 40% [16, 426].

2.5.3.2 Identification of Precipitants of AHFS

Typical features precipitating acute decompensations may include:

- Ischemia/acute coronary syndromes;
- Systemic infections, notably respiratory tractus infections;
- Poorly controlled co-morbidities, such as exacerbated COPD with and without pneumonia;
- Uncontrolled hypertension/acute hypertensive dysregulations;
- Arrhythmias (atrial/ventricular arrhythmias);
- Nonadherence to medication;
- Renal failure/worsening renal function;
- Nonadherence to diet/inappropriate salt intake;
- Inappropriate physical stress;
- Drugs like NSAID's, corticosteroids, chemotherapeutics;
- Pulmonary embolism;
- Enhanced sympathetic discharge as in Takotsubo cardiomyopathy

[138, 139, 158, 159, 431, 439].

To identify an acute coronary syndrome is of critical importance as immediate coronary intervention is acknowledged to significantly reduce complications and mortality [437, 440, 441].

2.5.3.3 Other Diagnostic Measures

Echocardiography, considered the "gold standard" for the detection of LV dysfunction [442], is an essential tool which should be performed to evaluate LV-function, structure, and any alterations to this; confirmation of the diagnosis (acute) heart failure is essential as well as identifying potentially reversible causes [4, 443]. However, an immediate echocardiographic examination is "only" imperative in patients with hemodynamic instability and in case life threatening conditions are suggested [431]. In de novo AHF, heart ultrasound is recommended to be performed in otherwise stable patients within 48 h [431].

Of note, ultrasound of the lungs to identify congestion and pulmonary edema (and their severity), substantiate [156, 444–446] or even diagnose AHF [447–449] in case the diagnosis is uncertain, may be of great value as recent publications revealed [444, 445].

The *chest radiograph* will aid diagnosis of congestion and/or pulmonary oedema [42, 82], and may identify cardiomegaly. However, in up to 20% of cases, the chest X-ray in AHF patients may be nearly normal [119].

The *electrocardiogram* (ECG) will help to identify a precipitating ischemic event or the new onset of atrial fibrillation inducing the AHFS [4, 429]. A normal ECG in a clinically suggested case of acute heart failure virtually rules out this diagnosis [429].

As the symptoms of acute heart failure may be non-specific and as the physical findings are sometimes not particularly sensitive [432, 450], the *Natriuretic Peptides*, ANP and BNP, may be helpful in the diagnostic and differential diagnostic considerations, particularly in the emergency department [194, 451–453].

It is in particular the excellent negative predictive value of BNP which can be used to exclude heart failure and to differentiate potential cardiac failure from other underlying diseases [454]. On the other hand, elevated levels do not automatically confirm the diagnosis of AHF, as natriuretic peptide serum levels may be enhanced in quite a number of other cardiac (LV hypertrophy, myocarditis, tachyarrhythmias, pulmonary hypertension) and non-cardiac reasons including advanced age, cardiometabolic disorders, severe infections, anemia, renal and liver dysfunction, ischemic stroke and subarachnoid bleed, and in the paraneoplastic syndrome [455–457].

Troponin T and I are highly sensitive and specific parameters, allowing identification of myocardial injury and play a well-established key role in diagnosing acute coronary syndromes (ACS) [458], as well as in the risk stratification and management of patients suffering from ACS [459–462].

An elevation of cardiac troponin is found in about 40% of all patients with acute decompensated heart failure [463, 464], is associated with a low LV-EF [465, 466], and is said to predict a poor short term prognosis [465, 467].

You [468] has shown that troponin I is a strong predictor of all-cause mortality in patients with acute decompensated heart failure. The study shows an independent 'dose'-response relationship between cardiac troponins and mortality in AHFS-patients. Thus, an association between elevated cardiac troponins and poor outcome in acute heart failure seems to be established [465, 467].

2.5.3.4 Special Remark: Non-invasive Estimation of Cardiac Index

Cardiac output and cardiac index are undoubtedly the parameters widely used in daily practice. In 1989, Stevenson published a method remarkably reliable, able to estimate CI non-invasively: If the ratio [sBP–dBP]/sBP < 25% then CI is highly likely to be less than 2.2 L/min/m^2. This prediction shows a sensitivity of 91%, its specificity is 83% [432] (Table 2.3).

Table 2.3 Summary of the clinical-hemodynamic findings [5, 7, 91, 158, 431–434, 436]

Warm and dry	Warm and wet (>50% of all patients)
Clinical: No specific heart failure symptoms; commonly signs of severe infection/sepsis, tachycardia, hyperthyroidism, etc.	*Clinical*: Symptoms dominated by the ↑ filling pressures causing shortness of breath—pulmonary congestion and/or acute and 'chronic' pulmonary oedema, peripheral oedema and ascites; S3 is heard
Hemodynamics: sBP low n/n/↑ ; CI/CPI n/↑↑↑, PCWP n *Hypoperfusion*: None	*Haemodynamics*: sBP low n/↑↑↑; CI CPI (↓)/n/↑; PCWP ↑/↑↑↑ *Hypoperfusion*: None to mild; end organ hypoperfusion: (CNS) only in HTN
Clinical scenarios most likely in this group: none, may be ESC-5, ESC-6, ESC-1?	*Renal perfusion*: discordantly ↓ RBF, impaired intra-renal autoregulation; ↑ renal venous pressure
Key question: Is the diagnosis AHF correct?	*Clinical scenarios* most likely in this group: ESC-1, ESC-2, ESC-3; ESC-5
Treatment: Treat other predominating non-cardiac disease, fluids	*Treatment*: Diuretics , and additional vasodilators (GTN) if appropriate (BP still >110 mmHg after diuretics are already applied) like in hypertensive acute heart failure/pulmonary edema
COLD and dry	**Cold and wet (>25% of all patients)**
Clinical: Often stable, symptoms dominated by hypoperfusion such as altered level of consciousness, cold peripheries (forearms, lower leg), ↓ toe tip temperature, oliguria, ↓ MAP, (sometimes unappreciated congestion). May be some occult signs of very mild fluid overload as in patients with significant ↓ contractile capacity and/or severely dilated chambers (ESC-1) otherwise no "specific" heart failure symptoms	*Clinical*: Dominated by symptoms of hypoperfusion such as altered level of consciousness, cold peripheries (forearms, lower leg) with cold skin, moist and clammy, mottled extremities and ↓ toe tip temperature, oliguria, congestion/ pulmonary oedema; ↓ MAP; S3 heard; often caused by AMI
Haemodynamics: sBP ↓/n; CI/CPI (low n)/↓/↓↓↓; PCWP n/↓ *Hypoperfusion*: Mild to moderate *Altered renal perfusion*: ↓/↓↓ RBF, impaired renal autoregulation	*Haemodynamics*: sBP ↓/↓↓↓; CI/CPI ↓/↓↓↓; PCWP ↑/↑↑↑ *Hypoperfusion*: Mild to severe *Renal perfusion*: ↓ RBF; impaired intra-renal autoregulation; ↑ renal venous pressure
Clinical scenarios most likely in this group: ESC: ESC-6, ESC-1	*Clinical scenarios* most likely in this group: ESC-4a and 4b (pre-shock* and manifest CS), ESC-5
Treatment: Fluids, inotropic support, vasopressors if sBP < 90 (85) mmHg; but may be diuretics are appropriate as in case "isolated" RV-F or biventricular, predominantly RV-failure with substantial pericardial constraint and DVI	*Pre-shock criteria: Hypoperfusion present but sBP > 90 mmHg, crackles ≥50% of total lung area, pulmonary oedema, cold and sweaty patient, history of previous AMI *Treatment*: coronary intervention in case of AMI; vasopressors (NA) in case of sBP < 90(85) mmHg in order to avoid myocardial ischemia/further myocardial ischemic damage. Inotropes may be considered before NA is started

2.6 Therapy [4, 5, 7, 431, 432, 437, 469–474]

2.6.1 Therapeutic Principles and Goals

Peripheral, namely **pulmonary congestion,** or even pulmonary edema, associated with elevated filling pressures decisively coin the clinical picture and dominate the patient's discomfort and symptoms. **Elevated afterload and pulmonary congestion** are a key clinical-pathophysiologic features in AHFS [5, 14, 50, 106, 114, 115, 122, 123].

Accordingly, the immediate goals of managing emergency cases of AHF are [157, 158, 432]:

- symptom relief;
- reversal of the haemodynamic abnormalities, in particular:
  - reduction of the elevated LVEDP (determines the outcome [157, 158, 475]), and
  - significant reduction of the increased afterload [13, 439];
- rapid stabilisation

To address the acute malady picture and pathophysiology dominating features, the administration of loop diuretics remain the cornerstone measure [5, 7, 16, 359, 476, 477].

In the ADHERE registry, 88% of all AHFS patients received intravenous (i.v.) diuretics as a first line measure [478]. Since diuretics lead to a very rapid symptom relief and further address the patho-physiological features (fluid overload and elevated filling pressures, both closely related to the clinical pictures), they have gained universal acceptance and priority in AHF treatment. However, no randomized placebo-controlled trials assessing diuretic use in AHFS exist [479]. Moreover, a number of study results even advise against diuretic use, particularly in high dosages, as diuretics may be accompanied by a number of adverse effects and even an increase in mortality cannot be excluded [480–483]. Especially dreaded are induction of vasoconstriction [484] and (relative) hypovolemia due to diuretic application [485, 486], associated with increased mortality rates [482, 487, 488].

Early on, diuretics exhibit vasodilatory effects, thereby causing transient venodilation, immediately lowering right atrial and pulmonary capillary wedge pressure, consequently left-sided filling pressure, thereby mitigating dyspnoea prior to the onset of diuresis [484, 489]. Further on, urinary output increases by excretion of fluid and sodium [433], reducing filling volume and filling pressures, and as such dilute peripheral and pulmonary congestion/edema [490]. Finally, extracellular fluid volume drops and the patients forfeits body weight. Thus diuretics given sufficiently early reduce intravascular volume and filling pressures, as well as peripheral and pulmonary congestion [490].

Even in case of no obvious relevant weight gain prior to decompensation, patients with acute heart failure are basically somewhat volume overloaded, thus diuretic therapy is required and absolutely indicated [35, 126, 358, 359]. Furthermore, in advanced heart

failure, with sometimes low normal blood pressures, the application of diuretics has been shown to be pretty safe, as Atherton demonstrated [131]: In advanced heart failure, roughly 50% of the patients suffer from clinically relevant right heart dysfunction/failure. Hence, diastolic ventricular interaction and pericardial constraint apply, affecting the pathobiology [131, 491]. Accordingly, even in case of relatively low pressures (<80–90 mmHg), diuretics are the drugs of choice to improve volume distribution between the ventricles and subsequently hemodynamics, leading to a substantial increase in BP. However, even in case relevant pericardial constraint and DVI are not effective in patients with advanced heart failure, no significant and clinically meaningful side effects have been observed if diuretics were applied [131]. However, keep in mind, patients suffering from HFpEF are exquisitely sensitive to volume and pressure changes and may reply to the effects of diuretic agents with substantial pressure drops [112, 113].

The administration of diuretics is validated and conceded to be a class I, level B evidence of the American ACCF/AHA [7, 319], while the European (ESC) society's recommendation discloses to apply diuretics as class I, level C [431].

Vasodilators, namely nitroglycerin (GTN), although exerting a direct lowering effect on elevated filling pressures and on the enhanced afterload, provide a 'physiological' therapeutic approach [157, 480], but have not gained as universal an implementation and acceptance as the diuretics [5, 7]. Vasodilators promote a rapid normalization of the altered hemodynamics [157, 492], as afterload reduction implies that LVEDP will drop: ↓ afterload → LVEDP ↓ [493]. Furthermore, the failing heart is exquisitely sensitive to afterload [494, 495] and hence a reduction in the LV outflow impedance (afterload) hampering the ejection by pharmacological vasodilatation will improve the LV ejection, and as such will significantly increase the LV-forward output [496, 497]. In addition, they will substantially reduce the regurgitant orifice and the grade of the mitral regurgitation, very often accompanying LV dysfunction [498, 499].

Thus, afterload ↓ → LVEDP ↓ [500, 501] → diastolic wall stress ↓ → O2-requirement ↓ [502] → LVEDD ↓ [500–502], subsequently, afterload ↓ → SV/CO ↑ [439].

Accordingly, the application of vasodilators are a rational and a clinically validated approach to acute left heart failure treatment [5, 7, 431, 503]. However, they do not address fluid accumulation and are associated with an increased risk and incidence of hypotension [84, 504]. Hypotension may jeopardize myocardial perfusion, and by blunting autoregulated cardiac/myocardial blood flow disturbs blood distribution, consecutively myocardial ischemia ensues (or is aggravated), which subsequently dilutes contractility and cardiac performance and that in the presence of an already compromised myocardial function as in heart failure [315, 316, 319, 505]. Furthermore, vasodilators unfortunately could neither provide substantial evidence that they ameliorate symptoms nor that they improve outcome, namely reduce mortality rates [316, 433, 481, 504, 506–508]. Probably therefore, the recommendations to use vasodilators are inconsistent and differ from society to society. As such the American societies ACCF/AHA recommend to use vasodilators "just" as an adjunct to diuretic therapy (class IIb, level A recommendation) [7], while the ESC validates nitrates as a class IIa, evidence level B measure, particularly to be administered in hypertensive patients [5, 431].

Applying the clinical-hemodynamic assessment results using the 2 min bedside tool by Nohria and Stevenson, the treatment of the "**warm and wet patient**" will need sufficient dosages of diuretics, furthermore hypertensive patients and those with a sBP above 110 mmHg may benefit from additional vasodilators (ESC types 1–3 and 5) [5, 7, 50, 308, 479]. In hypertensive AHF, vasodilators, e.g. GTN, may be initially be preferred [431, 481, 509].

Type ESC-1 may be warm and wet, but could be cold and wet as well. As such, sBP is in general normal, hence those patients will basically be treated solely with diuretics as typically considerably fluid overloaded when acutely decompensated [5, 7, 50, 308, 479].

The "**cold and wet patients**" are a risky group as they are in, or may develop, cardiogenic pre- and manifest shock. Thus, those patients require thorough monitoring and besides diuretics either vasodilators (if sBP is well above 110 mmHg) or non-vasodilating inotropes (or a combination of noradrenaline and dobutamine) in order to improve perfusion. In case of manifest cardiogenic shock, vasopressor application may be required as the very first measure.

In any case, (further) coronary hypoperfusion needs to be avoided completely, otherwise a progressive detrimental loop resulting in cardio-circulatory collapse and multiorgan dysfunction may ensue. Typically within this class profile ESC-4, ESC-5 (with peripheral edema but clear lungs), but ESC-1 may fit as well [5, 7, 50, 308, 479].

The **"cold and dry patient"** is rare (typically ESC-6, may be ESC-1, 4 and 5), but difficult to treat. Aside from isolated or predominantly acute right heart failure patients (ESC-6), ESC-1 patients with significant impaired contractile function, markedly dilated heart chambers, and significant dynamic mitral regurgitation with diminished BP and a low tendency to retain fluids, may present "cold and dry". These patients will probably need inotropes, maybe vasopressors as well, due to hypoperfusion and hypotension, as usually BP will be low rather than high. Treatment of hypoperfusion is essential, diuretics are here second line to those with enlarged hearts [5, 7, 50, 308, 479]. However, if a predominant or isolated right heart failure (ESC-6) is the reason of concern, diuretics (possibly in combination with vasopressors and or inotropes) may be absolutely indicated as, due to acute RV dilation and pericardial constraint, diastolic ventricular interaction is present and effective (overview by Harjola [510])—read more about this issue in Chap. 4.

Patients with *ACS complicated by acute heart failure* (ESC-5) may show a warm and dry picture, however usually a **"warm and wet profile",** sometimes a pre- shock or cardiogenic shock constellation. They represent in any case a high risk group and immediate (<than 2 h after admission) invasive coronary intervention for both, ST elevation myocardial infarction and non–ST-elevation myocardial infarction is mandatory [25, 431, 511, 512]. As up to 70–80% of the patients suffer from multi-vessel (stenosis/occlusion >1 vessel) disease [13, 513–515] even CABG may be necessary. For further details regarding this issue, please read Chap. 3, cardiogenic shock.

2.6.2 Initial Therapeutic Approach

2.6.2.1 Treatment of Underlying Diseases [25, 470, 471, 511, 512, 514]

- Primary angioplasty or thrombolysis of acute ST- and non-ST elevation myocardial infarction;
- Percutaneous coronary intervention (PCI) in patients suffering from refractory myocardial ischaemia;
- Antibiotic treatment for patients with endocarditis;
- Pericardiocentesis in order to relieve cardiac tamponade caused by trauma, acute pericarditis, malignancy or other cause;
- Treatment of acute arrhythmias (i.e. pacemaker, antiarrhythmic drugs, acute ablation);
- Urgent surgical intervention on complications of myocardial infarction or aortic dissection;
- Antibiotic treatment for systemic infectious diseases with heart failure as a complication.

2.6.2.2 Common Basic Measures

The patient should also be assessed according to the ABC (airway, breathing, circulation) method of resuscitation, which tends to be standard but with emphasis on particular areas:

The patient should sit upright;

- If peripheral *O2-saturation* is <90% (p_aO_2 < 60 mmHg (8.0 kPa) [5, 431, 516] (an ESC class I level C recommendation [5]). A saturation of <90% is an important sign that the patient most probably has pulmonary oedema [481]—these patients should be classified as 'wet' [158, 408, 432, 436]. Note: Oxygenation of non-hypoxic patients or even hyperoxygenation can be associated with reduced coronary blood flow, increased systemic resistance (vasoconstriction), reduced cardiac output and shows a trend to higher mortality [517, 518] and should therefore be restricted to hypoxemic patients [431].
- *Morphine sulphate*: 1–3 mg IV, may be given to very anxious and distressed patients, can be repeated several times. Class II a recommendation, Evidence level C [5].

However, some trials expressed concerns, morphine may show adverse effects [519–521].

2.6.2.3 Typical and Specific Measures

Diuretics and Ultrafiltration

Loop diuretics are first-line therapy of AHFS [5, 16, 359, 476]. They should, due to usually peripheral congestion, be given preferably intravenously (i.v.) [5, 490].

Diuretics directly reduce excess levels of extracellular fluid [157]. They indirectly exert hemodynamic effects and reduce the LVEDP by venodilation [489],

hence promote the relief of symptoms caused by congestion [145, 157]. Loop diuretics given i.v. commence their diuretic effect after approximately 30 min with the venodilating effects commencing already 15 min after administration, and both actions last up to 2 h [506]. Diuretics are indicated in basically all patients with acute left heart failure who show symptoms secondary to congestion and fluid retention/fluid overload [4, 145, 478, 480].

A class I, level B recommendation of the ACCF/AHA [7] and a class I, level C by the latest ESC recommendation from 2016 [431].

Diuretics may produce complications due to reduction of glomerular filtration rate (GFR) [522] and a further activation of the neurohumoral systems [482, 493, 523] with amplification of vasoconstriction, hence a (further) decrease in SV may apply [480]. Unfortunately, there have even been hints that higher dosages of diuretics may increase in-hospital and overall mortality [480–483]. However, by reducing intravascular volume and filling pressures, as well as peripheral and pulmonary congestion [490], diuretics may even blunt neurohormonal activation [484]. The most relevant undesired side effect that diuretics may induce in the acute setting clearly is vasoconstriction [484].

Dosage of *furosemide*: Start with 20–40 mg i.v. [145, 431, 504], 80 mg if serum creatinine >200 µmol/L [471].

Avoid higher dose boluses (>1 mg/kg) which may induce reflex vasoconstriction [484] and worsen the vascular resistance.

Dosing is still a matter of debate [524, 525]: A Cochrane analysis by Salvador [526] established clues that a continuous infusion of loop diuretics provides a larger diuresis and greater safety than intermittent bolus doses. In contrast, the DOSE-study (Diuretic Optimalization Strategies Evaluation) evaluating i.v. bolus vs. continuous infusion application of loop-diuretics, as well as high dosages (2.5 times the patient's dose prior to admission, on average 773 mg within 72 h, usually roughly 130 mg every 12 h) vs. low dosages (the same dose the patient was on prior to admission, mean 358 mg within 72 h, usually every 12 h 60 mg) found no superiority of the continuous infusion in either group, but an earlier symptom relieve in the high dose group was seen, probably at cost of a transiently worsened renal function recorded [359]. Furthermore, a number of secondary end points were in favour of a high dose application.

Progressive edema development despite sufficient increased oral or i.v. dosages of diuretics is referred to as diuretic resistance [527]. 20% to 30% of patients with severe LV dysfunction develop diuretic resistance [527]. Therapy-resistance implies a poorer prognosis [528].

To overcome, higher dosages and/or combinations of diuretics, and the avoidance of nephrotoxic agents like NSAID's are recommended [5, 7, 16]: As such, in patients resistant to diuretic therapy, higher dosages [16, 195, 359] or a combination of diuretics [529–531]) are indicated. The ACCF/AHA suggests a combination of loop-diuretic and another, preferably thiazide, a class IIa, level B evidence [7]. The ESC valuates the combination therapy as a class IIb, level C recommendation [431].

Of proved value in daily practice is a combination of *furosemide plus metolazone* [530, 532].

Torasemide (a typical loop diuretic agent [7, 533]) has shown a better functional improvement, a lower incidence of hypokalaemia and a lower mortality [533] when compared to furosemide and other loop diuretics [534]. It produces a lower transcardiac aldosterone gradient due to mineralocorticoid receptor blocking effects [535].

Continuous renal replacement therapy (precisely continuous ultrafiltration—UF) has initially been considered to start up early on in patients with acute severe heart failure, who are fluid overloaded, in order to mitigate symptoms attributed to fluid overload, or who show an inadequate response to diuretic therapy, are oligo-anuric [536–538] and/or have deteriorating renal failure as described by Mehta [482] and others [537, 539]. The Unload Trial (Ultrafiltration vs. Diuretics for Patients Hospitalised for Acute Decompensated Chronic Heart Failure) [539] was the first study showing a superiority in clinical outcomes of the ultrafiltration group compared to the diuretic agent group. Furthermore, very progressively, peripheral venous access and new, small sized ultrafiltration equipment was used. Two further small trials confirmed those results, stating that using peripheral ultrafiltration, more fluid was removed and renal function was not further compromised compared to diuretic therapy [538–540].

Applying UF, the negative effects of diuretic drugs can be avoided [472, 482]. Furthermore, it should be stressed that continuous UF exhibited, in fluid overloaded patients, if any at all, only a minimal effect on MAP [537, 539, 541].

Meanwhile, the initial encouraging aspects could not be substantiated and a recently published larger trial did not find UF to be more effective than medical therapy [542, 543]. However, creatinine elevation in itself should not be perceived as a principally worse sign and hint of unfavorable prognosis in ADHF [544], and as such, the big cardiological societies have become far more restrictive and recommend to consider UF only in case of refractory congestion due to diuretic—resistant cases [539, 542, 545] (ACCF/AHA II b, level C [7], ESC class II b, level B [431]) and in severely fluid overloaded patients to cope symptoms [539, 542, 545], rated as a class II b level B by both, the ACCF/AHA [7, 539, 545] and by the ESC [5, 431].

Vasodilators

Nitroglycerin (GTN) may be added to diuretics in all patients as long as the systolic BP > 110 mmHg [5, 7, 546], MAP >60–70 mmHg [481, 536], however may be applied as first line drug in hypertensive individuals [5]. The ESC [431] even recommends vasodilators to be considered as initial therapeutic measure in hypertensive (sBP > 140 mmHg) AHF in accordance to several study results [481, 504, 509, 547], as well a class II a, level B evidence [5, 7, 431, 481].

Namely if applied early on, the ADHERE register found a significant lower in-hospital mortality rate and a shorter length of stay in patients who received vasodilating drugs within the first 6 h after admission compared to those who received them later—indeed, most of them in addition to diuretics [195, 548].

Dosage: 20 μg/min up to 200 μg/min [4, 5, 7]. GTN-resistance can be remedied by increasing doses [549].

In case of phosphodiesterase 5-inhibitor treatment, GTN is contraindicated [550].

Note that even very low doses (<0.5 μg/kg/min) of GTN will decrease the LV wall stress (end-diastolic and end-systolic) with reductions of the aortic (central)

blood pressure (direct afterload faced by the ventricle), but without a detectable drop of systemic pressure or perfusion in the periphery (tissue perfusion)—a very welcome and desirable effect [551, 552].

Nitroglycerin, although never evaluated in prospective randomized AHF trails [318], definitely displays, compared to diuretics, a few beneficial effects which potentially should favour GTN to be used as first-line approach: Cotter found a greater effectiveness in controlling severe pulmonary oedema [481], nitrates exhibit a more balanced hemodynamic profile [157, 480] with faster reduction in wall stress and LVEDP without reducing the CO [553], very low dosages diminish ventricular load without the risk of systemic blood pressure drop [551, 552], and there are no significant side effects (predominantly only headache) to be expected [504]. However, unfortunately the beneficial properties GTN shows do not translate into a clinical benefit which has lowered its usage and rating [316, 433, 481, 504, 506–508].

Cause of concern is especially that vasodilators may induce *hypotension* [84, 504] which is associated with several adverse effects, most important myocardial ischemia [68, 554]. However, a reduction in afterload will, as a rule, lead to an increase in flow (SV/CO), preventing the development of hypotension, thus the MAP will be maintained or may increase but at least should not fall [555–557]. In daily clinical practice, when the peripheral resistance (afterload) is lowered by administration of vasodilating agents, the LV wall stress (end-diastolic and end-systolic) will be reduced [500, 501]. Simultaneously the SV will increase due to the reduction in afterload [407, 439] with an increase in forward flow [496, 497, 556]. Furthermore, particularly in severe dilated heart failure, the reduction in LV outflow resistance and filling pressures leads to a concomitant substantial decrease in mitral regurgitation potentially increasing in SV/CO [131, 493, 496, 497, 502].

However, if, with this approach, the blood pressure cannot be maintained and there is no increase in SV/CO, one of the following circumstances should be considered and treated:

- Severe mitral regurgitation [15, 499, 502, 558];
- Inappropriate filling volume (LVEDV) [131, 399, 502];
- Disrupted ventriculo-arterial coupling [559] (see Chap. 1, paragraph 9);
- Relatively low intravascular volume (relative hypovolaemia) [560]—seldom.

Nevertheless, if vasodilators are applied, there is some justified risk for blood pressure drops which may have serious adverse effects: Several recently published large studies [30, 35, 49] have all found that a sBP < 120 mmHg is a strong indicator of poor (short term) outcome. Hypotension impairs autoregulation [505, 561–563] and, if persistent, will aggravate any myocardial perfusion deficit [554] and will play a part in a vicious cycle leading to a more and more severe ischaemic myocardium [68], worsening the situation. Therefore caution is recommended in initiating vasodilator therapy or drugs with vasodilative effects (i.e. Dobutamine, Levosimendan) if sBP < 120 mmHg.

As such, although somewhat arbitrary, most authors recommend not to use vasodilators if sBP is below (100-) 110 mmHg [5, 21, 433, 546, 564]. Just to reiterate, the ECS sets sBP lower than 90 mmHg as the limit [431] which is really surprising and not consistent with the literature results, e.g. in the French survey, a sBP of ≥120 mmHg showed a better (short-term—long-term has not

been studied) outcome [49], the OPTIMISE—study revealed a significant higher mortality if the sBP was below 120 mmHg [69].

Nitroprusside is a potent venous and arterial vasodilator [565] and is extremely effective in reducing the afterload as well as reducing the pre-load, and thus lowering end-systolic and end-diastolic wall stress [497]. It decreases the neurohumoral activation markedly [566]. In patients where the systolic BP exceeds 120 mmHg, and particularly in hypertensive crises underlying pulmonary edema, the use of nitroprusside should be seriously considered [137], as some authors recommend [4, 565]. A further important indication is severe mitral regurgitation [498, 499].

Dosage 0.3 µg/kg/min to 5.0 µg/kg/min. [5, 7, 431] (Class II b recommendation, evidence level B [5, 431]).

Nitroprusside has substantial dose dependent arterial dilating effects which, in the case of fixed arterial narrowing, may cause a significant reduction in blood flow distal to the stenotic area, a so-called 'steal-phenomenon' [565]. Hence, it may cause a regional decrease in coronary flow [533, 567] in patients with CAD. In acute myocardial infarction, nitroprusside should not be used because ischaemia may be worsened, inducing or exacerbating left sided heart failure [568].

A novel approach in the treatment of acute left heart failure is *nesiritide*. It is chemically identical to human BNP, acting via cGMP to produce a balanced (arteriovenous) vasodilatation, precipitating a pre- and afterload/wall stress (end-diastolic and end-systolic) reduction [569, 570]. There is an increase in SV/CO without direct inotropic effect [571, 572], enhanced sodium excretion and suppression of the renin-angiotensin-aldosterone axis as well as of the sympathetic nervous system [4, 193, 504, 549, 571]. A beneficial effect on renal function [573] and an enhanced diuresis has been demonstrated [504, 571].

Dosage: Initial 2 µg/kg bolus, followed by 0.01 µg/kg/min infusion [504, 574].

Nesiritide is thought to be safe; its use does not require ICU admission or invasive monitoring and it is associated with a low incidence of tachycardia and arrhythmias [571, 575, 576].

The initial studies using nesiritide as a first line drug in acute heart failure treatment have been very encouraging [193, 472, 504, 577] and, in Japan, it is the preferred drug in acute heart failure therapy [218]. Compared to the classical inotropic drugs, particularly to dobutamine, nesiritide shows fewer arrhythmias and a better outcome [472, 575–577].

In comparison to nitroglycerin the hemodynamic improvements (reduction of LVEDP and thus pulmonary hypertension) [504, 549] of nesiritide are even more intensive and the relief of the patients' dyspnoea is more rapid [193, 504]. There are even fewer side effects, although this did not translate into better mortality outcomes [472, 504]. Unfortunately moreover, a recently published meta-analysis by Sackner-Bernstein described a trend to a higher mortality in the group treated with nesiritide compared to standard therapy (GTN and diuretics) [578]. Not at least, in the large, over 7000 patients encompassing ASCEND-HF-study, nesiritide, compared to placebo, could not give evidence for reduced mortality, symptom improvement or diminished re-hospitalizations within the first 30 days [84].

Accordingly, nesiritide may be recommended as therapy in cases complicated by renal failure and for patients with signs of congestion but with adequate perfusion [573]. Thus, in 'warm' patients without shock, nesiritide may be used, and was formerly rated as a class II b, level B recommendation (by both, the ESC and the ACCF/AHA) [5, 84, 193]. However, there is no re-appraisal and rating provided in most recent, up-dated guidelines [7, 431].

Inotropic Drugs

Inotropic drugs are traditionally used to increase CO (SV) and improve peripheral and organ perfusion [145, 573] in cases of low output, hypoperfusion and in life threatening situations [13, 498].

In recent years the use of inotropic drugs has been overshadowed by growing, clear evidence of adverse clinical outcome and increased mortality [469, 472, 577, 579, 580], particularly in patients with reasonably [4] preserved left ventricular function (LV-EF > 40%) [472, 478, 579, 581, 582]. Conners [583] and Sandham [584] found a significantly increased mortality when clinically stable patients were treated with conventional inotropic agents due to numerically low cardiac output. The ADHERE register [472] revealed that the use of dobutamine or milrinone compared to GTN led to a significantly higher mortality in the treatment of AHFS.

[472, 585].

Inotropes definitely do not improve outcome [472, 579, 586–588]. The potential danger of catecholamines is due to their effect of increasing the myocardial oxygen requirement and overloading the myocytes with calcium [589].

Accordingly, **only** patients who absolutely require inotropic support due to hypoperfusion secondary to low output as the result of a severely reduced contractility, and who are resistant to other treatment attempts, should be treated by such agents [35, 300, 478].

Therefore, the ESC notes and emphasizes, "inotropic agents may be considered in patients with hypotension (sBP <90 mmHg), and/or signs and/or symptoms of hypoperfusion despite adequate filling status, to increase cardiac output and blood pressure, to improve peripheral perfusion and to maintain end-organ function" [431]—a class II b, level C recommendation. The ACCF/AHA states, a short-term application of inotropes may be reasonable in AHF patients with documented severely impaired systolic function "who present with low blood pressure and significantly depressed cardiac output to maintain systemic perfusion and preserve end-organ performance"—class II b, level B evidence [7].

Thus, *dobutamine* can be considered in case of hypoperfusion and/or hypotension due to a markedly reduced contractility. These circumstances should be present despite optimized pre-and afterload. As dobutamine displays peripheral vasodilatory effects, most authors request a blood pressure limit of not less than 80 mmHg (sBP) as a prerequisite to commencing dobutamine, otherwise the blood pressure may (further) drop and hypoperfusion may deteriorate [4, 66, 590, 591]. However as long as the patient is euvolaemic, a blood pressure drop due to the peripheral vasodilatory effects of dobutamine is reported to be rare because the peripheral vasodilation will generally be compensated for by the increase in CI/SV (forward flow) [496, 497, 592, 593].

Dobutamine has positive inotropic and chronotropic effects [594, 595]. It decreases the sympathetic tone producing reduced peripheral resistance [596] (↓ wall stress, i.e. ↓ afterload) without a significant drop in MAP due to compensatory increase in SV/CI [4]. Dobutamine is associated with an increased risk of arrhythmia [574] and it may worsen the splanchnic tissue perfusion [597].

At low dosages up to 5 µg/kg/min, dobutamine is reported to lower pulmonary vascular resistance and PAP, may slightly diminish MAP while there is a slight increase in CO [598]. With higher dosing (reported are dosages up to 20 µg/kg/min), BP may increase (due to vasoconstrictive effects [206]), but also heart rate and the risk for arrhythmias [599]. Furthermore, although it usually decreases pulmonary wedge pressure (PCWP) there are patients in whom PCWP remains unchanged or even increases [470], as higher dosages of dobutamine will cause vasoconstriction [567].

Dosage: 2–20 µg/kg/min, usually initiated at 2–3 µg/kg/min [4].

After 24–48 h of use patients develop tolerance with partial loss of haemodynamic effects [470].

Phosphodiesterase inhibitors are indicated in cases of peripheral hypoperfusion with or without congestion, refractory to diuretics or fluids and vasodilators at optimal dose (choice the appropriate measure), if the systolic blood pressure is >80–85 mmHg) [4, 66, 590, 591]. They show positive inotropic, lusiotropic as well as vasodilatory effects with improvement of SV/CO and reduction of the systemic (afterload) and pulmonary resistance [600]. Due to their site of action (via intra-cellular inhibition of type III phosphodiesterase, thus increasing cardiac cAMP concentration, the second messenger used for intracellular signal transduction [601]) they may be administered even if the patient is on β-blockers [602, 603]. Unfortunately, there is growing evidence that phosphodiesterase-inhibitors increase mortality and complications when compared with other treatment regimen (vasodilators, diuretics, levosimendan) [472, 579, 588, 604, 605].

Dosage of milrinone: 25 µg/kg bolus over 10–20 min, followed by an infusion of 0.375–0.75 µg/kg/min [4].

Levosimendan is a relatively recently developed agent acting as a calcium-sensitiser which may be an alternative in the treatment of hypoperfusion due to ‘symptomatic low cardiac output and left heart failure secondary to severe systolic dysfunction’ [4].

Myocardial contractility is ultimately determined by the effects of calcium on the actin-myosin complex. Calcium-sensitisers, ‘sensitise’ the actin-myosin complex to the effect of calcium [606].

Levosimendan will increase the contractility of the heart by increasing the stability of the calcium-troponin-complex in the cardiac myocyte, without increasing the intracellular ionized calcium concentration (as catecholamines and phosphodiesterase inhibitors do) [607, 608]. Levosimendan has vasodilatory effects with peripheral vasodilation, producing a reduction in afterload and of end-systolic all stress, which is beneficial in terms of the underlying patho-physiology [609]. Levosimendan also exerts positive effects on the diastolic properties [610, 611]. Therefore, in comparison to catecholamines and phosphodiesterase-inhibitors, levosimendan does not impair diastolic relaxation, thus avoiding an increase in myocardial stiffness with consecutively impaired LV compliance, lowering the filling pressure, LVEDP, rather than enhancing it [612–614].

Several studies [605, 615–618] underline the favourable effects of levosimendan in the treatment of acute left heart failure syndromes, particularly in patients with post-myocardial infarction left heart failure and acute decompensated chronic heart failure: The 'CASINO'-study showed that patients who were treated by levosimendan experienced a significantly lower mortality rate compared to those treated with dobutamine, milrinone or to the placebo-group [619].

Results and the reevaluations from the REVIVE I &II [620] and SURVIVE [621] studies—although not as convincing as expected—are not contradictory insofar as the mortality rates in the levosimendan groups are significantly lower compared with dobutamine or phosphodiesterase-inhibitors, if the "correct" patient and indication is taken into consideration: The most recent ESC guideline recommends to prefer levosimendan in case hypoperfusion is associated with and/or contributed by β-blocker therapy. [622]. However, we think levosimendan may also be considered in case acute heart failure is complicating AMI [535, 617, 621]. Furthermore, levosimendan is shown to be applicable in combination with noradrenaline in case of cardiogenic shock [623–626] or on top of a combination of NA and DOB not effective enough [627, 628]. Current evidence validates levosimendan as a level C, class IIb recommendation if given in case of cardiogenic shock, if patients are on β-blockers, or on top of the combination NA plus DOB [5, 431].

Most authors recommend an sBP of at least 85 mmHg in otherwise stable patients (in particular if the peripheral vascular resistance is normal or low) as a necessary prerequisite to commencing levosimendan in order to avoid a BP drop due to its vasodilative abilities [4, 629, 630]. The potential for a blood pressure drop can be diminished by avoiding hypovolaemia prior to starting the infusion of levosimendan [625].

Dosage [629]: Loading dose 12 µg/kg–24 µg/kg administered over 10 min followed by a continuous infusion of 0.05–0.1 µg/kg/min, up titrated to max. 0.2 µg/kg/min for 6–24 h. If there are concerns of inducing a blood pressure drop, levosimendan may be initiated without a loading dose.

Levosimendan LEVO 0.1 µg/kg/min (0.05–0.2 µg/kg/min), bolus (optional) of 12 µg/kg over 10 min, if appropriate initial BP, iv.

2.6.2.4 Essential, Permanent Medication in the Acute Phase

ACE-inhibitors should not be initiated in the early phase (first 24 h) [433], but as soon as possible and may be continued (preferably at a lower dosage in case of hypotension) if administered prior to acute decompensation [586]. Of course, they are indicated in case of hypertension [433].

The same approach is principally suggested for *β-blockers* [631, 632], but should be initiated as soon as possible *after stabilization* [5].

There is no place to initiate *calciumantagonists* (dihydropyridine) therapy early on [586].

2.6.2.5 Arrhythmias and Heart Failure

There is an increased incidence of ventricular [633] and supraventricular arrhythmias, particularly atrial fibrillation and flutter [634] in chronic congestive heart failure. Ventricular arrhythmias are associated with an elevated risk of sudden death and non-arrhythmic death [635, 636].

The new onset of an arrhythmia during the exacerbation of chronic heart failure characterizes a high-risk patient group with increased morbidity and mortality in the short and long-term [537]. While the severity of heart failure does not predict the likelihood of the development of new arrhythmias, there is a strong relation between the use of inotropic drugs and the onset of new arrhythmias [637].

Roughly 40% of all new arrhythmias are atrial fibrillation (AF) [637]. New onset of AF is associated with a significant clinical and hemodynamic deterioration [638], increased risk of death [639, 640] and conversion to sinus rhythm lowers the mortality rate [640]. *Amiodarone* is shown to be beneficial because of its effectiveness and only mild negative inotropic side effects in heart failure patients with arrhythmias [641–643]. Amiodarone application is rated as a class IIb, level B evidence by the ESC [431].

Interestingly, the most recent guideline of the European Society of Cardiology recommends alternatively digoxin to be applied i.v. (0.25–0.5 mg, 0.0625–0.125 mg if used by the patient already daily) in case of AF—a class IIa, level C recommendation [431].

2.6.2.6 Continuous Positive Airway Pressure (CPAP) and Non-invasive (positive pressure) Ventilatory Support (NIPPV)

CPAP may be indicated in acute heart failure patients who, despite oxygen delivered via face mask and drug therapy, are still de-saturated ($SaO_2 < 90\%$) [4] and where the patient is exhausted from the high respiratory workload required due to pulmonary congestion/edema [547, 644, 645]. By decreasing the left-ventricular afterload and the respiratory work, CPAP improves oxygenation, decreases symptoms and significantly reduces the need for endotracheal intubation and mechanical ventilation [646–650]. A statistically significant reduction of mortality has not been shown as of yet, probably due to the small populations studied. However, a systematic review has found a trend towards decreased in-hospital mortality [645, 651].

NIPPV is more helpful in hypercapnic pulmonary oedema, where there is failure of respiratory musculature as well. A recent study found that NIPPV was at least as effective as CPAP, but the effect of unloading the respiratory muscles led neither to a lower rate of endotracheal intubation nor to a shortened recovery time [652].

CPAP/NIPPV are, based on study results by Gray [653], recommended by the ESC "to be considered in a dyspnoic patient with pulmonary edema and a respiratory rate above 20/min in order to improve breathlessness and reduce hypercapnia and acidosis" a class II a, level B evidence [5]. ACCF/AHA do not include any discussion about non-invasive ventilator support in their most recent guidelines [7].

2.6.2.7 Anticoagulation

Prophylactic anticoagulation with low molecular weight heparin (LMWH) or unfractionated heparin is strongly recommended in order to prevent thromboembolic complications, and is, based on study results by Guyatt [654], Alikhan [655], Tebbe [656], and Dentali [657, 658] as a class I, level B recommendation by both ACCF/AHA [7, 448].

Dosage: 40 mg enoxaparin (or equivalent) s. c. [658] or 5000 Units unfractionated Heparin s. c. × 3 daily [659, 660].

Table 2.4 summarizes the initial medical approach in AHFS (see Table 2.4).

Table 2.4 *Modified from McMurray [5] and Braunwald [91, p 494], further supported by [7, 157, 319, 431, 435, 478, 481]; ¤Metra et al. [321, 564]

<table>
<tr><th colspan="2">Warm and dry</th><th colspan="2">Warm and wet</th></tr>
<tr><td colspan="2">Treat underlying disease, e.g. septic shock</td><td>sBP ≥ 85–110 mmHg*
I. diuretics i.v.
IIa. if sBP drops to <85 mmHg, consider inotropic agents or even NA stop β-blockers, intensify diagnostic measures
IIb. consider to add vasodilators, if sBP increase to >110 mmHg</td><td>sBP ≥ 110 mmHg*
Ia. diuretics i.v
Ib. in case of sBP ≥ 140 mmHg vasodilators (GTN or nitroprusside i.v.) may be first choice
IIa. consider to add vasodilators (GTN i.v.) early on
IIb. Intensify antihypertensive medication if BP remains high, e.g. ACE-inhibitors</td></tr>
<tr><td colspan="2"></td><td colspan="2">– If no response to diuretics increase dosage
– If BP drops considerable think about HFpEF, to perform an echocardiogram, possibly apply carefully fluids, consider to stop β-blockers
– Consider NIV if O_2-saturation < 90%
– Avoid hypotension and/or coronary hypoperfusion at all (cave: vasodilator therapy)</td></tr>
<tr><th colspan="2">Cold and dry</th><th colspan="2">Cold and wet</th></tr>
<tr><td>sBP ≤ (85) 90 mmHg</td><td>sBP ≥ (85) 90 mmHg</td><td>sBP ≤ (85) 90 mmHg</td><td>sBP ≥ (85) 90 mmHg</td></tr>
<tr><td>A differentiated, individual approach is mandatory as the patient may ether require fluids, inotropic support or even NA, or indeed diuretics</td><td>A differentiated, individual approach is mandatory as the patient may ether require fluids, inotropic support or even NA, or indeed diuretics</td><td>NA ≥ 0.02–1.0 µg/kg/min or higher if appropriate</td><td>Inotropic support (DOB or LEVO—DOB: 2–20 µg/kg/min, LEVO: 0.1 (0.05–0.2 µg/kg/min), but may consider combination with NA</td></tr>
<tr><td>For more details, see Chap. 3</td><td>For more details, see Chap. 3</td><td>For more details, see Chap. 3</td><td>For more details, see Chap. 3</td></tr>
<tr><td colspan="2">Avoidance of hypotension and particularly coronary hypoperfusion is paramount as (aggravated) myocardial ischemia is potentially deleterious¤, hence a sufficient perfusion pressure (MAP ≥ 70–80 mmHg) is paramount</td><td colspan="2">Avoidance of hypotension and particularly coronary hypoperfusion is paramount as (aggravated) myocardial ischemia is potentially deleterious hence a sufficient perfusion pressure (MAP ≥ 70–80 mmHg) is paramount</td></tr>
</table>

2.7 Valvular Heart Diseases Presenting as Heart Failure Overview [661, 662]

Acute heart failure due to valvular disease is found in 4% [663] to 24% [30] of all patients admitted with the clinical picture of an AHFS.

2.7.1 Mitral Regurgitation

Acute MR is a serious emergency situation, as flash pulmonary oedema may occur [662]. The main causes of acute MR are rupture or insufficiency of a papillary muscle (mostly posterior) due to acute myocardial infarction (AMI) or rupture of the chordae tendinae as a complication of AMI, endocarditis, chest trauma and myxomatous degeneration of the valve [664].

Main pathophysiology:

Acute pressure increase in the non-adapted LA due to regurgitation leads to an increased pressure in the pulmonary circulation and thus pulmonary congestion/oedema [67, 665].

The left ventricular ejection is bidirectional [666, 667], the regurgitation area is often dynamic and depends on the dimension of the LV [666]. The increased diastolic volume induces, via the Frank-Starling mechanism, an increase in SV, but due to the bidirectional ejection the effective SV (forward output) will be reduced [662].

In case of chronic MR, where the heart and in particular the LA are adapted, the acute decompensation is most often due to muscle failure, triggered by acute arterial hypertension, acute myocardial ischaemia and arrhythmias such as the new onset of uncontrolled AF [662].

Special therapeutic aspects:

- In acute MR, nitroprusside is the most effective drug and may reduce MR by up to 50% [498]. GTN is also strongly recommended [662, 668];
- Control of fast AF/cardioversion in case of new onset AF [662];
- Chronic MR: Diuretics and ACE-inhibitors [661]. Quinapril improves the clinical situation and reduces the volume of regurgitation [669]. It has not been clarified whether this is a class effect (all available ACE-inhibitors) or not.

2.7.2 Mitral Stenosis

MS does not develop acutely [662]. The main cause is rheumatic endocarditis. Vegetations are rare in cases of acute endocarditis. Myxoma of the atrium involving the valve (prolapsing into the valve area) or severe calcification of the annulus and the leaflets may provoke MS [662].

Main pathophysiology:

The pressure in the LA increases substantially [662]. There is left atrial hypertrophy and dilatation [661]. The filling of the LV depends increasingly on the active

atrial contraction (active filling component of the LA). Each increase in heart rate with shortening of the diastole will lead to a further rise in left atrial pressure [661] and accompanying risk of pulmonary congestion or oedema [67, 662]. In the vast majority of cases a marked increase in heart rate (physical stress) and, in particular, new onset of AF will cause an acute decompensation [662].

Special therapeutic aspects:

- Primary therapeutic aim is a reduction of the heart rate:
  Lengthening of diastole leads to:
  - Increase in LA filling volume with consecutive increase in LV-filling and thus SV,
  - A substantial decrease in pulmonary pressure [662].
    Administer β-blockers or a Calcium-channel blocker such as Verapamil in order to slow down the heart rate, aim for a heart rate of 60–70 bpm [661, 662]. In certain conditions (duration of AF, size of LA, etc) cardioversion should be considered.
- Diuretics and/or nitrates will reduce left atrial pressure and will therefore relieve the symptoms of pulmonary congestion. However, caution should be used and low doses are preferred as diuretics or nitrates may reduce LV filling causing the CO/SV to drop [661].

2.7.3 Aortic Regurgitation

The main causes of acute AR are acute bacterial endocarditis, chest trauma and aortic dissection.

[670, 671].

Main pathophysiology [662]:

In acute AR the LV is confronted by a rapid and substantial increase in filling volume causing a rapid rise in diastolic ventricular pressure. This pressure rise leads to an abnormally fast equalisation of the LV- and LA-pressure and premature closure of the mitral valve. Both effects may result in the development of pulmonary congestion/oedema [662] and the effective SV is reduced [662].

The determinants of the regurgitation volume are the opening area (mostly fixed aortic valve), the duration of diastole (the longer the higher the regurgitation volume) and the diastolic transvalvular gradient [666]. Additionally, due to compensatory mechanisms the peripheral vascular resistance will increase (afterload ↑), causing the regurgitant volume to increase further (ejection into the lower pressure compartment) [662]. Therefore, aim to avoid bradycardia and arterial hypertension [661, 662].

Special therapeutic aspects:

Vasodilators of the arterial vessels will reduce AR and enhance forward flow with redistribution of SV.

Nitroprusside is the drug of choice in acute decompensated states [672, 673].

Good results can be achieved if using nifedipine [674] or ACE-inhibitors [675] in clinically stable situations. Vasodilators which affect mainly the venous system as well as diuretics will reduce preload, left-ventricular end-diastolic pressure, and end-diastolic volume [672, 676]. Their effect is of symptom relief until valve replacement, which is needed in most cases, can be performed.

2.7.4 Aortic Stenosis

Currently the main cause of AS is gradual valve calcification and degeneration, whereas previously a rheumatic background was common [677].

Main pathophysiology:

The fixed obstruction of the LVOT (due to AS) limits the output. The pressure burden leads to LV hypertrophy and consecutively to an elevation of the LVEDP. Over time the contractility will be affected and LV dilatation will occur [662]. Psychological and physical stress may precipitate hypotension and syncope [661].

Khot [678] recently suggested that, aside from the fixed valvular obstruction, the effective afterload affecting the LV exerts a systemic component as well: "Since the resistances in series are additive, the total resistance seen by the left ventricle is the sum of the resistance across the aortic valve plus the systemic vascular resistance. Therefore, increasing or decreasing systemic vascular resistance directly leads to proportional changes in the effective afterload of the left ventricle, even when there is severe aortic stenosis [679, 680]"—just as it is in conventional heart failure.

Special therapeutic aspects:

The conservative treatment options are very limited and all therapeutic measures run the risk of inducing haemodynamic deterioration [662]. Each therapeutic intervention should be initiated with caution.

- In case of acute decompensation and evidence of LV-dysfunction (as a component of ↑ ↑ ↑ afterload) vasodilators are indicated: Nitroprusside can be considered but GTN is probably referable as it reduces afterload and blood pressure less aggressively than nitroprusside [678].
  Classically GTN and other vasodilators have been avoided in the treatment of acute heart failure due to decompensated severe aortic stenosis, but, as mentioned above, Khot [678] showed improved outcomes of the GTN group (reduces the increased filling pressures and so will relieve dyspnoea in cases of pulmonary congestion or oedema [661, 662]). Diuretics (in low dosage) improve the symptoms of pulmonary congestion, but can induce hypovolaemia with a further drop in CO [681].
- Of special importance is the maintenance of sinus rhythm in order to retain the atrial component of LV filling, which now plays an important role in haemodynamic stability [663, 682]. Cardioversion should be considered in cases of new onset AF [662]. β-blockers or calcium-channel blockers should be titrated cautiously, aiming to lower the heart rate to at least 110 bpm or less [661, 662].

2.8 Summary

AHF is acknowledged as a systemic disease [412–414] of complex and multi-facet pathogenesis [17, 53, 54]. The most common underlying disorder is CAD, followed in Europe by hypertension and valvular heart disease [28–30, 49]. The clinical picture is coined by signs and symptoms related to elevated ventricular filling pressures [17, 50, 54, 106], a universal finding in heart failure [8–10], causing central and normally peripheral congestion [14, 15, 122, 123, 153]. The pathophysiology is basically characterized by an imbalance between altered (impaired) cardiac capabilities and actual loading conditions, namely afterload and consequently vascular properties [325, 683–685], referred to as afterload mismatch [54, 160, 299, 300, 303, 304, 308, 683]. In fact, the circulatory conditions are considerably determined by the cross-talk between cardiac and vascular features [53, 54, 410, 411]. These findings are consistent with the complex and multi-facet pathobiology of AHFS, however are largely related to the effects precipitated by the mechanical-hemodynamic disorder, the primarily adaptive and compensatory efforts of the neurohormonal systems, and of the endothelial-inflammatory reaction caused by the circulatory malfunction, and the intricate interrelation between these [54, 162–164, 227, 228, 288, 409]. Cotter translated these insights into a new concept describing two principal pathways, a vascular and cardiac one, of which one of them will be the predominant, leading to acute heart failure [308]. He thereby stressed that fluid redistribution rather than fluid accumulation may be the final precipitant. Meanwhile, this new paradigm could be broadened, substantiating Cotter's concept, as results by Fallick describe that even physiological trigger may induce sympathetically–mediated fluid redistributions from the venous reservoir (namely splanchnic veins) into the effective circulation and thus provoke acute decompensations in patients with otherwise missing flash points [60]. Furthermore, Colombo could establish that the vascular and cardiac pathways are closely linked, as vasoconstriction and fluid redistribution may foster fluid accumulation and vice versa [297].

The diagnosis of AHFS is based on the patient's history and clinical examination [14, 417–419]. However, to diagnose acute heart failure may be difficult as the symptoms and physical findings are non-specific and insensitive [432, 686, 687]. Echocardiography is, for sure, the most valuable tool to underline the diagnosis, if uncertain, and may furthermore identify underlying valvular and other, especially mechanical reasons [156, 431, 446, 449].

All patient admitted with AHF should undergo a 2-min bedside assessment, clinically–hemodynamically classifying the patients, providing prognostic hints and seminal for the general therapeutic approach [426, 427, 431]. BP on admission is as well an easy to assess but quite robust and well-evidenced feature in prognostic and therapeutic perspective: sBP < 120 mmHg should give raise of concern [14, 35] and the application of vasodilators, mainly GTN, should be considered, if at all, thoroughly if sBP < 110 mmHg [5, 92, 564].

Diuretics stay a cornerstone and first line medication in treatment of AHFS [5, 7, 359, 476], vasodilators may be added in case the blood pressure is above 110 mmHg [5, 92, 433, 564], but can even be applied as first line drug in hypertensive AHF.

Inotropic support should be avoided whenever possible due to potentially harmful effects and a confirmed negative impact on the patient's outcome. This is particularly true in case where the systolic function is reasonably preserved (EF > 40%) and in clinically stable conditions [469, 472, 478, 577, 579–582, 584]. Inotropic agents are only indicated in patients with significantly impaired systolic function, impending cardiogenic shock refractory to other measures, and in life threatening situations with tissue and organ hypoperfusion [13, 35, 300, 472, 478, 482, 498]. In such circumstances, usually a combination with vasopressor substances is necessary and advisable, in order to ensure sufficient myocardial perfusion pressure with maintained or re-established autoregulation, avoiding incipient ischemia [68, 554, 688, 689].

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Cardiogenic Shock

3

3.1 Definition

Shock is defined as the maximal variant of dysregulation of the sophisticated regulatory systems of the organism due to a harmful event [1]. Central to this description we find a systemic derangement in perfusion (hypoperfusion), secondary to the critical decrease in cardiac output (CO): There is an inadequate CO in respect to the patient's requirements, with disturbed microcirculation and insufficient supply to the tissues and organ systems causing widespread cellular hypoxia and vital organ dysfunction [1].

Cardiogenic shock (CS) [2] describes a severe primarily myocardial dysfunction with systemic hypocirculation and inadequate tissue perfusion (global tissue hypoxia) in the setting of adequate vascular volume [3]—and cellular, as well as multi-organ dysfunction or failure [2, 4].

The US shock trial defines cardiogenic shock as [5]:

Hypotension with a systolic blood pressure < 90 mmHg lasting ≥ 30 min

or

the necessity for catecholamines and/or rather IABP in order to maintain sufficient circulation with a sBP ≥ 90 mmHg

and

hypoperfusion of the end organs due to the severely impaired cardiac performance, clinically characterised by cold peripheries (forearms and/or lower legs [6, 7]), disturbance of consciousness (altered mental status [8]) and oliguria (<30 mLs/h),

hemodynamically

described by CI ≤ 2.2 L/min/m^2 as well as PCWP ≥ 15 mmHg (or pulmonary congestion on chest X-ray).

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Menon [3] strongly recommends diagnosing CS in all patients exhibiting signs of inadequate tissue perfusion in the setting of severe cardiac dysfunction, irrespective of the BP, non-hypotensive [9] or pre-shock [3, 10].

3.2 Epidemiology

Studies from unselected populations report an overall incidence of CS of 7.1% [11].

In the vast majority of cases, CS develops secondary to myocardial ischaemia (and its complications such as mitral regurgitation) [11–14] either due to chronic [1, 15, 16] or acute [17–21] coronary artery disease. In 70–80% of cases the patients suffer from an acute coronary syndrome [5, 14, 22, 23], most of them with ST-elevation, acute myocardial infarction and multivessel (stenosis/occlusion in more than 1 vessel) disease [5, 14, 23].

The incidence of CS complicating acute myocardial infarction (AMI) is reported as between 5% and 10% [11, 17–21, 24]. LV-dysfunction is the main reason for the development of cardiogenic shock also in patients not suffering from CAD and thus not a result of ischaemia [25, 26].

The shock register and trial [27, 28] revealed that (in any aetiology)

74.5%	CS was due to predominant LV-heart failure,
8.3%	due to acute MR,
4.6%	due to ventricular septal rupture,
3.4%	were isolated right heart shock situations,
1.7%	were induced by tamponade or cardiac rupture,
3.0%	due to other reasons.

The overall in-hospital mortality of patients with CS attributed to AMI is still high: between 40 and 50% as recent studies verified [14, 22, 29].

CS is more likely to develop in the elderly [21, 30–32], diabetic [21, 30–32] patients suffering from acute anterior myocardial infarction [21, 27, 28, 31, 32], patients with a history of previous infarction(s) [21, 32], patients with peripheral vascular disease [21, 32] and patients with cerebrovascular disease [21, 32].

CS often develops over hours, the shock trial [27], as well as other publications [20, 33, 34] found that 75% of all shock states developed within 24 h of presentation, and in the GUSTO-study [17, 35] it was even higher at 89%.

3.3 Aetiology

The most common causes of cardiogenic shock are [12, 36–38]:

- acute impairment of myocardial pump function from:
  - acute myocardial infarction and associated complications, including rupture of a papillary muscle or septum, severe MR and pericardial tamponade,
  - acute myocarditis,
  - intoxication with negatively inotropic drugs,

  - myocardial contusion,
  - sepsis and septic shock.
- acute valvular disease (AR or MR due to endocarditis, aortic dissection or chordae rupture)/acute exacerbation of a chronic valvular disease,
- acute decompensated chronic heart failure, particularly end-stage cardiomyopathy,
- acute right heart failure (right ventricular myocardial infarction; acute, severe broncho-pulmonary diseases),
- persistent severe rhythm disturbances (e.g. tachycardiomyopathy),
- acute decompensation of hypertrophic cardiomyopathy (i.e. due to acute atrial fibrillation),
- left atrial myxoma

3.4 Pathophysiological Aspects and Special Features

3.4.1 Classical Pathophysiology and New CS Paradigm

In cardiogenic shock, the overwhelming majority of cases are caused by an abrupt depression and/or loss of contractility (intrinsic performance) of the heart irrespective of loading conditions with a subsequent significant fall in SV/CO [1, 2, 5, 37].

This occurs most often due to a critical loss of contractile tissue/mass [37] secondary to acute myocardial infarction [17–19, 24], resulting in acute loss of total pump force [39] and altered diastolic properties (diminished relaxation and compliance) [5, 37, 39]. Hence, in CS both systolic and diastolic function are considerably failing [40, 41]. Traditionally, CS is seen as a mechanical problem [37] with corresponding neurohormonal (namely enhanced sympathetic discharge and activation of the renin-angiotensin-aldosterone-system, RAAS) activation and response [40, 42]; this paradigm is summarized in the diagram (see Fig. 3.1).

Severe myocardial dysfunction, as in the case of CS, leads directly to both decreased SV and an increase in LVEDP [37, 40, 41]. Subsequently, the marked reduction in SV causes hypotension [37] and systemic hypoperfusion [37], compromising the coronary perfusion, causing myocardial ischaemia or aggravating existing myocardial ischaemia [5, 40, 42, 43] leading to progressive impairment of myocardial function [5, 40, 42, 43]. Furthermore, as depicted by the diagram by Antman [42] (see Fig. 3.1), in response to the considerable impairment of the cardiac contractility [16, 37, 43, 44], a compensatory systemic vasoconstriction [37, 40, 42–44] secondary to neuroendocrine [37, 43–45], in particular sympathetic activation [37, 40, 42–44], occurs. The neurohormonal—mediated systemic vasoconstriction exerts additional substantially adverse loading conditions (enhanced pre- and afterload) [42–44, 46] onto the already compromised myocardial function. Vasoconstriction, of course, includes the venous system and it is particularly the splanchnic venous constriction which directly provokes, due to considerable fluid redistribution, acute cardiac volume loading [47–49]. However, it is namely the increase in afterload due to arterial vasoconstriction which has substantial detrimental effects as the left ventricle is highly afterload-sensitive [43, 44, 46, 50]. Renal sodium and water retention (attributed to non-osmotic arginine vasopressin effects and to the actions of the

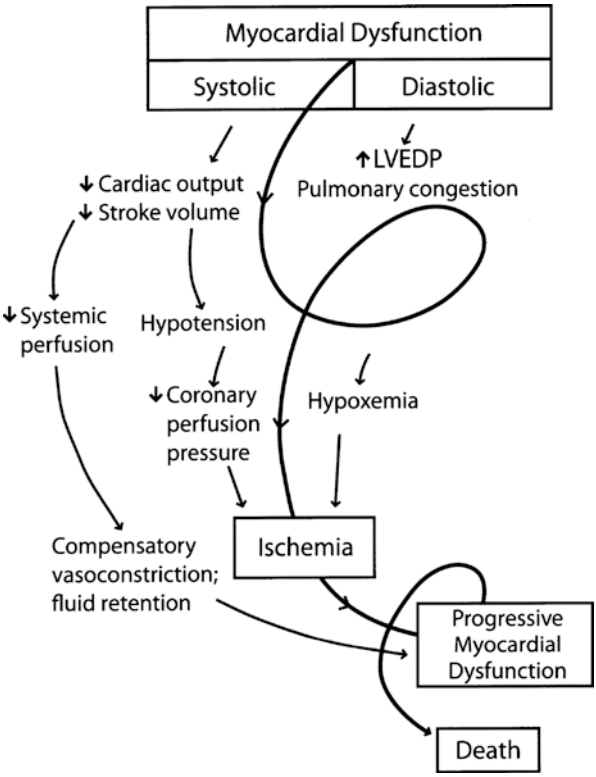

Fig. 3.1 Classic shock paradigm, mechanical and neurohumoral aspects (modified by Antman [42], who confirmed work by Califf [40] with permission)

activated RAAS) aggravates the overfilling by fluid accumulation [45, 51] and thus contributes, in the presence of already elevated filling pressures, to the precipitation of pulmonary congestion or even pulmonary edema [52].

However, obviously a severely diminished contractility alone does not precipitate CS [53–55]:

LV-EF is found to be on average 30% in patients with CS and thus lies absolutely within the range many stable post-AMI patients display [5, 56, 57]. Furthermore, LV-EF stays the same 2–3 weeks after CS when functional circulatory conditions are markedly, if not completely, different [58]. Even patients with low normal EF and without severe mitral regurgitation may present or develop CS in the acute setting [59]. Furthermore, several studies on cardiogenic shock [5, 54, 60–63] have revealed a fundamentally different hemodynamic profile than expected and previously established: Although the contractility is severely impaired with a marked fall in SV and a compromised diastolic function, the peripheral systemic resistance is often only marginally to moderately elevated (see Fig. 3.2 by Cotter [62]).

Moreover, this "inappropriate" vasoconstriction (inappropriate low systemic vascular resistance) in relation to the severity of the myocardial depression, and the consecutive circulatory implications, first and foremost hypoperfusion, is found in the majority of patients [62–65]. Thus, CS affects the integral circulatory system

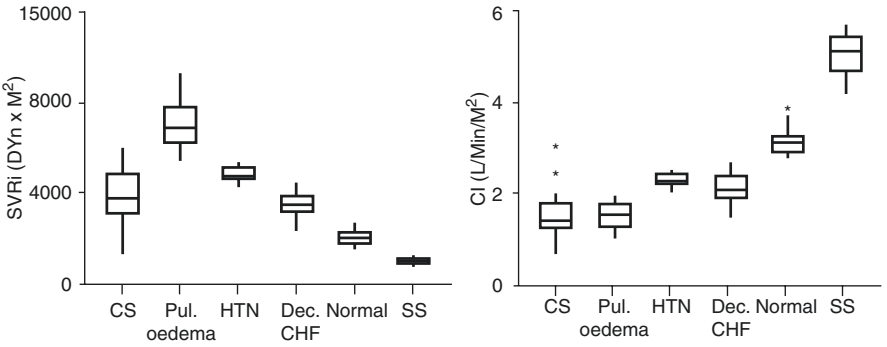

Fig. 3.2 By Cotter et al. [62] with permission. The level of peripheral resistance in CS swings in a wide range and may be in single patients as low as found in sepsis. On average, SVRi is comparable with that found in acutely decompensated chronic heart failure, but clearly lower than in pulmonary oedema or decompensation following hypertensive dysregulation. Likewise, cardiac index in CS is, on the first glance, not that bad and ranges, besides single cases, on average at the same level found in patients with pulmonary edema. Furthermore, CI is not substantially lower than in acutely decompensated chronic heart failure. However, the combination of both, relatively low SVRi and CI is hemodynamically unfavourable and indicates circulatory disaster. *CS* cardiogenic shock, *Pul. oedema* pulmonary edema, *HTN* hypertensive crisis, *Dec. CHF* decompensated chronic heart failure, *SS* septic shock

[55, 66] and has to be considered to be a systemic rather than a solely cardiac disorder [67–69]. Indeed, the considerable myocardial dysfunction initiates CS development [55] at which the primarily underlying myocardial dysfunction directly leads to both, reduced SV (and thus diminished CO) resulting in global tissue and cellular hypoperfusion and thus oxygen and nutrient undersupply [70–74], and to elevated filling pressures [64, 75]. The latter potentially provokes pulmonary congestion/edema [37, 40, 76]. Consecutively, compensatory, mainly neurohormonal, response is launched [37, 40, 42, 55], intending to stabilize preferentially cardio-circulatory and cerebral functions by diverting the blood flow to "vital" organs via several complex and interconnected neuroendocrine pathways [49, 55]. Accordingly, CS obviously is a systemic affliction and an integrative malfunction of the circulatory system applies [55, 66, 68].

In fact, CS is a so–called central shock characterized by scarce peripheral and organ perfusion attributed to substantial pump failure and therefore organ derangement right from the onset of the disorder [77]. The "unexpected and surprising" hemodynamic profile predominantly featuring inappropriately and functionally insufficient vasoconstriction in the presence of a, by all means, "comparably" not too bad LV-EF of around 30% (however remember, EF is a coupling indicator and is inversely related to afterload [78–81], therefore an EF of 30% in the presence of low SVR as in CS is absolutely not comparable with an EF of 30% in the presence of normal or high SVR as in stable heart failure patients!) is consistent with and reflects the systemic inflammatory response (SIR) applying in CS [5, 12, 54, 55, 61, 65]: Hypoperfusion, a hallmark of CS [55], restauration of blood pressure by neuro-endocrine activation as well ischemia and reperfusion precipitate a

systemic inflammatory response [5, 49, 55, 82] and thus are coining a clinical-hemodynamic picture quite similar to that in sepsis [65].

Namely the ischemia—reperfusion conditions are associated with the generation and the release of vasodilative acting mediators [83–85]: First and foremost high concentrations of NO and peroxy-nitrites (mediators with vasodilative effects) offset and counteract the neurohormonal mediated compensatory vasoconstriction, and, in fact, lead to an inappropriate circulatory response with potentially net vasodilation [5, 9, 62–64, 83, 84]. Indeed, elevated plasma levels of inflammatory markers and cytokines including TNF alpha and IL-6, indicating activated systemic inflammatory cascades, are demonstrated in CS [55, 61, 86, 87], while procalcitonin concentrations stay low reflecting the absence of a microbial infection underlying this setting [86]. Kohsaka [65] detected high levels of inducible NO-synthetase (iNOS) subsequent to the release of inflammatory mediators in patients with acute myocardial infarction. In fact, substantial evidence suggests that high levels of iNOS are expressed, attributed to the inflammatory response arising in the setting of AMI which is attended by and intrinsically tied to ischemia-reperfusion issues [83, 84]. This implies inadequate high levels of NO, potentially contributing to vasodilation, and of peroxynitrite, the latter with not only vasodilative [88] but also cardiotoxic and negative inotropic effects [82]. Elevated iNOS levels are per se associated with myocardial dysfunction [89, 90]. Raised, high levels of iNOS and NO are found after trauma and as a result of exposure of cells, particularly endothelial cells and cardiomyocytes, to inflammatory mediators, inducing the cells to express iNOS in unphysiological high ranges [84]. This has been specifically observed in experimental models of AMI and subsequent reperfusion [85]. Cytokine levels are reported to even increase after reperfusion following PCI applied in the setting of AMI [83]. Unphysiologically high levels of NO and iNOS and the subsequent generation of NO-derived species like peroxynitrite are reported to exhibit several deleterious effects: (a) to directly inhibit myocardial contractility, (b) to display pro-inflammatory effects, (c) to induce systemic vasodilation (d) to suppress mitochondrial respiration in non-ischemic myocardium, (e) to reduce catecholamine responsivity [54, 91–93], and (f) to mediate myocardial stunning [54]. iNOS induced NO production is found to be particularly deleterious during ischemia-reperfusion episodes [91, 92]. Accordingly, the effect of the compensatory released vasoconstrictive mediators (catecholamines, angiotensin II, endothelin-1) attaining intermittent stabilization and/or even improvement of coronary and peripheral perfusion [82] will be markedly attenuated and may be even off-reverted by the vasodilative effects of those agents generated in general in the setting of systemic inflammation but specifically in the wake of ischemia-reperfusion issues associated with AMI [67, 82]. This particularly occurs if the hemodynamic alterations and the compensatory response persist [82] and Rudiger strongly recommends to reverse CS within hours [66]].

As such, CS is also a result of the mismatch arising from substantially impaired myocardial performance and disproportionate, inadequate peripheral vascular dilation [63, 64].

Nontheless, additional “infectieous” features may trigger and aggravate the inflammatory cascades: Disrupted intestinal mucosal barrier function due to gut

hypoperfusion may allow for translocation of bacteria or bacterial material like toxins [49, 82]. In the shock trial, 18% of all patients with CS were suspected of suffering from sepsis, and indeed, of those 18%, 74% had positive blood cultures (that means, in total about 14% of all CS patients showed a bacterial infection/bacterial-associated inflammation) [65] which, in turn, fuels the inflammatory cascades.

Moreover, systemic inflammation is further reported to stiffen large, elastic arteries like the aorta while simultaneously the medium-sized and small peripheral vessels dilate [94]. Large artery stiffening arises most likely due to altered NO bioavailability as acute inflammation is shown to impair normal endothelial performance and reduces NO bio-availability, possibly through the cytokine cascade [95–98]. Arterial stiffening is recognized to increase the vascular load imposed on the left ventricle [99, 100] and to directly affect ventricular arterial coupling [101]. However, as reduced wave reflections (pulsatile load) due to peripheral vascular dilatation are noticed and total peripheral resistance is measured lower under these inflammatory conditions [94], net LV afterload may not increase. Reduced peripheral resistance (resulting from peripheral vasodilation) and concomitantly blunted wave reflections will diminish the afterload. However, in total, LV afterload is supposed to increase in inflammatory conditions since (1) peripheral vascular resistance is generally only mild to moderately reduced in CS [62], (2) the changes in vascular resistance precipitate just minor changes on ventricular wall stress (which reflects "true" afterload) [102], and (3) central vascular stiffening directly alters ventricular–arterial coupling (uncoupling) [101]. This suggestion is supported by the fact that peripheral vascular resistance is not really seen by the heart [78]. Unfortunately, studies systematically evaluating this issue are missing. Increased pulse wave velocities and a raised augmentation index as demonstrated in SIRS [94], are independently associated with systolic and diastolic dysfunction [103–105] and hence inflammation, in fact, impacts on disease course and is markedly involved in CS pathobiology.

SIRS may result in further troublesome hemodynamic effects contributing to CS disorder: CS, as the other shock types, features and suffers from microcirculatory dysfunction being part of the pathobiology [106]. Increasing heart failure severity is associated with NO imbalance and endothelial dysfunction (ED) [107, 108]. Low peripheral resistance predisposes patients to endothelial damage [65], and inflammatory agents like TNF alpha induce endothelial dysfunction [109]. Hypoxic/ischemic injury affiliated with hypo- and/or malperfusion is demonstrated to insult endothelial cells causing ED [110–113]. Hence, as the vascular endothelium takes a crucial role in regulating and is central to functions of microcirculation [114, 115], there is no doubt that microhemodynamics are altered in AHFS, particularly in severe AHF and CS [108, 116–118]. ED is meanwhile a widely recognized and an acknowledged feature in circulatory shock pathobiology [119, 120], where the endothelial cells are ascertained to be both target but also contributor to the disease development and progression [112, 121]. Indeed, endothelial cells are considered to take a central and crucial role in the pathophysiology and pathogenesis of acute and chronic heart failure [122–125].

Furthermore, since autoregulation is a hallmark and a critical issue in the physiology of microcirculation [108, 113, 114], a compromised autoregulation (which

inevitably ensues in case of hypoperfusion and hypotension [126, 127]) contributes to, and is part of, the microcirculatory alterations found in CS [39].

Microcirculatory alterations display as their most deleterious impact heterogenous blood flows [108, 128], a hallmark of shock [108, 129], and as such generate hypoxic and non-hypoxic areas in close vicinity, called dysoxic tissue regions [130, 131]. Heterogenous microvascular perfusion has been demonstrated in patients with CS [108]. Heterogenous perfusion is associated with disturbed oxygen extraction [70] and thus may lead to further cellular injury [132] in the heart as well as in distant organs [68, 108, 114, 119, 133].

Noteworthy for therapeutic management, in contrary to septic shock, where at least in advanced disease states micro- and macrocirculation are dissociated (which means that a successfully recuscitated macrocirculation will not subsequently translate into an improved or even normalized microcirculation [134, 135]), a close correlation between macro- and microcirculation seems to exist in cardiogenic shock states and thus microcirculatory alteration will usually improve when marcocirculation can be restored [136, 137].

As such, altered microcirculation has to be seen as an essential element in the pathobiology of shock states [77, 108] and the aberrations are basically referred to as a loss of regulation of the peripheral vasomotor tone, associated with endothelial cell dysfunction [138], eliciting heterogenous and maldistributed blood flows creating dysoxic tissue regions [72, 139].

In conclusion, the systemic inflammatory reaction contributes substantially to the pathogenesis and the course of CS [52, 54, 55, 61, 65, 82]: The mismatch between marked myocardial depression caused by loss of contractile mass [24, 37, 40, 54], ischemia-reperfusion injury [42, 49, 65, 82–85], cardiodepressent substances [82, 89, 90, 109], and the inappropriate vasodilation may result in CS [63, 64]. Incipient CS leads to profound, persistent, and refractory vasodilatation and hypotension [1, 54, 83, 84] and to the development of MODS/MOF [5, 54, 61] with its deleterious outcome, if not treated adequately and in time [54, 55, 66].

Hence, the pathogenesis of CS is largely determined by

1. the initial substantial myocardial damage, generally of ischemic genesis with consecutively marked systolic and diastolic cardiac dysfunction,
2. the consecutively precipitated compensatory, mainly neuro-endocrine reply, and
3. the associated systemic inflammatory response,

the latter with inherent vasodilatory properties, thereby altering macro- but also microcirculatory hemodynamics [52, 54, 55, 61, 65, 82, 86, 87, 108]. The ‘only’ marginal to moderate, disproportionate increase in peripheral resistance (SVR/SVRI) has gained pathognomonic meaning for CS: The relatively low SVR/SVRI is essentially caused by the vasodilative mediators (largely NO, peroxynitrite), which are generated in the context of the inflammatory reaction and the ischemic-reperfusion issues that apply in the setting of CS complicating AMI. This

vasodilative capability basically offsets the vasoconstrictive effects (mainly) launched by the neurohormonal-based compensatory mechanisms precipitated in response to the loss of pump function [54, 60–62, 65].

It has to be noted that a small group of patients in the SHOCK registry and trial [5, 27, 28] were clinically normotensive, or only mildly hypotensive, but still diagnosed as cardiogenic shock: They were systemically hypoperfused with low CO and elevated left ventricular filling pressures but with an "elevated" SVR and therefore able to maintain a reasonable blood pressure [9]. These patients should have been classified as being in a pre-shock state [3], where the systemic inflammatory response is not (yet) significantly active/activated.

There is quite a wide range of intensity and impact of the inflammatory response reported, afflicting some patients severely and some more marginally, as such, the violence of SIRS decisively impacts on the malady course [54, 140, 141].

Hochman [54] suggested a new cardiogenic shock paradigm, having integrated the newer pathophysiological aspects [61, 62, 65, 82] within the older existing concepts [42], as depicted in Fig. 3.3.

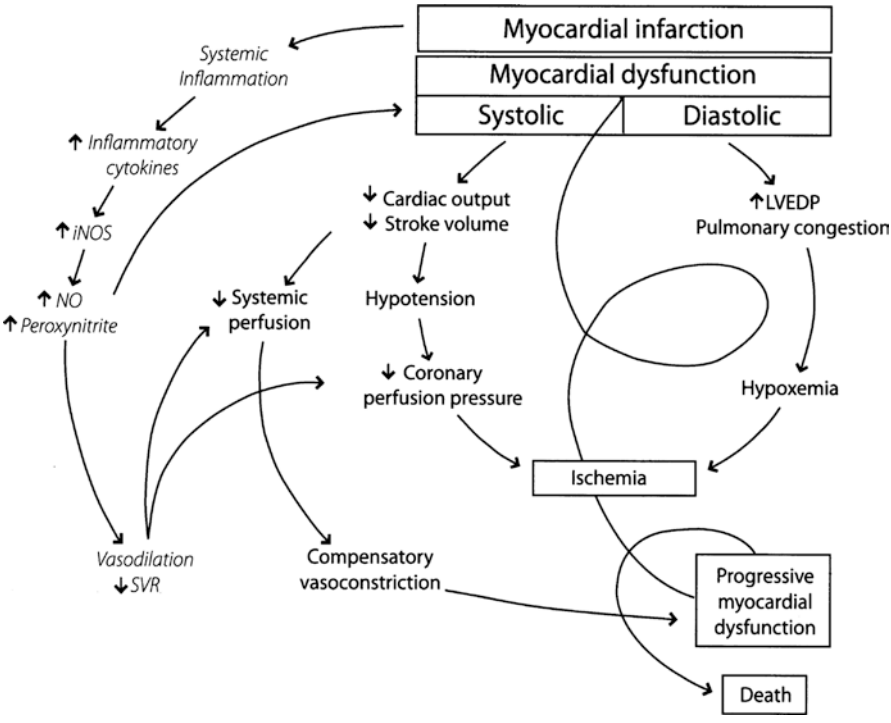

Fig. 3.3 Right side: classic shock paradigm, mechanical and neurohumoral aspects; left side and in italics: influence of the inflammatory response syndrome: New cardiogenic shock paradigm by Hochman [54], with permission. NO: nitirc oxide; iNOS: inducible NO-synthase

3.4.2 The Role and Impact of Hypotension in CS

Myocardial perfusion is compromised by hypotension [5, 43] and may induce ischaemia or exacerbate existing ischemia [37]. The decreased coronary perfusion pressure (especially in multi-vessel coronary disease [40]) secondary to the decrease in MAP, caused by the poor cardiac performance/contractility and vasodilatation, may lead to a critically low BP [5, 40, 42, 61]. Critical hypoperfusion itself aggravates the myocardial perfusion deficit [142], exacerbating the myocardial ischemia and implementing a vicious cycle leading to a more and more severely ischemic myocardium [40, 42]. This is seen even in shock states not initially caused by impaired myocardial contractility [1, 2], but when the blood pressure is so low that the perfusion of the end-organs [1, 13] (especially the heart [13, 143–145]) becomes critically dependent on the hemodynamics [5, 40, 145].

The compensatory neuroendocrine response may also contribute to this deleterious development, thus showing to be maladaptive: Initial vasoconstriction and fluid retention increase pre- and afterload, thereby enhance ventricular wall stress and consecutively myocardial oxygen demand, as does the tachycardia often resulting from the catecholamine release within the compensatory features [52, 55, 146].

Accordingly, "ischemia causes myocardial dysfunction which, in turn worsens ischema" [37]. Topalian [52] expresses this as "ischemia begets ischemia" and Hollenberg [37] strongly advises against the incidence of a vicious cycle arising consisting of ischemia, deterioration of myocardial function, and shock.

3.4.3 Myocardial Ischemia and LV-Compliance

The compliance, a diastolic property, of the left ventricle will be reduced by myocardial ischemia, and subsequently the LVEDP will rise [147–151], as will the pulmonary capillary pressure, putting the patient at risk of developing pulmonary congestion / edema [76, 149–152]. Additionally, LV end-diastolic filling increases in situations of severely impaired systolic LV-function in order to maintain SV (via Frank-Starling- mechanism) [37, 40, 153]; this will augment the LVEDP further, putting the patients at even higher risk of pulmonary congestion/oedema [40, 76] and further ischemia [37, 40].

Thus, both, altered systolic and diastolic properties contribute to the increase in LVEDP [40, 76].

However, LVEDP reflects the compliance of the left ventricle [153], and abnormally high LVEDPs indicate enhanced LV-stiffness [154]. Since the compliance of the heart chambers is demonstrated to continuously vary, particularly in critically ill patients [155, 156], but even in healthy persons [157], changes in LVEDP may not correlate with changes in left ventricular filling volume at all. As such, some patients with CS will definitely show normal or even low filling pressures [9, 158, 159]. Hence, caution is advised in interpretation of LVEDPs as the value, and even changes, may not correctly indicate LV- preload and

intravascular volume conditions [156, 157, 160]. Anyway, essentially and typically, LVEDP is elevated and CO low in CS [40].

3.4.4 The Right Ventricle in CS

Sharing the interventricular septum and being enclosed by "one" (the) pericardium, interactions between left and right ventricle occur [161–164]. As such, RV function may be affected by a dysfunctional LV, and may contribute to CS [55].

Foremost, the increased left-sided filling pressures being transmitted back, precipitating pulmonary hypertension [165, 166], acutely afterload the RV [152, 165–170]. Consecutively, as the right ventricle can poorly tolerate and adapt to pressure loading [171, 172], an immediate dilatation of the right chamber (with an increase in RVEDV) occurs in order to compensate for the elevated load imposed on RV [172–174]. Concomitantly with that increase in RV filling volume (RVEDV), both RVEDP (increase due to (a) the rise in filling volume [174, 175] and due to (b) pericardial constraint following the rule of constant total cardiac volume [161, 163, 176, 177]) and LVEDP increase (pericardial constraint associated with diastolic ventricular interdependence [178–181]). Attributed to the stronger impact of the pericardial constraint on the thin-walled right heart, the rise of RVEDP is disproportionally higher than the rise of LVEDP [178, 179]. RV-dilatation and the marked increase in RVEDP may result in deleterious consequences, since, due to diastolic ventricular interdependence [178–180, 182], the shift of the IVS towards the cavity of the left ventricle will impair the net space for LV filling volume, (further) compromising LV–SV and LV performance [163, 182–185]. Moreover, up to 40% (Diamino allocates up to 66% of RV pressure generation and up to 80% of the RV flow to LV contraction/LV assistance [186]) of RV contractility force, due to anatomical arrangement of myofibres [182], is generated by LV-contraction, referred to as systolic ventricular interdependence [164, 187, 188]. Therefore, an impaired LV contraction may markedly affect RV systolic performance and reduce RV-SV, subsequently supplying the LV with an even more inappropriately low filling volume [189, 190]: Thus, only a sufficient RV pump ensures appropriate LV preload and consecutively guarantees LV output [191, 192], hence prevents (further) LV pump failure—a series effect as the two ventricles are arranged in a row [191–193].

Moreover, RV may be involved in the ischemic process, although a predominant RV—infarction and associated shock is a rare event: In only 5% of patients predominant RV—infarctions are reported [194], however, acute RV myocardial involvement is complicating 50% of all inferior AMIs [195]. As such, if ischemia involves the RV, any additional threat (e.g. RV afterloading) may cause fatal consequences.

The haemodynamic alterations and the severity of circulatory compromise in predominantly RV- AMI are determined by the damage to the RV itself (extent of RV ischaemia and the subsequent RV-dysfunction), the ventricular interaction (mediated by the septum and by the restraining pericardium [196] affecting the LV-function), and the involvement of the LV in the ischemic injury [194].

Since RV contractility considerably depends on systolic LV-function, particularly on the contraction of the helical fibres of the IVS [197–199], a loss of systolic LV support (e.g. due to LV infarction—the perfusion of the IVS may be provided to a considerable amount by a big right coronary artery!) may result in deleterious hemodynamic consequences [197–201] and early onset of hypotension and shock [202].

Accordingly, a predominant RV-infarction, or a relevant ischemic involvement of the right ventricle in LV-AMI requires special attention and a sophisticated therapeutic approach: The traditional and common practice of aggressive volume loading [55, 163] may be erroneous and disastrous, as volume loading in the presence of elevated RVEDPs and/or a dilated RV (and thus relevant pericardial constraint) may, due to DVI, further impede LV-filling and hence markedly diminish LV-SV [163, 177, 179, 183, 184]. In addition to the altered LV-geometry following the septal shift towards the left chamber cavity, LV systolic function is affected as well [203]. Thus, fluid application may end up in full-blown circulatory failure [55]—thus, in contrary, volume unloading is necessary and the appropriate way!

3.4.5 Other Acute Causes of a Substantial Impairment in Contractility

- Transient acute myocardial ischemia [1, 15, 16] on a background of chronic CAD and the accompanying diastolic dysfunction [204–206] is able to induce an abrupt impairment of the contractility of viable myocardial tissue;
- Considerable regurgitant flow [1] from acute mitral insufficiency (acute MR) as a mechanical complication of acute myocardial infarction [12, 37], ischemic MR [207–210], and mitral valve insufficiency subsequent to transient hypo-perfusion (ischemia) in case of chronic CAD [211] can be responsible for a sudden decrease in SV/CO;
- Acute AR is most commonly caused by infective endocarditis [212]. The rapidity of occurrence of the regurgitant flow does not allow the establishment of any specific compensatory mechanisms (i.e. LV-dilatation) [213, 214]. Consequently the SV/CO (forward stroke volume) will significantly diminish as well as the LVEDP increasing [1];
- Myocarditis sometimes causes markedly impaired contractility and hence reduced forward flow [215, 216];
- Drugs may have negative inotropic potential and the ability to initiate the production and release of pro-inflammatory mediators from cardiomyocytes and other (hematological) cells which can promote the inflammatory process and be directly cardio-depressive [205, 217]. Even catecholamines (released as part of the compensatory mechanisms or administered as therapeutic agents) may induce the production of pro-inflammatory cytokines (i.e. Inter-leukin IL-6) and thus provide a further direct depression of contractility [205, 218, 219].

- Since the vast majority of patients (roughly 75%) develop CS after presentation [20, 220], it has been supposed that our medication may contribute to ensuing CS [37, 55]. The whole spectrum of cardiac drugs usually used in AMI including β-blockers, angiotensin-converting enzyme inhibitors, morphine and diuretics potentially display deleterious effects affecting disease course and thus contribute to CS [221–224]. Timing for applications may play a decisively role [37, 55].

3.5 Clinical Features and Diagnostic Remarks

3.5.1 Hypoperfusion

In the vast majority the diagnosis of CS is established by clinical signs of hypoperfusion, ischemic chest pain, enzymatic analysis and ECG [37, 49, 55, 225, 226]. A normal ECG virtually excludes the possibility of CS caused by myocardial infarction [40]. In addition, an echocardiogram is absolutely essential in the initial assessment of all patients suffering from (cardiogenic) shock [3, 37, 227–229] and should be performed as early as possible.

The crucial aspect in the diagnosis of CS is the identification of hypoperfusion in the setting of considerable cardiac dysfunction [1, 3, 5, 37, 40]. The following signs and features are suggestive of organ/tissue hypoperfusion [3, 5, 225, 230, 231]:

- pallor, ashen grey or cyanotic skin,
- cold peripheries (forearms and/or lower legs [7]), cold skin, moist and clammy, mottled extremities,
- altered mental status [8]: quiet, apathetic patient, sometimes restless, apprehensive or confused,
- reduced urine production/oliguria, <30 mL/h or <0.5 mL/kg/h for ≥2 h [230],
- thready pulse of poor quality,
- arterial hypotension.

CS should be considered in all patients presenting with unexplained hypotension and/or low cardiac output, unexplained impairment of mental function and unexplained pulmonary congestion [5, 13, 37]. In fact Menon [3, 9, 10] strongly recommends diagnosing CS in all patients exhibiting signs of inadequate tissue perfusion in the setting of severe cardiac dysfunction irrespective of the BP.

"CS is diagnosed after documentation of myocardial dysfunction and exclusion of alternative causes of hypotension like hypovolaemia, haemorrhage, sepsis, pulmonary embolism, tam- ponade, aortic dissection and pre-existing valvular disease" [37].

Ander [232] expresses doubts that clinical signs are sensitive enough to detect occult cardiogenic shock, particularly in patients with congestive heart failure because clinical signs may fail to diagnose inadequate oxygen delivery

[233–236]; thus, the measurement of $ScvO_2$ and serum lactate are recommended [232, 237]:

A lactate > 2 mmol/L together with a $ScvO_2$ < 60% (SvO_2 < 65%) suggests occult shock [232].

64% of all patients included in the US shock register presented with hypotension, evidence of ineffective CO/hypoperfusion and pulmonary congestion [8], but 28% had evidence of peripheral hypoperfusion and hypotension and did not suffer from pulmonary congestion [8]. Thus, clear lungs may still be present even with elevated PCWP and CS [8]. This phenomenon (elevated PCWP but no clinical or radiological signs of pulmonary congestion) has been described previously [238]; it deserves emphasis because administration of large amounts of fluid will be deleterious [8, 239]. Do not treat these patients with large boluses of fluid [3, 239].

The timely identification of patients in a pre-shock [3, 10] or non-hypotensive shock [9] state is of special value to allow therapeutic intervention and prevent decline. Clinical signs of hypoperfusion (in particular cold, clammy skin and oliguria) are strongly associated with increased mortality, independent of blood pressure and other haemodynamic parameters [240]. Hypoperfusion may be a marker of impending haemodynamic collapse [9] and tachycardia in this setting (HR > 90/min) should be interpreted as a pre-shock symptom and not as a response to low cardiac output and subsequent increased sympathetic tone [3]. Take care particularly in patients with anterior AMI and keep in mind that up to 30% of patients with AMI develop cardiogenic shock late (day 5) in their disease course—and with a very poor prognosis [241].

In this situation the choice of medication should be made carefully. The use of β-blockers, in general indicated and life-saving in AMI [242, 243], may precipitate shock development in these patients [3, 12, 143, 244]. Additionally, the possible life saving compensatory activation of the renin-angiotensin system should not be counteracted by administration of ACE-inhibitors [245, 246].

3.5.2 Right Ventricular Infarction

A significant infarction of the right ventricle (RV-AMI) complicates 50% of all inferior myocardial infarctions [195]. On an ECG, ST-elevation in VR3 and/or VR4 (right praecordial leads) in patients with inferior ST-elevation, acute myocardial infarction is specific for RV-ischaemia due to a proximal RCA-lesion [196]. Predominantly the inferior and posterior parts of the RV are involved [194]. In this case, RV may be the crucial component in the disease process, responsible for the development for CS [178].

The recognition of this special issue is important due to a three-fold risk to develop ventricular arrhythmias and AV-nodal block [247, 248] and due to the special treatment needs: well-balanced and monitored fluid administration, fluid restriction in case of manifest RV-failure, and CS [178, 184, 249], preservation of AV-synchrony, and reduction of increased RV-afterload [250–252]. On the other

hand, RV is reported to be highly resilient and may recover soon completely, possibly indicating that RV-dysfunction is probably due to stunning myocardium rather than true myocardial necrosis [253].

3.5.3 The LVEDP in Cardiogenic Shock

The LVEDP and its measurement in the definition and diagnosis of cardiogenic shock should be assessed critically; an elevated LVEDP may not be a sensitive or specific parameter with which to diagnose CS:

- Acute severe heart failure is not necessarily accompanied by high LV-filling pressures. Some patients will definitely have normal or even low LVEDP's [8, 159, 254, 255];
- The LVEDP (PCWP) does not reflect the amount of extravascular lung water [256–258] due to cardiac dysfunction in a uniform way [159, 256–258];
- An abnormally high LVEDP (≥15 mmHg as described in the definition) may only reflect an abnormal stiffness of the LV [259] (impaired LV-compliance, i.e. due to ischaemia [147, 148]). It is well known that, particularly in critically ill patients, the compliance of the ventricles continuously varies, contributing to the heterogeneous response and changes of the LVEDP value [155, 156, 260, 261]. Even in healthy persons absolutely no correlation was found between changes in ventricular filling and the change in value of LVEDP [157];
- The PCWP (as well as the CVP) does not adequately represent the pre-load or intravascular volume status and its changes in volume loading or unloading, either in healthy subjects [157] or in the critically ill [156, 160].

Thus, no reasonable correlation between LVEDV and LVEDP could ever be established [156, 157, 160] and in preference, the transmural LVEDP may be helpful to guide and monitor disease and therapeutic measures [262]. For further details see Chap. 1, paragraph 3b.

3.5.4 Important Differential Diagnosis of Cardiogenic Shock [3, 40, 225]

- hypovolaemic shock,
- dissection of the aorta,
- pulmonary embolism,
- bacteraemia and septic shock,
- neurogenic shock,
- anaphylactic shock,
- Takotsubo syndrome [263, 264].

Table 3.1 Summarizes the most relevant clinically-hemodynamic findings as collected by the physical examination of the patient ,applying the "4-panel test" by Stevenson and Nohria

Warm and dry	Warm and wet
See Chap. 2	See Chap. 2
Cold and Dry	**Cold and Wet**
28% of all CS patients *Clinically:* often surprisingly stable but otherwise dominated by symptoms of hypoperfusion *Haemodynamics:* sBP ↓/↓↓↓ (<90 mmHg for ≥30 min or catecholamines are required); or pre-shock criteria ; CI/CPI ↓/↓ ↓ ↓ (CI ≤ 2.2 L/min/m^2); no pulmonary congestion and often with a normal PCWP *Hypoperfusion:* mild to severe. *renal perfusion*: ↓↓ RBF; impaired intra-renal autoregulation Performance of an echocardiogram is paramount **CS should be considered in all patients presenting with unexplained hypotension or low cardiac output and unexplained altered consciousness, irrespective of BP.** *Clinical scenarios most likely in this group:* ESC 4a and 4b (mostly due to ESC -5), ESC- 6 (peripheral (systemic) edema but clear lungs), (ESC 1?)	**64% of all CS patients** *Clinically* dominated by symptoms of hypoperfusion: pallor, ashen grey or cyanotic skin, cold peripheries, thready pulse, altered mental status, oliguria (<30 mL/h), arterial hypotension and pulmonary congestion; auscultated S3. *Haemodynamics*: sBP ↓/↓↓↓ (<90 mmHg for ≥30 min or catecholamines are required); or pre-shock criteria; CI/ CPI ↓/↓↓↓ (CI ≤ 2.2 L/min/m^2); PCWP ↑/↑↑↑ (≥15 mmHg or pulmonary congestion on chest X-ray) *Hypoperfusion:* mild to severe *renal perfusion*: ↓↓ RBF; impaired intra-renal autoregulation; ↑/↑↑ renal venous pressure Performance of an echocardiogram is paramount. CS should be considered in all patients presenting with unexplained hypotension or low cardiac output, pulmonary congestion and unexplained altered consciousness, irrespective of BP. *Pre-shock criteria:* signs of inadequate tissue perfusion in the setting of severe cardiac dysfunction irrespective of the BP. Often a history of AMI, a cold and clammy patient with tachycardia and crackles ≥ 50% of total lung area suggesting pulmonary oedema. *Clinical scenarios* most likely in this group: ESC 4a and 4b (mostly due to AMI, ESC-5), ESC 6 (peripheral and pulmonary edema- severe biventricular failure)

3.6 Therapy

A substantial number of publications have addressed the best therapeutic approach to CS complicating AMI – the most likely scenario in the vast majority of patients with CS [5, 143, 265–271].

Both retrospective [143, 265–268] and prospective randomized controlled trials [5, 269, 270] have produced considerable evidence that an invasive approach (emergency revascularization by PCI/operation with and without prior thrombolytic therapy) is definitely beneficial. Although in the SHOCK-trail [5], the landmark study on the treatment of AMI complicated by CS, the primary endpoint, 30-days mortality rate, showed "only" a non-significant reduction in mortality compared to medical treatment alone, did the secondary endpoints demonstrating an absolute reduction in mortality after 6-month and 12 months of 13% definitely satisfy [5, 269]. This result equals a number needed-to-treat ratio (NNT) of less than 8, which means, that for to save 1 life, less than 8 patients need to be treated with this approach [82]. Even the 6 years mortality rate is significant better if early PCI is provided [271].

The effect was similar for both manifest CS at admission and in the event of delayed onset of cardiogenic shock [220]. The hospital mortality could be reduced from 75% (occluded vessel) to 33% (re-opened vessel by PCI) [220, 271–273].

3.6.1 Main Therapeutic Strategies

- Coronary intervention in acute coronary syndromes [5, 54, 265–271, 274].
  This comprises PCI or emergency CABG: a class I, level B evidence rated by the ESC [275, 276] as well by the AHA/ACCF [277]. The time frame covers ideally the first 6 h after symptom onset [5], but is still quite effective within the first 12 h after symptoms arose in STEMI patients [278]—a class I, level A AHA/ACCF recommendation [277].
  70–80% of the patients suffering from CS complicating AMI suffer from multivessel (stenosis/occlusion > 1 vessel) disease [5, 14, 23, 279].
  This vast majority has a grim prognosis (higher mortality) [279]. Although no substantial and conclusive data are available [67] and the optimal strategy is unclear [280], guidelines encourage for PCI on additional non-culprit lesions in that patient group, a class IIa level B ESC recommendation, based on pathophysiological considerations [276]. However, standard and accepted practice is to intervene only on the culprit lesion [67], and although until now all but one study did not report of increased mortality in case of an multi-vessel PCI approach [23, 281–284], individual decisions should be made (morphology of lesion, hemodynamic state, etc.) [82].
  Fibrinolysis is clearly less effective and thus reserved for patients not able to undergo early intervention, e.g. delays in transport [285], admitted to a non-PCI capable hospital and transport will exceed 120 min [286, 287]—class I B AHA/ACCF recommendation [277].

If thrombolysis is needed and considered, it should be applied within 30 min after hospital admission [288, 289], a class I level B AHA/ACCF recommendation [277].

- Emergency operation for mechanical complications following acute myocardial infarction include rupture of the free wall, acute MR [276, 290], ventricular septal defect, the latter is treated by intra-aortic ballon pump followed by early surgical repair [291]. Patients with free wall rupture require immediate pericardial drainage and prompt surgical intervention [276], however, even than may not benefit from the surgical approach [292].
- Emergency valve replacement/repair in case of acute/acutely decompensated AR or MR [293, 294],
- Emergency operation for acute ascending aortic dissection [293, 294],
- Pericardial puncture/drainage if pericardial tamponade (traumatic or inflammatory) is the reason for shock [293, 294],
- Thrombolysis/thrombus fragmentation/operation in case of acute fulminant pulmonary embolism [293, 294],
- Adequate treatment of rhythm disturbances if they are the main reason for shock: Temporary pacemaker in bradycardia [295], DC cardioversion, emergency ablation or anti-arrhythmic medication (Amiodarone) in case of sustained VT [293, 294], magnesium in case of torsade de pointe tachycardia [296–298].
- Immediate pleural drainage in tension pneumothorax [299].
- the aim and the target for "initial medical therapy in cardiogenic shock is to maintain arterial pressure adequate for tissue perfusion and to increase tissue perfusion" [300].

3.6.2 Adjunctive Treatment

3.6.2.1 Maintaining or Re-establishing Appropriate Coronary and Systemic Perfusion

Critical hypoperfusion reduces the myocardial perfusion or aggravates an already present myocardial perfusion deficit [142]. Persistent myocardial ischaemia and hypoperfusion will cause a vicious cycle leading to an increasingly ischaemic myocardium [40, 42]. The perfusion of the end-organs [1, 13] (especially the heart [13, 143–145]) becomes critically dependent on the haemodynamics [5, 145, 301].

In order to provide an appropriate coronary perfusion pressure in patients with ischemic heart disease, avoiding (further) ischaemia, and preventing the intact myocardium from hypoperfusion, a **MAP ≥ 70(75) – 80 mmHg** [302–305] should be sufficient. In patients with other reasons than ACS for CS, such as acute myocarditis, a MAP ≥ 65 mmHg may suffice [306, 307]. Guidelines recommend keeping the sBP ≥ 100 mmHg in case of CS, but no studies are available to substantially support this value.

Furthermore, although a higher perfusion pressure does not automatically improve tissue perfusion, in the case of the heart there is evidence that an increase in systemic and hence coronary perfusion pressure indeed means an improvement in the tissue perfusion (coupled macro- and microcirculation) [136, 137]. Both, Vlahakes [304] and Di Giantomasso [305] found a significant increase in myocardial tissue perfusion while administering noradrenaline to treat hypotension, increasing the systemic as well as the coronary perfusion pressure.

Autoregulation has turned out and can be considered being a decisive feature and mechanism to provide for adequate blood distribution and thus appropriate tissue oxygen and nutrient supply [113]. Furthermore, GFR and hence basic kidney excretion function seems to be assured as long as autoregulatory capacity is secured and uninterrupted [308–310]. Accordingly, if autoregulation is compromised, the expansion of myocardial ischemia is highly likely and disease immanent in coronary artery disease, particularly in AMI [37]. Thus this expansion may be critically and crucially hampered by maintaining and/or re-establishing (as soon as possible) working cardiac autoregulation, thereby allowing for sufficient oxygen supply of the "healthy" myocardial mass [136–138]. To do so, coronary perfusion pressure is not allowed to fall below the autoregulatory threshold at all. As such, early and resolute initiation of noradrenaline, NA [311] application aiming for a MAP between 70 and 80 mmHg seems to be an essential and life saving measure [302, 303, 306] even if this implies that LV afterload increases in a situation where the systolic LV function is already markedly compromised. However, ongoing and dispersing ischemia, especially ensuing in the setting of AMI, affecting with ongoing hypoperfusion also primarily healthy myocardial regions, will inevitably lead to complete cardiac collapse as there will be not enough myocardium left for contraction at all if ischemia spreads. As such, securing coronary perfusion keeping auto-regulation working is paramount.

3.6.2.2 Fluid Administration

In life-threatening situations with severe hypotension and tissue hypoperfusion, a fluid challenge as described by Vincent and Weil [312] is justifiable, even in cases of cardiogenic shock [8, 313]. But remember that only 10–15% of all patients with CS suffer from a relative or absolute volume deficit and thus are in need of fluid loading [314]. Although, understandably, Hunt [313] demands that a confirmed volume deficit has to be treated before commencing any other measures. However, as Michard has shown, in the case of severely impaired contractility no significant increase in SV and blood pressure can be expected by volume loading [160].

As such, a monitored bolus of 250–500 mL crystalloid in case of hypoperfusion/hypotension seems to be reasonable [8, 226, 315] and is an endorsed first-line measure, as long as no signs fluid overload are present, a class I, level C ESC recommendation [315]. Nevertheless, a *sustained* effect on BP increase cannot be expected [316]. Accordingly, close monitoring and a careful assessment are essentials in order to avoid volume overloading with its harmful consequences [317].

3.6.2.3 Vasopressor Administration

In critical hypoptension (usually defined as sBP < 90(85) mmHg or MAP < 65(60) mmHg) in the setting of AHF/CS [276, 315, 318–320]) noradrenaline (NA) is by now the preferred vasopressor drug: Compared to dopamine, NA shows an improvement of renal and myocardial tissue perfusion [304, 305, 321, 322], and within reasonable dose ranges no unfavourable effects on renal, mucosa/gut or thyroid perfusion [301, 323–325] have to be expected. Particularly the study by De Backer substantially supports to use NA as first-line vasopressor in shock states [311] and confirms results by Sakr who found that the administration of dopamine or adrenaline was associated with a

Table 3.2 Main effects of catecholamines (adapted from Ellender and Skinner [327] and Van Thielen [328], with permission)

Drug	Main receptor activity				Clinical/hemodynamic effects						
	α1	α2	β1	β2	CO	dp/dt	HR	SVR	PVR	PCWP	MVO_2
NA	4+	3+	3+	0(+)	↑	↑	±	↑↑	±	±	↑
DOB	0(+)	0(+)	4+	3+	↑↑↑	↑	↑↑	↓	↓	↓/±	↑

α1 - adrenergic receptor
α2 - adrenergic receptor
β1 - adrenergic receptor
β2 - adrenergic receptor

significantly higher mortality when compared to dobutamine and noradrenaline [326]. A subgroup analysis even found a lower mortality rate in those patients treated with NA and dobutamine [311].

Accordingly, the most recent ESC guideline (finally) recommends NA being the preferred vasopressor in case CS conditions persist, "despite treatment with another inotrope, to increase blood pressure and vital organ perfusion" [315], a class IIb, level B evidence [311]

The main effects of the catecholamines usually applied in daily practice are summarized in the following table, adapted from Ellender and Skinner [327] and from Van Thielen [328]. (Table 3.2)

3.6.2.4 Inotropic Medication

As mentioned in Chap. 2, inotropic drugs are traditionally used to increase CO (SV) and to improve peripheral and vital organ perfusion [334, 335] in low output situations which may be life threatening [62, 144, 301, 336].

As such, inotropic drugs may be considered in conditions of persistent organ hypoperfusion and/or hypotension associated with low output after carefully monitored and well balanced volume therapy [276, 315, 319, 337]. In the event of a reasonable BP (Ryan [301] and others [276, 315, 319, 320] suggest a sBP ≥ 90 (85) mmHg) or in pre-shock situations, *dobutamine* is still validated as the first choice drug when aiming to support and improve the contractility, to increase BP, CO and thus tissue perfusion [1, 40, 300, 301, 318, 329, 336]. However, as BP may further decrease under dobutamine infusion or does not increase, and as further ischemic threats definitely have to be avoided, a combination of NA and dobutamine is often indicated [300, 311]. The combination of NA and DOB (compared with other catcholamines like dopamine, adrenaline/epinephrine) has turned out to probably be the most reliable and safest strategy in those circumstances [300]. Further, DOB may be added to NA in patients with pre-shock/shock, once a systolic blood pressure > 90 mmHg is achieved and maintained [145, 197].

However, as mentioned, there is growing and clear evidence of adverse events and increased mortality when using inotropic agents [75, 338–340], and catecholamine application should be as short as possible and the doses used as low as possible [67].

Phosphodiesterase-inhibitors do not have any benefits when compared to dobutamine, with the exception that they are effective in patients who are on regular β-blocker medication, and patients do not develop tolerance as with dobutamine [341, 342]. Further, they may be an alternative in patients with CS of non-ischemic reason [343, 344].

Levosimendan, a calcium sensitizing agent, has shown very encouraging results in the treatment of severe heart failure [345–349]. Some studies found a significantly lower mortality when compared to dobutamine in patients treated for AHFS [346–350]. Levosimendan not only has favourable effects on systolic function but, in contrast to dobutamine, the diastolic function substantially improves as well (no adverse influence on relaxation) [351–354]. Furthermore, there is a considerable beneficial impact on the failing right ventricle [355–358]. The RUSSLAN-study also found a substantial benefit for patients with heart failure as a complication of AMI when treated with levosimendan rather than with dobutamine [347]. In refractory shock, levosimendan was shown to be not inferior to DOB (there was even a trend to be better), and superior to enoximone [359]. However, unfortunately, the recently published Revive I & II [360] and SURVIVE-study [361] could not demonstrate substantial favourable effects, particularly not a better outcome when comparing levosimendan with dobutamine.

Nevertheless, in case AHF/CS is associated with β-blocker treatment contributing to and/or even causing AHF [275, 362], levosimendan may be the preferred drug, as recommended in the most recent guidelines of the ESC, a class II b, level C evidence [315]. Furthermore, levosimendan may be applied in CS complicating AMI [347, 363] on top of an already administered combination of dobutamine and NA, if required to stabilize the patient [359, 364].

As mentioned previously, an aggravation of hypotension and hypoperfusion may be fatal and should be avoided [37, 40, 42, 142–144, 301], and as such, levosimendan should not be commenced if systolic blood pressure is less than 85 mmHg [355, 365, 366]. Restoration of normovolaemia and omitting the loading dose are measures which will avoid BP drops and hypoperfusion secondary to levosimendan administration [145, 365, 366].

In the US, levosimendan, due to the fact of not showing a better outcome compared with dobutamine in the SURVIVE- and REVEIVE studies, has not been approved [361].

Dosing of NA and inotropic drugs [145, 315, 327–329]

Noradrenaline NA	0.2–1.0 **µ**g/kg/min, (ranges reported vary between 0.2 and 5.0 **µ**g/kg/min, however, most intensivists do not increase NA-dosage above 1.2 **µ**g/kg/min [300, 311, 330–332])
Dobutamine DOB	2–20 **µ**g/kg/min; tolerance to be effective after 24–48 h with partial loss of hemodynamic effects [329] low dose (up to 5 **µ**g/kg/min), DOB lowers PVR and PAP, thus is important in case of RV failure due to pulmonary hypertension [333]
Levosimendan LEVO	0.1 **µ**g/kg/min (0.05–0.2 **µ**g/kg/min), bolus (optional) of 12 **µ**g/kg over 10 min if appropriate initial BP [315]
Enoximone	5–20 **µ**g/kg/min; bolus of 0.5–1.0 **µ**g/kg over 10–20 min. [315]

3.6.2.5 Intra-Aortic Balloon Counter Pulsation (IABP)

IABP has for a long time been a standard component in the therapy of CS [40, 285, 367]. IABP provides effective haemodynamic support and, of extreme importance, increases the coronary blood flow. In particular, IABP is efficient in the initial stabilisation of patients suffering from CS [368–372]. IABP improves outcome [369–371] and shows at least a trend towards lower mortality even when used as a single treatment tool [17, 27, 372].

However, since early coronary intervention (PCI or surgical revascularization) has provided impressive and substantial evidence of being the most favourable and effective initial approach [5], the effect of IABP is pulverized and IABP has lost its special position: As a biphasic recent high-quality study (IABP-SHOCK II) by Thiele and coworkers revealed, there is no additional beneficial effect of IABP therapy if patients with AMI complicated by CS have undergone successful coronary intervention [14, 373].

Accordingly, IABP application is not for standard use any longer, but may be considered in selective patients, particularly in those with mechanical complication of the infarction such as acute ventricular septal defect, a class II a, level C recommendation [276, 315]. IABP may be also valuable if the patients do not stabilize quickly after coronary intervention and applied medical measures [33, 374, 375], a class IIa, level B recommendation by the AHA/ACCF [277].

3.6.2.6 Renal Function

Renal dysfunction is known to accompany acute heart failure syndromes in a substantial number of cases [376–378]. If present, the patient`s prognosis is poor [376, 379]. Primary disorders of heart function affecting the kidney function and vice versa are termed cardiorenal syndrome [380], and “acute worsening or de novo afflicted heart function leading to acute kidney injury” is referred to as cardiorenal syndrome type 1 [381]. The CRS type 1 pathophysiology basically includes hemodynamic features such as diminished renal blood flow and deficient renal perfusion pressure, increased intra-renal vascular resistance and enhanced renal venous pressure (with concomitant renal venous congestion) [309], the latter being identified as “the major driver of acute cardiorenal syndrome” in CSR type 1 [382–386]. As such, altered renal perfusion in the setting of acute heart failure is attributed to and may be the result of impaired CO, combined pre-glomerular vasoconstriction and renal venous congestion [387]. In CS, renal dysfunction has traditionally been attributed to renal hypoperfusion following low cardiac output [380, 388–391], however, other pathophysiological features contribute, in particular attenuated or even disrupted renal autoregulation [384]—further details, please see Chap. 7 on cardiorenal syndrome.

Therefore, shortly following restoration of an appropriate circulation, attention should be directed to the renal function [392, 393]. The main prerequisites are eu/normovolaemia and an adequate perfusion pressure (MAP ≥ 70–80 mmHg) [322, 392, 394].

If an adequate diuresis does not commence spontaneously after volume status and blood pressure are optimized, one attempt to induce diuresis by administration of diuretics (bolus application) appears to be reasonable [392, 395]. If this is ineffective and there is persistent oligo/anuria or increasing (>1.5–2.0 of baseline level) serum creatinine levels signalling acute kidney injury [396] and a poor prognosis [397], combinations of diuretics, e.g. furosemide and metolazone, may be indicated [398, 399]. However, recurrent unsuccessful attempts with diuretics are likely to be harmful [400–402].

So, in the face of ongoing oligo/anuria, early consideration should be made of CRRT, continuous renal replacement therapy. CRRT has a 'neutral haemodynamic behaviour' with only a minimal effect on MAP [393, 394], which is essential, especially in the case of fluid overload [393]. Continuous renal replacement therapy also eliminates cardiopulmonary toxic substances and, most relevantly, myocardial depressant factors [403].

3.6.2.7 Compensation of Acidosis

In shock states, metabolic acidosis occurs due to elevated serum lactate in response to peripheral hypoperfusion [404]. Buffering should only be considered if the pH < 7.1, or if it is evident that the vasopressor or inotropic medication is not effective due to the low pH. In that setting, one should aim to raise the pH only moderately, not exceeding a target pH of 7.2–7.25. The decision to use buffer agents is controversial [405–408] and some authors refuse to do so [409]. There exists very little evidence as to beneficial effects of buffer agents [410], however if buffering is necessary, on current evidence tromethamine should be the preferred drug [411, 412], as it has less side effects than bicarbonate solutions.

In mechanically ventilated patients, mild hyperventilation is a nimble tool to remove excess acid in the form of carbon dioxide [413].

3.6.2.8 Anticoagulation therapy

Patients with cardiogenic shock essentially need thromboembolic prophylaxis and should be on low molecular weight heparin or equivalent drugs and doses, a class I level B recommendation [315].

Medical patients in general should be prophylactically anticoagulated in order to avoid disseminated intra- vascular coagulation (DIC) or thromboembolic events [414–418]. Although lacking definite studies, in case of CS, intravenous (to avoid inadequate absorption in peripheral hypoperfusion) administration of 500–800 IU/h unfractionated heparin is recommended [414]. Otherwise, prophylaxis of thromboembolism may be achieved either by 5000 IU of unfractionated heparin three times a day, or an adequate dose of low molecular weight heparin [417, 419].

Dosage: 40 mg enoxaparin [420, 421] (or equivalent) s. c. or 5000 units unfractionated Heparin s. c. × 3 daily [2, 422].

Table 3.3 Summary of the therapeutic measures to treat CS, based on the recommendations discussed above [317, 320, 339; ¤ 40, 42, 143 and Metra M, Heart Fail Rev 2009; 14: 299–307]

<table>
<tr><th colspan="2">Warm and dry</th><th colspan="2">Warm and wet</th></tr>
<tr><td colspan="2">See Chap. 2, Table 2.4.</td><td colspan="2">See Chap. 2, Table 2.4.</td></tr>
<tr><th colspan="2">Cold and dry</th><th colspan="2">Cold and wet</th></tr>
<tr><th>sBP < (85) 90 mmHg</th><th>sBP ≥ (85) 90 mmHg</th><th>sBP < (85) 90 mmHg</th><th>sBP ≥ (85) 90 mmHg</th></tr>
<tr><td>Ia. Careful and closely monitored fluid loading, crystalloids 250– 500 mLs/10–20 min, if acute predominant RV-failure* and relevant DVI are excluded. Simultaneously or if effect is insufficient, apply NA ≥ 0.02–1.0 µg/kg /min immediately.
Ib. In case of (predominant) acute RV-failure* and obvious DVI, start with NA immediately, add diuretics if appropriate (relevant systemic congestion and high CVP and sufficient BP is achieved)
Ic. If primarily euvolemic, apply NA ≥ 0.02 to 1.0 µg/kg/min
II. Consider to add DOB or LEVO if sBP > 90–100 mmHg but hypo-perfusion persists
III. In case of “isolated” RV-failure due to (acute) PH, consider selective pulmonary vasodilators</td><td>Ia. Careful and closely monitored fluid loading 250–500 mLs crystalloids/10–20 min if acute predominant RV-failure* and relevant DVI is excluded. Simultaneously or if effect is insufficient, apply NA ≥ 0.02–1.0 µg/kg/min immediately.
Ib. In case of (predominant) acute RV-failure* and obvious DVI, start with inotropes, add diuretics if appropriate (sufficient BP is achieved in the presence of relevant systemic congestion
Ic. If primarily euvolemic, consider inotropic support , e.g. DOB or LEVO
II. Add NA simultaneous while awaiting effect of measure I, or start NA early on if BP does not increase under the measures of Ib or Ic.
III. In case of “isolated” RV-failure due to (acute) PH, consider selective pulmonary vasodilators</td><td>Ia. NA ≥ 0.02–1.0 µg/kg/min or higher, if appropriate
IIa. In case of biventricular failure or predominant RV-dysfunction with considerably high CVP (pericardial constraint and DVI), diuretics may be added immediately after BP properly rises [161]
IIb. add DOB (LEVO) if still hypo-perfused although BP increases to ≥90–100 mmHg and substantial DVI is excluded
III. add diuretics if hemodynamically stabilized under measures I and II</td><td>Ia. Inotropic support (DOB or LEVO – DOB: 2–20 µg/kg/min, LEVO: 0.1 (0.05–0.2) µg/kg/min), but may consider to combine with NA
Ib. In case of biventricular failure or predominant RV-dysfunction with considerably high CVP (pericardial constraint and DVI), inotropes and diuretics may be applied simultaneously [161]
IIa. add diuretics if appropriate BP increase due to measures of Ia
IIb. add NA (≥0.02–1.0 µg/kg/min) early on, if BP does not increase, if there are ongoing signs of hypo-perfusion or if BP even drops under inotropic agents</td></tr>
<tr><td colspan="2">*Acute isolated or predominant RV-failure may go along without any relevant pulmonary and only marginal systemic congestion but with marked increased filling pressures and DVI [162, 178]. Further details on predominant right heart failure, see Chap. 4
Maintenance/restauration of adequate coronary perfusion and perfusion pressure (MAP ≥ 70–80 mmHg [302–306]) is paramount</td><td colspan="2">Maintenance/restauration of adequate coronary perfusion and perfusion pressure (MAP ≥ 70–80 mmHg [302–306]) is paramount</td></tr>
</table>

3.7 Summary

Cardiogenic shock is characterized by global tissue hypoxia and vital organ dysfunction secondary to severe, in general **myocardial** dysfunction with systemic hypocirculation [1, 2]. Accordingly, CS affects the complete circulatory system [55, 66], and has to be understood as a systemic rather than solely cardiac disorder [67–69]. As a central shock type, CS displays scarce peripheral and organ perfusion right from the beginning [77].

Characteristic clinical signs of hypoperfusion are cold, mottled, and clammy peripheries [6, 7], altered mental status [8], oliguria (<30 mL/h) and pulmonary congestion. Arterial hypotension (sBP < 90 mmHg) although a criterion of CS [5], is not a decisive parameter and a sBP ≥ 90 mmHg will not exclude the presence of non- hypotensive or pre-shock [3, 9, 10]. CS should be considered in all patients exhibiting signs of inadequate tissue perfusion in the setting of severe (systolic) cardiac dysfunction irrespective of the BP [3, 9, 10].

Acute or chronic myocardial ischemia is the underlying aetiology [11–13, 37] in the vast majority (70–80%) of CS cases. 5–10% of the patients with AMI develop CS [11, 17–20, 24, 35]. Other underlying aetiologies are valvular heart diseases, drugs with negative inotropic effects, and infections like acute myocarditis and sepsis [12, 36, 37].

Pathophysiologically both, systolic (due to the acute loss in pump force [37, 40]) and diastolic properties (abnormal stiffness [154], mainly related to impaired compliance [147, 148]) are acutely markedly altered [5, 37, 55, 75, 148]. Traditionally, a marked neuro-endocrine [37, 43–45], namely sympathetic [37, 40, 42, 43, 62] activation inducing compensatory fluid retention [43, 45] and systemic vasoconstriction [37, 40, 42–44] applies, also attended by fluid redistribution largely form the venous reservoir resulting from the sympathetically-mediated, generalized vaso- and thereby as well venoconstriction [47–49].

However, in the vast majority of patients [62–65], a considerably different hemodynamic profile can be observed characterized by an “inappropriate vasoconstriction” (inappropriate low systemic vascular resistance/inappropriate compensation) in relation to the severity of the myocardial depression / cardio-circulatory disorder [5, 54, 55, 61–65]. This reflects and is attributed to a systemic inflammatory reaction (SIRS) present in CS [5, 9, 12, 54, 60, 61, 83, 84]: Global tissue and cellular hypoperfusion (resulting from substantially reduced SV/CO following the severely impaired contractile capabilities) [71–73], neuroendocrine activation and ischemia-reperfusion issues precipitate a systemic inflammatory response [5, 49, 55, 82] coining a clinical- hemodynamic picture which, in several aspects, is alike that of sepsis/septic shock [65]. Consecutively, the effects of the initial cardio-circulatory disorder, of SIRS, and of the usual compensatory reaction interfere with each other, resulting in this diverse hemodynamic profile with an ‘only’ marginal to moderate compensatory increase in systemic vascular resistance, consequently pathognomonic for CS [5, 54, 60–62]. Particularly NO, generated following high expression of iNOS in the setting of inflammation and ischemia-reperfusion conditions [84, 85, 91, 92], and its

derivates offset the vasoconstrictive neurohormonal effects and bring about net insufficient vasoconstriction or even, in a few cases, net vasodilation [5, 62–64, 83, 84]. Associated with and in consequence of peripheral vasodilation (predisposes for endothelial dysfunction [65]), inflammation and hypoperfusion, and endothelial dysfunction will ensue [109–113]. Subsequently, the microcirculation will be even more decisively affected [108, 116–118], inclusively autoregulatory capabilities [126, 127], displaying heterogenous blood distribution [108, 128] thereby substantiating and aggravating the hypoperfusion induced, and the altered and poor tissue and cellular oxygen and nutrient supply [132] in the heart but as well in distant organs [68, 108, 114, 119, 133].

As such, CS pathobiology is largely determined by an acute, substantial **loss of myocardial performance** and the associated **systemic inflammatory reaction** with vasodilatory impact counteracting the **neurohormonal compensatory reply** thereby decisively altering macro- and microhemodynamics [52, 54, 55, 61, 65, 82, 86, 87, 108].

In spite of all therapeutic improvements, the overall in-hospital mortality remains high at 40–50% [14, 22, 29] .

Fundamental to therapeutic efforts are reperfusion procedures in case of AMI [5, 143, 271]. The hospital mortality can be reduced from 75% to 33% by addressing the culprit lesion via PCI [271–273], and the longer term (6 months, 12 months and 6 years) survival benefit of this invasive approach is impressively [5, 269, 271].

Critical hypoperfusion must be avoided and restoration of sufficient coronary perfusion is of vital importance [5, 40, 42, 142]. The use of vasopressor medication (in which NA should clearly be the preferred drug [300, 311, 321]) aiming for a MAP between 70(75) and 80 mmHg [302, 303, 306], thereby maintaining or re-establishing cardiac autoregulation [309, 310, 423, 424], may be an essential, life saving measure [144, 301, 326].

Inotropic drugs (in the first line DOB) may be indicated in life threatening circumstances [62, 144, 301, 334–336], and conditions of (persisting) organ hypoperfusion and/or critical hypotension in euvolemic patients [276, 315, 319, 337]. They may also be considered to be added to NA, when blood and perfusion pressure have stabilized [300, 311], in order to (further) improve LV contractility intending to support restoration and/or maintenance of a suitable tissue perfusion [144, 301, 310, 334]. However, inotropes (including NA which, of course, has inotropic effects) are associated with increased mortality and should be avoided whenever possible [75, 338–340].

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Acute Right Heart Failure

4

4.1 Definitions

Right ventricular failure (RV-F) is a complex, heterogeneous clinical syndrome, characterized by dyspnea—fatigue complaints and normally systemic congestion, which "can result from any structural or functional cardiovascular disorder that impairs the ability of the RV to fill or to eject blood" [1–3].

Thus, and in analogy to the definition of left ventricular (heart) failure, *RV-F may be defined as*:

"Inability of the RV to generate adequate forward flow with normal central venous pressure" [4].

A definition which has been endorsed by the fifth World Symposium on Pulmonary Hypertension in 2013 is set somewhat broader, but contains the same basic and essential pathological elements of heart failure, altered RV properties and performance, and the presence of increased filling pressures [5, 6]: "**RV failure is a dyspnea fatigue syndrome with eventual systemic venous congestion, caused by the inability of the right ventricle to maintain flow output in response to metabolic demand without heterometric adaption, and consequent increase in right ventricular filling pressures**" [7].

This definition outlines a wide range of clinical scenarios ranging from clinically a- or oligo-symptomatic and compensated conditions even under stress, which may be referred to as RV-D, however functional compensation is largely achieved by RV hypertrophy and in any way at the cost of elevated filling pressures, and ending with clinically overt malady with low output states and imminent circulatory collapse [3].

As such, right ventricular dysfunction (RV-D) is referred to as "abnormalities of RV-filling or RV-contraction without signs and symptoms of heart failure" [1].

4.2 Epidemiology and Aetiology

Right heart dysfunction/failure has a quite remarkable incidence, affecting approximately 5% of the US population [8] with the outcome largely depending on the

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underlying cause [9]. Three to nine percent of all admissions with acute heart failure syndromes (AHFS) are related predominantly to RV-F, with an in-hospital mortality rate being as high as 5–17% [10–13].

A wide variety of reasons altering right ventricular loading conditions, as occurring in case of pulmonary hypertension, or primarily diminished RV myocardial contractility as found in ischemia, cardiomyopathy, and arrhythmias, may lead to and provoke RV-D/RV-F [1, 2, 14].

Pulmonary hypertension (PH) actually is the most frequent pathogenetic feature causally involved in and contributing to RV-F genesis [14, 15]. Increases in pulmonary pressures, mostly due to and associated with an elevated pulmonary vascular resistance as the predominant underlying alteration in any setting [16], precipitate an increase in the input impedance[1] of the pulmonary artery and thereby on the RV-outflow tract, thus afterload the right ventricle [14, 19–23]. RV failure is the potential consequence of this increased RV afterload [14].

RV pressure overload is usually associated with and due to LV-dysfunction [24]. The most evident and determining implication of LV failure is indeed a rise in LV intra-cardiac filling pressure, implying elevated downstream pulmonary pressures [25], causing pulmonary venous hypertension [26]. A diseased left heart, LHD, is the most common cause of PH at all [27, 28], and accounts for 65–80% of all PH cases [15, 28, 29].

Further, acute RV-D/RV-F due to acute pulmonary hypertension is a common condition in the ITU setting (overview by [21, 30–33]):

(a) Acute respiratory failure per se leads to an increase in pulmonary vascular resistance [34] and to a change in pulmonary compliance inducing an increase in RV-afterload [35]. Hypoventilation of the alveoli, hypoxia and/or hypercapnia from respiratory insufficiency (type I and type II) cause an increase in pulmonary pressure and thus promote PH [36–38]. ARDS is frequently associated with PH due to an increase in pulmonary vascular resistance (PVR) [34]. Pulmonary vascular resistance (PVR) may be elevated by an increase in lung volume (emphysema) and by any decrease in functional residual capacity, and so lead to RV-D/F [29]. It is well established that acute respiratory failure leads to an increase in pulmonary vascular resistance, an increase in RV-afterload and reduced RV-function [39–41].
(b) Mechanical ventilation (positive pressure ventilation) compromises the pulmonary (micro) circulation through an increase in transpulmonary pressure causing an increase in the systolic load of the RV (↑ RV-afterload) [33, 42–44]. With progressively increasing tidal volumes the RV has to generate a higher and higher pressure to open the pulmonary valve and to eject blood into the pulmonary vasculature [42, 45]. PEEP induces a rise in the intrathoracic pressure

[1] Impedance may be the most complete description of the vascular load imposed on the ventricle [17, 18].

[46–50] and, at the very least, higher levels of PEEP (>8–10 cm H_2O) will substantially increase the RV-afterload [46, 51, 52]. Thus, a protective ventilatory approach keeping the plateau pressure within the airways below 27 cm H_2O, adapting pCO_2 to less than 8 kPa (60 mmHg) and PEEP-levels as low as possible is required [53].

(c) "Aggressive" volume loading, not being unusual in intensive care units, increases RV preload, and may in already stressed but until then compensated RV conditions precipitate acute RV-D or even RV-F [54, 55]—animal studies demonstrated that chronically volume overloaded right ventricles are compensated and show normal contractility, but decompensate in case they are faced with any additional burden like sepsis or mechanical respiratory support [56, 57].

Factors contributing to an increase in pulmonary vascular resistance are [58, 59]:

- Lung parenchymal destruction,
- Airway collapse,
- Microthrombi in the pulmonary vessels,
- Excessive pulmonary vasoconstriction,
- Hypercapnia,
- General and local release of pulmonary vasoconstricting mediators.

These features underlying cellular and molecular pathways are characterized by an imbalance between endogenous vasoconstrictors (in particular endothelin-1) and vasodilators (in particular nitric oxide and prostaglandins) produced and secreted by the pulmonary endothelium leading to an increase in pulmonary vascular resistance and an elevated RV outflow impedance [15, 60–62]. As such, haemostatic imbalances, secondary to pulmonary endothelial dysfunction and/or injury considerably contribute to the rise in PVR [63].

Failure of the right ventricle is often the final and crucial point in acute critical illness [9, 64]. This is not at least because acute right heart failure substantially influences the LV performance in these conditions [65, 66]. In cases where cardiopulmonary resuscitation is necessary patients with moderate or severe pulmonary hypertension are unlikely to survive [67].

Accordingly, acute/acutely decompensated left heart failure, acute respiratory failure conditions including mechanical ventilation, acute coronary syndromes causing myocardial ischemia, particular if involving the RV, sepsis and other severe infections, and acute pulmonary embolism represent the vast majority of maladies underlying acute RV-D/RV-F [68–70].

Table 4.1 lists a range of reasons causing RV-F (adapted from predominantly Harjola [2], and others [19, 71]:

Table 4.1 Causes of RV-F and differential aetiological and diagnostic considerations

• Acute left heart failure [1, 14, 71, 72]	• Right ventricular ischemia/infarction [70, 73, 74]
• Acute pulmonary embolism [1, 2, 31]	• Acute respiratory failure [33] due to
	– Acute exacerbations of chronic broncho-pulmonary diseases with and without hypoxic/hypercapnic pulmonary vasoconstriction [75–77]
	– Hypoxia to varies reasons like obesity hypoventilation syndrome [78] or obstructive sleep apnoea [79, 80]
	– ARDS [53, 81, 82]
• Mechanical ventilation [1, 83, 84]	
• Sepsis [9, 85–88]	• Pericardial disease (tamponade)
• Cardiomyopathies	• Valvulopathies
• Arrhythmias	• Congential heart disease
• Pulmonary hypertension due to hematological, e.g. sickle cell disease, infectious, e.g. HIV, and miscellaneous systemic and vascular diseases e.g. sarcoidosis	

4.3 Physiology and Pathophysiology

4.3.1 General Physiological and Pathophysiological Issues

The main functions the right heart has to comply with are to accommodate the entire venous return and to transmit the blood into the pulmonary circulation for gas exchange [89, 90], thereby maintaining low right atrial (RA) and pulmonary pressures and optimizing varying amounts of venous return [15, 17, 83]. In order to do so, the right ventricle function has to integrate preload, afterload, contractility, pericardial constraint, interaction with the left ventricle, and cardiac rhythm [1, 3, 91].

The pressure difference between the pressure in the periphery (systemic filling pressure) and the right atrium (central venous pressure) determines the amount of venous return and ranges usually between 7 and 10 mmHg at which the RA-P is normally 0 mmHg [92]. In healthy persons, only a very low isovolumetric contraction pressure is needed to be generated by the RV [93, 94] in order to eject blood into the low-resistance, high-compliance and low-impedance pulmonary vessel system [95–97]. Thus, in healthy individuals with notable physiological LA filling pressures and pulmonary vascular resistance, a negligible RV contractile contribution is required to allocate adequate CO [17]: Simply the negative pleural pressures physiologically produced by normal breathing promote blood flow through the pulmonary circulation [97].

Indeed, the anatomical conditions of the right ventricle (thin-walled, crescent shaped in a cross sectional view, but triangular in a side view [98], and particularly the direct geometry of the RV) allow not only to adapt to large increases in right ventricular filling volumes due to high venous return [99, 100], but also, despite

often dramatic varying amounts of venous return, to definitely maintain a more or less constant CO [101, 102]. This crescent shape with a concave free wall and a convex septum [99] means that the RV has a markedly lower volume to surface ratio in comparison to the left ventricle and thus a much higher compliance [103]. However, these anatomical features and physiological properties of both the RV (high compliance, increasing not declining wall stress during systole [17, 104]) and the pulmonary vascular tree (low-resistance, high-compliance and low-impedance), predispose the RV to significant chamber dilatation in case of acute after-loading [19, 103, 105–107], and imply that the right chamber can very poorly (even worse than the LV [108])—see Fig. 4.1—adapt to acute increases in PA input impedance [16, 19, 20, 109]. As such, in case RV afterload acutely increases, the until then healthy RV is found to be unable to generate mean pulmonary artery pressures of more than 40 mmHg [110].

Acutely elevated pulmonary pressure is the most frequent cause of acute right heart failure [14, 27–29]. It is predominantly an increased pulmonary vascular resistance (PVR) which leads to PH in any setting [16]. PH generally results from increases in pulmonary vascular resistance, pulmonary blood flow, pulmonary venous pressure, or a combination of these features [6, 111, 112]. Vasoconstriction (e.g. hypoxic alveolar vasoconstriction via direct pressor effects or due to mediators), thrombosis, and vascular remodelling may all cause PH [113], and are generally associated with increases in PVR [3, 15, 27, 41, 60, 114–117]. An elevated PVR indicates functional and/or structural pulmonary vasculopathy [115, 118–121].

Elevated left heart filling pressures, a hallmark of (left-sided) heart failure [111, 122], are recognized to cause pulmonary venous hypertension (PvH) [123] irrespective of LV-EF [124]. This is attributed to a backward, downstream transmission of the elevated left-sided filling pressures, precipitating a rise in pulmonary venous pressure [6, 115, 118, 122]. An elevation of the pulmonary venous pressure directly elicits higher intrapulmonary vascular pressures, particularly of the PAP, and a decrease in pulmonary vascular

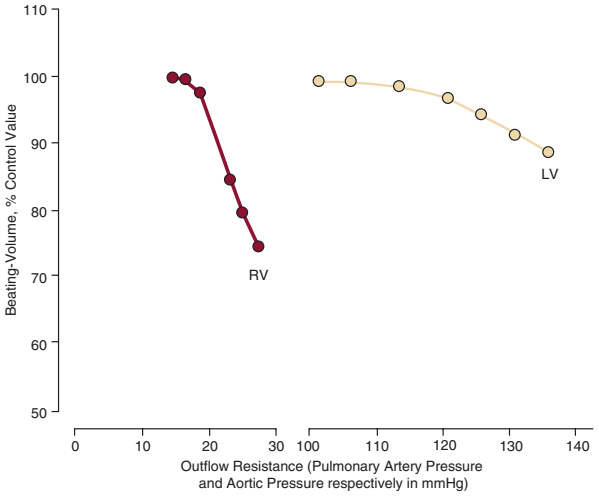


Fig. 4.1 Illustrates the high sensitivity to afterload of both ventricles. Any increase in afterload affects the systolic performance, indicated by stroke volume, of the *right ventricle* markedly stronger than the *left ventricle*. The reduction in stroke volume is considerably higher in RV compared to LV for any increase in ventricular load imposed. Adapted from Greyson CR. The right ventricle and pulmonary circulation: basic concepts. Rev Esp Cardiol. 2010;63: 81–95 [17] with permission

compliance, hence stiffens the pulmonary artery(ies) [25, 98, 100]. Consecutively, RV afterload and RV systolic wall stress increase, potentially compromising RV function [25]. However, in early stages, PvH is not found to exhibit abnormal high pulmonary vascular resistance and thus does not cause pulmonary vasculopathy [96, 125].

As such, LHD: ↑ in LVEDP → ↑ LA-P → ↑ downstream pulmonary venous p → ↑ pulmonary p and ↓ pulmonary vascular compliance (respective PA stiffening) → ↑ PAP [14, 25, 98, 125].

Finally, high flow conditions may be associated with PH, but show a normal PVR [120, 126].

Accordingly, although in most circumstances enhancements of the pulmonary artery pressure, PAP, are related to an increase in PVR, an increase in pulmonary pressures, namely mean PAP, and thus PH is not inevitably coupled with an increase in PVR [25, 125]. PH simply stands for elevated pressures in the pulmonary circulation rather than explicitly indicating pulmonary vascular alterations which are reflected by an elevated PVR [112, 118, 121]. However, PH may lead to increased PVR and to decreased pulmonary artery compliance [127]. A reduction in vascular compliance means an increase in vascular stiffness, which will cause a rise in vascular load on the upstream ventricle [96, 128–130]. RV-afterload is determined by the dynamic interplay between (1) pulmonary vascular resistance, (2) pulmonary vessel compliance, and (3) wave reflections [127], where PVR reflects the resistive RV-load component, and vascular compliance the pulsatile one [7]). Hence, PA stiffening also increases RV work load [127].

If PH is accompanied by a pathologic increase in PVR, adverse prognostic implications apply [131, 132].[2]

Anyhow, pathologically elevated pulmonary pressures, defined as a mean pulmonary arterial pressure **≥25 mmHg at rest**, measured invasively by right heart catheterization [71, 126, 134], will impose an un-physiological pressure load (largely due to altered vascular properties) on the RV, provoking adaptive measures to face this burden potentially leading to right heart failure [14, 19, 20, 22, 23].

Physiologically, beat-to-beat variations in RV preload or afterload are addressed by adaption in right chamber dimension, applying Frank-Starling's law of the heart: Abrupt, beat to-beat, increases in pre- or afterload are met with a mild rise in RV size, the so-called *heterometric* dimension adaptation (a diastolic effect), known as and described by Frank and Starling's law of the heart [3, 135]. However, within a couple of minutes, starting already 20–30 s after the **heterometric adaption** applies, an increase in RV contractility, and as such a systolic adaptive effect, will firstly supplement but quickly completely replace the initial heterometric adjustment [3, 135]. This so-called **homeometric** reply, which does not require any pre-existing muscle or cellular hypertrophy [136], is referred to as "Anrep's law of the heart

[2] Since an elevation of the mean PAP is coupled to a decrease in systolic function [133], and RV afterload literally determines RV systolic function [14], PAP reflects RV afterload and an elevated mean PAP indicates an increased RV afterload [14].

[137]. It has been G von Anrep who demonstrated more than 100 years ago an intrinsically mediated increase in LV contractility in response to a raised LV afterload [137]. This reaction affecting the strength of contraction occurs independent of end-diastolic fibre length (the Frank–Starling–mechanism relies upon fibre stretch) or other extrinsic issues, like neuro-endocrine stimulation [138].

It has been challenged that the homeometric autoregulatory effect applies in vivo in the setting of a rapidly raised afterload since this mechanism has originally been demonstrated "only" in isolated muscle strips [139]. However, homeometric adaptation to afterload has been reported to apply in case the RV is exposed to pulmonary constriction if coronary perfusion is held constant [140]. Furthermore, some recent evidence even suggests that homeometric autoregulation may be the primary mechanism launched already for "initial" response and adaptation to brisk RV pressure load [141, 142].

However, physiologically, homeometric adaption replaces the heterometric adjustment after a few minutes as indicated by the chamber dimension, which returns to baseline after a few minutes, demonstrating the predominant role of homeometric (that is without chamber dilation), systolic function adaption in both acutely increased pre- and/or afterload [136].

Anyhow, up to 40% of RV systolic function, that means 2/3 of pressure and 80% of flow generation under healthy terms [143, 144], is derived from the LV systolic performance, largely from the septal oblique/helical orientated muscle fibre contraction, a feature referred to as *systolic ventricular interdependence* [14, 145, 146]. Of special note, these septal fibres, originating in the LV, reach up to the right ventricular outflow tract [147]. These bundles of muscle fibres functionally link RV and LV together and directly transmit contractile force generated by the LV to the RV [147, 148].

Oblique orientated myocardial muscle fibres are demonstrated to develop clearly more contractile power than transverse orientated ones [149], the latter typically found in the right ventricle [14]. RV dilatation, due to volume loading, increasing preload, or particularly due RV filling overload, as typically resulting from tricuspid regurgitation/insufficiency following RV dilatation, leads to a change in septal muscle fibre orientation, and the more transverse configuration implies loss of muscle strength [14]. This phenomenon is especially evident in LV systolic dysfunction where the naturally oblique orientated muscle fibres of the LV, and thus of the septum, take a gradually more and more transverse position, losing part of their power generation capacity, consecutively affecting RV systolic function as well [14]. On the other hand, an enhancement of the LV systolic function in the setting of a compromised RV function displays beneficial effects on RV performance [150].

Any **rapid rise in pulmonary pressure** (increase in PA input impedance) due to altered pulmonary vascular load, after-loading the right ventricle and/or a **loss of RV contractility** (altered myocardial properties, e.g. acute myocardial ischemia) causes an immediate increase in RV size, **RV dilation**, and concomitantly a rise in RV-end-diastolic filling volume (RVEDV) **ensues** [1, 3, 7, 16, 105–107]. However, RV adaption to PH is acknowledged to be decisively depend on the ventricle's ability to adjust contractility in order to match the increased afterload the ventricle is

facing in case of increased pulmonary vascular load [151, 152]. Accordingly, if the homeometric adaption is too short or even fails and cannot (fully) compensate for altered RV loading conditions, and/or if systolic RV (and/or LV) capabilities (contractile power) are suddenly lost (e.g. due to acute myocardial ischemia/infarction) [70, 74, 153, 154], heterometric measures persist or apply in addition, potentially able to meet (by applying the effects of the Frank-Starling-mechanism) the challenge imposed, although certainly at the cost of considerably increased RV dimensions (↑↑ RVEDV) [138, 155, 156]. This increase in RV size and filling is inevitably attended by increased right ventricular filling pressures (RVEDP) [23, 157–159].

If the RV dilates, it becomes a more cylindrical shape and thus the efficacy of the Frank-Starling-mechanism increases [141, 142]. However, under those circumstances, RV contractility is compromised (e.g. septal muscle fibre orientation, RV free wall performance) [14, 17, 133, 160], RV-EF impaired [31, 84, 161, 162], and RV pump failure and even cardiogenic shock may promptly ensue [89] if the compensatory mechanisms (most notably the increase in RV contractility as the predominant and physiological adaptive feature and alternative to match and face the elevated pressure load [135, 151, 152]) are insufficient and afterload mismatch persists [7]. As such, RV afterload has to be acknowledged as the major determinant of RV systolic function, and RV failure is commonly the result of increased RV afterload [14]. RV systolic function is much more than LV performance literally and crucially dependent on afterload [19, 163] (see Fig. 4.1).

Tricuspid regurgitation following RV enlargement may compound the conditions [1, 7], although they may also disclose a path to reduce RV afterload by offering a less restrictive way for the blood stream [164–166]. Furthermore, **diastolic ventricular interaction** (DVI) applies compromising left ventricular filling and thereby worsens global cardiac function and systemic circulation even more [83, 167, 168]. In any way, ventricular interactions (the ventricles are even more directly intertwined in malady [101]) play an important and critical role in RV-F pathobiology by taking a crucial impact on left heart and subsequently systemic cardiovascular function [145]. DVI, mediated by the pericardium and the interventricular septum (IVS) [1–3]), restricts left ventricular filling due to a leftward shift of the IVS in the presence of elevated pericardial constraint [1, 167, 169], thereby changing LV geometry [1, 170] resulting in impaired LV-contractility [3, 83]. Furthermore, due to the enhanced pericardial constraint resulting from RV-dilation, LV distensibility decreases, consecutively (as well) impeding LV filling, ultimately diminishing LV-SV [1, 3]. Subsequently, the compromised LV contractility may display considerable deleterious effects on RV systolic performance, systolic ventricular interaction, as about 1/3 (20–40%) of systolic RV pressure generation and up to 80% of RV flow generation [143, 144] results from LV contraction [145, 146, 171].

It is exactly **ventriculo-arterial coupling** which specifically refers to the relationship between ventricular contractility and afterload, in this case between the right ventricle and the pulmonary vascular tree [7]. As such, assessment of RV-PA coupling is a physiologic approach to this interrelated system [172]. **Disrupted RV-PA-coupling** is considered to contribute to progressive RV-malfunction [17]. RV-PA-uncoupling ensues as RV contractility does not match afterload [107, 173,

174]. Altered coupling may affect the efficiency of power transmission and thus dilutes blood flow output from RV to and within the pulmonary vessels, diminishing LV preload [22]. Indeed, recent studies report a reduced RV-PA coupling efficiency in different forms of PH [151, 175, 176]. In experimental tachycardiomyopathy RV-PA-uncoupling has been observed related to lack of a sufficient adaptive increase in RV contractility [177]. In a sepsis model with endotoxic-induced elevated PVR, initial preservation of RV-PA-coupling could not be maintained as the incipiently adaption in contractility did not persist [178]. On the other hand, several studies demonstrated preserved RV-PA-coupling in patients and animals with acute hypoxia related pulmonary vascular constriction (displaying acute RV pressure load), when RV contractility increased, matching the pulmonary artery input impedance [173, 174, 179, 180]. Accordingly, adaption of RV systolic function to increased pulmonary vascular load, causing PH, is necessary to maintain proper RV-PA-coupling. Uncoupling occurs in case of inflammation, long-lasting PH and left heart failure resulting in deficient RV contractile adaption (systolic ventricular interaction) [3].

The results consistently confirm the crucial role of homeometric adaption (incremental contractility) in case the RV is faced with a rapid or substantially raised afterload [151, 152]. RV-PA uncoupling is related to the onset of RV-failure and can be seen as an early sign of maladaption [181]. Deterioration of RV-PA coupling is associated with increased RVEDV [135], while the absence of increased RVEDV in the presence of raised pulmonary pressure indicates sufficient coupling [135].

As the hemodynamic aspects of the pathobiology of RV-F are decisively characterized by the alterations in RV pressures and volumes and the interventricular interactions it is worth and necessary to further discuss in depth v**olumes and pressures issues:**

Both, **brisk** increases in **RV afterload** (e.g. a sudden rise in pulmonary pressures inducing PH, but substantial and/or prolonged enhancements in RV vascular loading conditions as well) and **rapid and/or particularly considerable** boosts in **RV preload** (e.g. quick volume loading) [7, 98] lead to a marked RV-dilation [1, 3, 7, 19, 23, 31, 106, 107] with increased right ventricular filling volumes (RVEDVs) [1, 3, 7, 19, 23, 31, 106, 107]. An increase in ventricular filling volume is in any case attended by a rise in filling pressure: “Acute increases in filling volumes yield higher filling pressures” [157]-a parallel upward shift of the PV-relation (see Chap. 1, Sect. 1.10). Acute volume loading of the RV or in case the RV dilates due to (abruptly) augmented RV afterload, both changes are enhancing RVEDV, and will thereby exert stress on the acutely literally indispensable pericardium which consecutively results in increased pericardial pressure and a noticeable parallel upward shift of the PV-relation, indicating that a higher absolute RV filling pressure is necessary to achieve a given RV filling volume [182]. As such, the increase in afterload itself exerts some impact on the position (parallel and upward) of the PV-relation. Hence, changes in vascular loading conditions result in parallel shifts of the diastolic PV-relation [157, 183] indicating alterations in pericardial and filling pressures (see chapter 1, section 1.10, extracardiac forces). Moreover, pericardial constraint will affect the thin-walled RV more than the LV, subsequently the increase in RVEDP is disproportionally higher than that in LVEDP [168, 184]. However, increasing

pericardial constraint, as with increasing RV enlargement, results in less RV free wall stretch, limiting the effect of the Frank-Starling-mechanism [17].

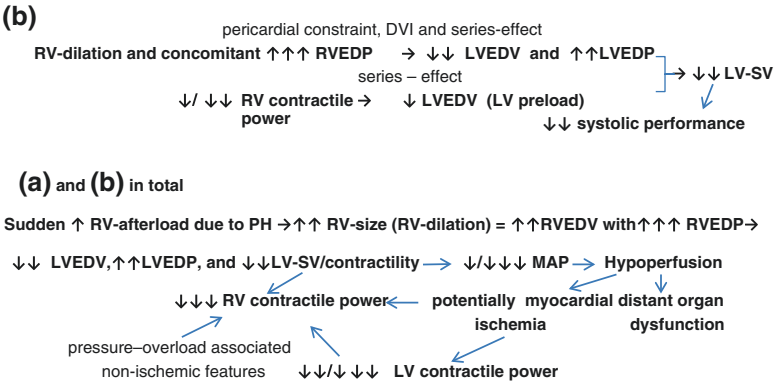
Furthermore, the markedly enlarged RV size is accompanied by altered diastolic RV properties, shifting the RV diastolic pressure-volume-relation to a steeper proportion of the curve (leftward and upward shift) as changes in systolic load affect diastolic properties as well [17, 156, 185–189]. This denotes RV stiffening, and as such, PH stiffens the RV [190]. RV stiffness dilutes the RV free wall stretch, consecutively blunting the Frank-Starling-effect [17], increasing RVEDPs and central venous pressures [1, 83]. RV diastolic dysfunction and elevated RV filling pressures induce renal fluid retention (arginine vasopressin effect) [1]. Thus, several effects are contributing to the quite substantial increase in RVEDP when suddenly after loading the right ventricle.

(a) **Sudden ↑ RV-afterload due to PH → ↑ RV-size (RV-dilation) = ↑ RVEDV → ↑↑↑ RVEDP**

The increase in RV-size has, due to the acutely literally nondistensible pericardium [191, 192], an impact on the LV [1, 2]:

1. LVEDP will firstly increase due to the increase in pericardial constraint, as described.
2. RV-enlargement leads, due to the restrictive properties (actually literally not distensible) of the pericardium and the limited space within the pericardial sack, to a competition of the two chambers for space resulting in a reduction in LV-preload [135]. This reduces LV-filling, **a series effect** as the two chambers are arranged in a row [169, 193, 194].
3. The compromised RV systolic properties ejecting a lesser extent of blood into the pulmonary circulation [14, 17, 133, 160] and RV-PA-uncoupling losing further energy, resulting in a loss of flow output [107, 173, 174] are both contributing to the shorted LV preload. Both issues may be interpret within the scope of and referred to as **series effects**.
4. Due to largely diastolic ventricular interaction, mediated by the shared structures of the ventricles (pericardium and the interventricular septum (IVS) [159, 191, 192]), the IVS will be shifted in the presence of increased pericardial constraint towards the LV cavity thereby changing LV geometry [1], compressing the left chamber subsequently impairing LV filling, and leading to impaired LV contraction [1–3]—and consecutively also to diluted RV contractile power. DVI, coming in general and particularly into effect with increasing RVEDP [72, 169], essentially contributes to acute right heart failure pathobiology and makes a crucial hemodynamic impact on right and left heart and subsequently systemic cardiovascular function [1, 145, 169].
5. LV diastolic properties are altered, largely an effect of DVI [195] and due to the increasing RV size and RVEDP, causing LV diastolic dysfunction: The LV becomes stiffer (reduced LV compliance) [185, 195–199], resulting in an increase in LVEDP (leftward and upward shift of the LV PV-relation) and may cause a reduction of LV-filling and consecutively diluted LV-SV [1, 3, 185, 197, 198].

Hence in summary, LV size will substantially decline (LVEDV ↓↓) while LVEDP will increase (LVEDP ↑↑)[3] and LV systolic capabilities will be diminished, as depicted by the following causal chain.



Noteworthy, RV accommodates much better and quicker to changes in *preload* (e.g. volume load) compared to the very poor tolerance of *sudden* (and/or substantial and/or prolonged) increases in afterload (pressure load) [19, 20, 100, 200]. In contrast to pressure overload, the right ventricle tolerates primary volume overload conditions over a long period quite well as evidenced by the clinical courses of patients suffering from intracardiac shunts (e.g. Eisenmenger's syndrome), and tricuspid or pulmonary regurgitation [15, 17]. This may be due to:

(I) RV volume overload does not relevantly impair contractile dysfunction [57],
(II) The RV is preconditioned to tolerate volume loading in the foetal period, and in case of congenital abnormalities, foetal right ventricular phenotype properties may persist [201, 202]. Furthermore, patients with Eisenmenger's syndrome decompensate if pulmonary vasculopathy and thus an afterload burden develop or shunt reverses [15].

Insofar, even acute volume loading alone will not induce predominantly acute right heart failure in otherwise reasonably normal hemodynamic conditions. However, *acute and rapid or extensive volume loading*, in particular over a certain limit [198] is reported to potentially cause *transient RV-dilation* in special circumstances [199, 203]. Volume loading should always be referred to as "pre-loading" the ventricle: In this respect, pre-load may be defined as the combination of all factors contributing to passive end-diastolic ventricular wall stress [7]. RV preload is determined by volume and pressure prior to contraction. Respiratory alterations affect the RV filling and the pericardium constrains the thinner, low-pressure RV more than the high-pressure LV [98].

[3] Again a hint that LVEDP may not represent LVEDV, since increasing LVEDP may not translate and indicate increasing filling volume.

Aside the more *specific hemodynamic factors and features*, further *issues* are demonstrated to significantly *influence* and *contribute to the pathobiology of acute right heart failure*:

A markedly enhanced activation of the **neuro-endocrine and the immunologic/inflammatory-endothelial cascades** displays a variety of functional alterations, particularly endothelial dysfunction (ED): Adrenaline and noradrenaline, angiotensin II (the most bioactive representative of the renin-angiotensin-aldosteron-system), cytokines, endothelin-1 in the presence of an altered NO metabolism and availability (a constellation typically indicative for ED), and natriuretic peptides (with their potential to counterbalance to some degree the effects of the aforementioned agents), are released and secreted, offering compensatory input, and as such are involved in and contributing to the pathophysiology of acute RV-D/RV-F [1, 83, 91, 204–211]. The release and discharge of adrenergic substances with positive inotropic and chronotropic effects may facilitate the contractile efforts [106], however, net contractility may be acutely even reduced [107].

These compensatory mechanisms applied with their predominantly pulmonary and systemic vasoconstrictive properties improve pulmonary blood flow and may temporarily stabilize the pulmonary and systemic hemodynamics [212], but are gradually maladaptive [27, 213, 214]. However, the increase in RV size and pressures lead to increased wall tension and cardiomyocyte stretch [106], consecutively the coronary perfusion is affected and a higher oxygen demand and consumption is displayed, potentially leading to **RV ischemia** [107, 215], at least if no effective reduction of RV afterload can be achieved [216]. In case of acute pulmonary embolism, causally responsible for the abrupt rise in afterload, RV ischemia is demonstrated to be of pathophysiological significance in the acute phase [217, 218]. Elevated RVEDPs and considerably diminished blood pressure not matching the metabolic demands may cause RV ischemia and compromised RV contractility [219]. Nevertheless, study results are inconsistent in regard to what degree ischemia is responsible for and contributes to RV contractile malfunction [220–222]. Moreover, myocardial stunning (even in case of RV-AMI) rather than true cardiomyocyte loss is suggested to underlie progressive contractile impairment [195].

Furthermore, there is some evidence suggesting that "just" **pressure overload itself may down-regulate RV contractility** [22, 223, 224]. In the absence of ischemia, activation of intracellular paths affecting the contraction sequence and procedure [225, 226], activation of apoptosis [227, 228] or even disturbed NO-pathways due to endothelial dysfunction may be involved.

As RV contraction will be prolonged (since myocytes prolong under stress contraction time action potential duration [7]) in case of RV strain, blood is still ejected into the pulmonary vessel system while the left ventricle already resides in diastole, the interventricular septum shifts to the left side in the late systole [229, 230] restricting and reducing LV-space [106, 107, 216]. This **desynchronization of both ventricles** will aggravate RV malfunction [7]. Dys-synchrony is reported to arise early on during the adaptive process, intended to support systolic function of the RV, however, this implies that LV-filling is blunted already early in the course [2].

If the hemodynamic compromise cannot be stabilized, as both, the (supplementary) heterometric efforts and especially the RV contractile power (homeometric adaption) are together not able to generate the performance necessary to match the acute increase in PA-input impedance (and/or the exposure of the RV to acute afterload mismatch persists), acute RV failure applies and may rapidly end up catastrophic with a circulatory collapse [95, 96, 135]. The progressive RV-dilatation and the accompanying, considerably elevated (and further rising) right ventricular filling pressure, reflecting and indicating RV-dysfunction/failure [25], may induce a vicious cycle ending up in circulatory collapse [135]. Even a mild acute elevation in pulmonary pressure eliciting mild PH may cause a substantial drop in RV-SV [231, 232]. Blunted RV-SV and thus reduced LV preload delivery (due to diminished SV generated by the weak RV [169, 194, 233] and due to RV-PA-uncoupling [107], both effects may be referred as to series-effects [169, 194, 233]), the excessive LV compression (largely due to DVI [135]), and the LV diastolic dysfunction (and therefore impeded LV distensibility) [81, 234], result in a marked LV underfilling [2, 3, 83] and a considerably impaired LV systolic function [2, 3, 83, 197, 198, 235].The combination of LV underfilling and compromised LV systolic function may inevitably precipitate hypotension and systemic hypoperfusion (adapted from Zochios, [93]). This will result in even less contractile support for the RV, while hypotension potentially dilutes right and left coronary perfusion contributing to circulatory collapse [107, 216, 236]. However, as discussed above, other, non-ischemic issues may contribute to the now progressively deteriorating RV systolic properties [22, 223, 224, 226, 228]. Though, "RV failure begets RV failure" leading into a progressive downward spiral of worsening myocardial dysfunction and incipient shock [93].

Once systemic pressure, e.g. MAP, begins to fall, hemodynamic collapse will ensue rapidly. As depicted in Fig. 4.2, a work by Guyton [89], the hemodynamic range within the disastrous malady course develops may be very narrow. Patients, of course with symptoms and signs of RV-F, although appearing to be in a clinically reasonable and stable condition with acceptable BP, but with no obvious evidence of relevant hypoperfusion, and only mild to moderately elevated CVP, may decompensate immediately and unexpected: Compensatory mechanisms may be already exhausted, but this is not recognized as clinical and hemodynamic features are still tolerable. Furthermore, no additional features (such as ischemia), typically aggravating the malady, may be observable. Nevertheless, issues including non-ischemic related paths [225, 227, 228], stunning myocardium [195] or RV-pressure overload associated, the contractile forces down-regulating mechanisms [22, 223, 237], and, hopefully not, therapeutic measures such as very cautious volume application (assuming a still available preload reserve in order to ameliorate rather than to destabilize the situation) may be the trigger of the disaster by initiating MAP to fall. Insofar, circulatory collapse may insert abrupt and quite unexpected in otherwise hemodynamically stable appearing patients.

In case of a gradual increase in PAP and/or PVR as usual in LHD, the so-called homeometric contractility adapation to afterload according to Anrep's law [137]

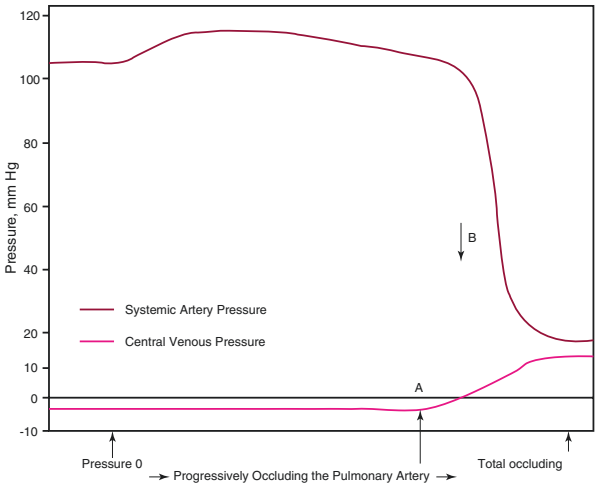


Fig. 4.2 At some point (*A*), RAP/CVP starts to increase with increasing pulmonary pressure/increasing RV-afterload. The increase in filling pressure allows for recruitment of contractile reserve via Frank-Starling-mechanism (heterometric adaption). However, this compensatory action of this crucially afterload-dependent right ventricle will soon reach a limit (point *B*), where systemic pressure is going to abruptly drop and circulatory collapse applies. As there is only a very small range between onset of CVP/ RVEDP increase and collapse (see difference between point *A* and *B*), caution is advised (e.g. to apply fluids), once CVP is elevated. There is no indicator notifying imminent circulatory catastrophe. Modified from Guyton AC. Circ Res 1954;2: 326–332 [89]. With permission

may ensue [135]. The homeometric adaption and remodelling is characterized by an increase in ventricular systolic function (e.g. contractility) without chamber dilatation in order to meet the load the ventricle is facing [138]: The right ventricle adapts to the increased afterload by increasing its wall thickness and contractility [7]. Homeometric adaption is shown to be the predominant feature of RV to face and to adapt to increased afterload and to ensure preserved RV-PA-coupling [3, 135].

Indeed, in case of gradual increases of pulmonary pressures or due to mild/moderately but chronically increased pulmonary pressures, RV develops a hypertrophy and thus concomitantly adapts [96, 151]. The initially enlarged RV end-diastolic volume triggers the development of RV hypertrophy enhancing contractile capabilities and thus adapts to the new challenge, maintaining RV-SV by increased contractile force [216]. In animal models, hypertrophy is recognized already 96 h after the onset of increased afterload [238]. This is principally confirmed by studies in humans suffering from ARDS where already after 2 days of PH (ARDS and mechanical ventilation cause an increase in transpulmonary pressure which correlates with the magnitude of RV afterload [95]), a moderate thickness of the free RV wall could be demonstrated [31]. Hypertrophy will reduce wall tension (LaPlace), and the interventricular septum, initially bulging to the left (D-shaping), flattens [216]. Notably, although the RV elastance may rise two-to three-fold during the acute phase, no acute systolic RV dysfunction

has been reported [141, 142]—accordingly the enhanced RV–elastance indicates true augmentation in contractility. Moreover, some degree of RV-dilation establishing heterometric, dimensional adaptation via Frank-Starling-mechanism will be implemented as well [2].

However, if the load rises further, becoming too high for a too long period, or if these compensatory mechanisms are insufficient to match the load imposed, RV-PA uncoupling associated with (further) increased RVEDV occurs [135, 138], a heterometric adaptive mechanism, indicating RV dysfunction [7], or even RV-failure [3, 135]. Severe inflammatory conditions (e.g. septicaemia), long-term increase in PVR or advanced heart failure are disorders predisposed for RV-PA uncoupling and RV-dysfunction [3, 135]. Furthermore, even the described remodelling may, after many years of compensation, progress to chamber dilatation, consecutive tricuspid insufficiency, and frank RV-failure [172]. It may be speculated that pressure overload downregulates RV contractility [22, 223, 224] and thus later in the course, heterometric compensation will become necessary due to decelerating contractility. This is in line with recent study results, showing that patients with long-standing volume overload conditions, although compensated and most often only marginally symptomatic over many years, nevertheless carry an increased risk for cardiac morbidity and mortality [239, 240]. Other precipitating factors discussed include *ischemia*, as RV hypertrophy potentially decreases RV subendocardial perfusion, while the arising *RV-dilatation* entails increased wall stress and thus a higher oxygen demand [96] and *neurohormonal/inflammatory issues* [241–245].

Acute and chronic RV failure, being attended by enhanced neurohormonal discharge and sodium and water retention, is thereby consecutively accompanied by elevated CVPs [1, 24] which may exert deleterious effects: Increased CVP impairs lung lymphatic drainage, leading to interstitial pulmonary fluid accumulation causing shortened lung compliance, impaired gas exchange, and promotes the development of pleural effusion [5, 246]. Renal venous pressure is subsequently increased and provokes cardiorenal syndrome [5, 247, 248]. Hepatic and intestinal congestion occurs facilitating cholestasis and ascites development [1, 5], impairs gut absorption and may allow for translocation of gut microbes into the blood stream [96].

4.3.1.1 To Sum Up (see Fig. 4.3)

Acute right heart failure is a complex, heterogeneous clinical syndrome of miscellaneous aetiologies [1, 2, 93, 96]. LHD is by far the most common reason causing acute RV-F [27, 28]. Any acute (rapid) increase in pulmonary vascular pressures imposing a (additional) load on the RV, precipitating an afterload mismatch, may provoke acute RV-F [14, 27–29, 95, 96, 135], and even mild increases in PAP are reported to potentially trigger acute right heart failure [231, 232].

Acute RV failure is characterized by RV dilatation [1, 3, 7, 19, 105–107], generally attended by increased right ventricular filling pressures [157–159, 186], and impaired RV contractile properties [2, 3, 14, 17, 160, 197] in the presence of clinical signs, foremost dyspnoea and fatigue, as well usually fluid accumulation and edema

formation, of RV dysfunction, furthermore evidenced by elevated CVP (RA-P/RVEDP) [1–3, 5, 7, 24, 25, 246, 247], often accompanied by organ, particularly renal, dysfunction [5, 24, 123, 246–248].

Acute RV-F arises if the load imposed on the RV, generally after-loading (but pre-loading principally may affect the RV as well) the right ventricle, cannot be met and counterbalanced by an appropriate increase in RV contractile power [95, 96, 135], referred to as homeometric adaption [137, 138]. Deficient RV systolic performance may be subject to impaired RV and/or LV contractile capabilities [3, 7, 16, 83, 105, 106, 143, 144], but is usually attributed to the brisk (and/or substantial) rise in afterload [1, 7, 14, 15] hitting a ventricle which is anatomically and functionally not designed and not evolved to deal with high pressure loads [19, 105–107, 200] and whose performance is literally crucially dependent on afterload [19, 163]. Adaption to pressure load can only succeed if the ventricle is able to strengthen its contractile capabilities [151, 152].

Neuro-endocrine and inflammatory-endothelial measures and replies support and govern in a sense the compensatory activities [1, 83, 91, 204, 206–211], but may turn to be maladaptive over time (e.g. fluid retention) [213, 214].

Anyway, in the case the homeometric adaptive efforts are too little or fail, substantial RV enlargement, accompanied by elevated RVEDP, immediately ensues [1, 3, 7, 16, 19, 105–107, 200]. This enlargement is an attempt to improve RV performance by applying the Frank-Starling-mechanism, facilitating blood ejection, output and blood flow [172, 173]. However, this approach has transpired to induce a series of potentially deleterious, although basically compensatory, measures and reactions, which are largely related to ventricular interactions [14, 72, 107, 145, 167–169, 173, 174]. These arrangements will substantially affect the LV resulting in diminished LV size, and LV diastolic and LV systolic malfunction [2, 3, 81, 83, 156, 196–199, 234]. Subsequently, hypotension, a jeopardized systemic circulation with lurking organ and tissue hypoperfusion and an even more compromised RV function are to follow, potentially ending up in circulatory collapse and shock [93, 95, 96, 135].

Of note, some correlations, relationships, interrelations and causative interconnections
(a) PVR is calculated by the ratio of the transpulmonary pressure to the transpulmonary flow [249]:
$PVR = PAP_{mean}/SV \times HR (SV \times HR = CO)$
(b) (Sudden) ↑ in pressure (volume) load of the RV causing PH [21, 32, 33, 59] →
↑RV - afterload/RV outflow impedance [21–23, 31, 161]
↓
• RV-dilatation (↑ RVEDV/RVEDD) [3, 7, 12, 21, 23, 103, 105–107, 161] (acute and rapid/or extensive volume loading, in particular over a certain limit [198] primarily causes RV-dilatation [156, 199, 203]),
• ↓ RV-EF [21, 31, 133, 161],
• ↓ RV contractility [22, 133, 160],
• ↑ Heart Rate (often the first attempt to compensate acute RV pressure and/or volume load [250])

4.3.2 Special Pathophysiological Issues

4.3.2.1 Diastolic Ventricular Interaction

The global hemodynamic consequences of RV-D are dependent on the critical interaction between the two ventricles [251, 252]. Under physiological conditions we will find similar end-diastolic volumes in RV and LV [31, 253]. The heart chambers are enclosed by the pericardium and share the interventricular septum and, as such, ventricular interactions occur [171, 254, 255].

"Diastolic ventricular interaction (DVI) refers to competition for space within the non-distensible pericardial sack when RV dilates" [135]. Changes (particularly sudden changes [168, 171, 254, 256]) in the end-diastolic volume (and intraventricular pressure) of one ventricle will directly influence the volume and intraventricular pressure and thus compliance [256] of the other ventricle [168, 169, 254].

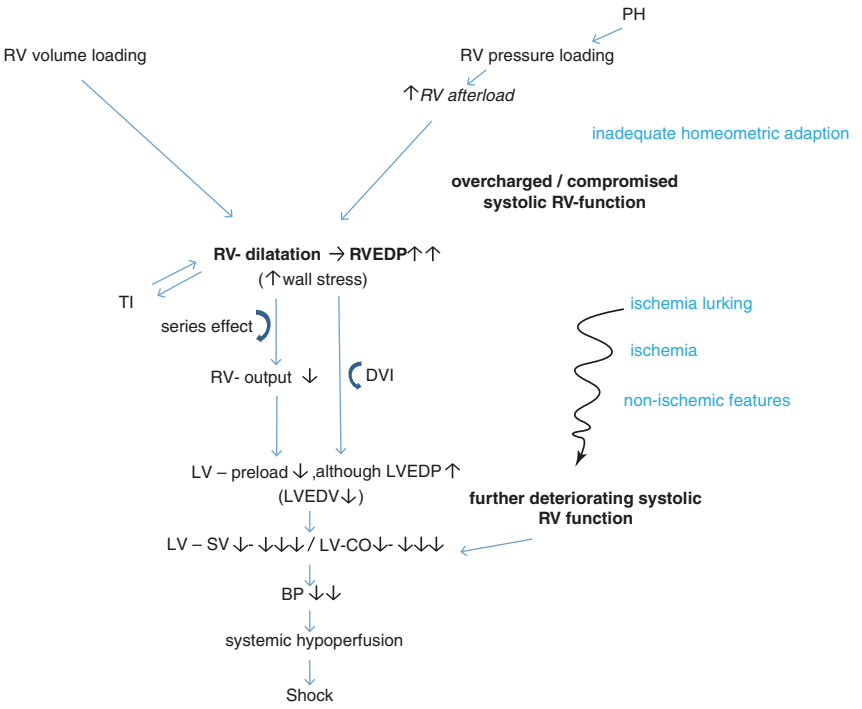
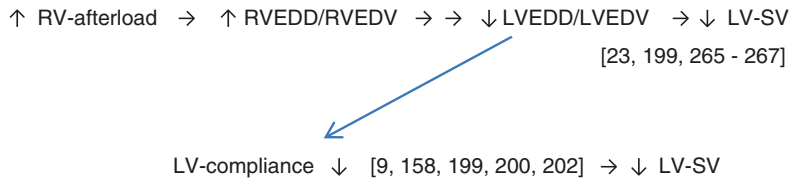


Fig. 4.3 Overview of the pathophysiology of right heart decompensation and failure: the diagram summarizes the most relevant pathobiological and pathophysiological features and sequences of acute right heart failure. It is based on publications by Price [16], Schwartz [14], Naeije [3], Vonk-Noordergraaf [7], Teichman SCCM 34th congress 15–19th Jan 2005, and Kucher Acute Cardiac Care Meeting of the Esc Prague 23rd Oct 2006. *TI* tricuspid insufficiency, *BP* blood pressure, *DVI* diastolic ventricular interaction, *PH* pulmonary hypertension

These diastolic interactions are mediated via the shared structures of the ventricles, the interventricular septum and the pericardium with its constraining effects on ventricular filling through poor distensibility [159, 191, 192]. Thus, an increase in the cross-sectional area of one ventricle, i.e. due to volume loading or enlargement, necessarily reduces the area of the opposite ventricle (resulting in less filling volume), and may simultaneously affect the pericardial pressure (PP) [72, 159]. The total cardiac volume (filling) remains unchanged [159, 257]. Therefore the pericardium plays a key role in the loading conditions [157, 258] and this is particularly seen in the acute situation.

The increase in RVEDV, which is accompanied by a rise in RVEDP and PP, shifts the interventricular septum towards the LV cavity. This occurs subject to the restrictions imposed by the acutely non distensible pericardium on the RV as the RV-cavity size increases [9, 196].

Furthermore, Kingma showed that in acute RV pressure or volume load (increased RV preload [7, 98]) the interventricular septum becomes flattened or even concave at end-diastole due to RV dilatation and raised RVEDP, diminishing the trans-septal pressure gradient (trans-septal pressure gradient = LVEDP − RVEDP [259]) and pushing the septum towards the left ventricle [259]. Numerous publications confirm the change in the septum position in different conditions such as acute and chronic pulmonary hypertension [168, 184], congestive heart failure [72, 254] and mechanical ventilation [260]. The leftward shift of the septum and the constraining effects of the pericardium compress the LV with a resultant decrease in LV-size and in end-diastolic LV-filling (reduced LVEDV) [9, 196, 261], producing a reduction in LV-SV [262, 263]. Furthermore, the LV diastolic properties are affected as well, and the reduction in LV compliance in so far contributes to the compromised LV-filling and, hence, the reduction in LV-SV [9, 196, 199, 264]: This is due to the flattening of the septum as RV dilates and as the RVEDP rises, subsequently affecting LV compliance [9, 197, 199], and thus resulting in altered LV diastolic function, diastolic dysfunction, with abnormal LV relaxation and reduced LV compliance [9, 196, 197, 199].



Remember, systolic interactions between the two ventricles basically refer to the LV contribution to RV performance [14, 143–146], as described above.

4.3.2.2 The Role of the Pericardium in Diastolic-Ventricular Interaction

The constraining effect of the pericardium not only limits the LV-filling but also the dilatation and filling of the RV: Under normal conditions RVEDP and PP are

low, with the natural pericardium contributing by 30–40% to the total RV end-diastolic filling pressure [268]. But in cases of raised intra-thoracic pressures [10, 42–44, 103, 153, 154] and/or (otherwise) altered pulmonary hemodynamics [9, 30, 156, 159, 198, 257, 269, 270], features typically associated with changes in RV loading conditions [21, 120, 251, 252, 269, 271, 272], "external" pressure is exerted on the heart [46, 273–275], exhibiting a noticeable constraining effect by the pericardium particularly on the thin walled RV [168, 184]. Both RVEDP and LVEDP will rise, but the rise affects the RVEDP more than the LVEDP (↑ RVEDP > ↑ LVEDP) [46, 168, 184]. In regard to DVI, changes in filling pressure are more pronounced in the RV than in the LV and thus volume loading would increase RVEDP more than LVEDP, whilst for unloading the fall in RVEDP exceeds the fall in LVEDP [72, 168, 254, 271]. Right-sided HF always implies an increased PP [276] and thus constraint should always be considered in case elevated PPs are commonly present.

Ventricular interaction due to pericardial constraint is diminished as long as the PP is <5 mm Hg [277]. In the thin walled RV, if RVEDP ≥ 4 mm Hg, PP will increase in a parallel fashion [278]. A PP exceeding 9–10 mm Hg will exert substantial constraint on ventricular filling [273, 278]. When LVEDP exceeds 10–15 mm Hg, the LVEDP-LVEDV relation becomes much steeper and the pericardium limits further increases in LV end-diastolic volume [279, 280].

As discussed in Chap. 1, the CVP reflects the pericardial pressure [281, 282], and pericardial constraint accounts for 96% of the RA pressure, if CVP > 10 mm Hg [273]. The ability to maintain an adequate RV-SV by RV-dilatation is very limited. RV-SV decreases almost linearly with an abrupt increase in afterload as soon as pulmonary hypertension (mean PAP ≥ 25 mm Hg) occurs, despite all compensatory attempts (RV-dilatation) [283]. Very soon the constraint exerted by the pericardium will restrict the dilatation and further fluid administration in order to increase RVEDV and thus ensure a proper RV-SV is, if at all, only of marginal help. Contrary to previous belief, fluid administration will be harmful because any further dilation of the RV cannot correct the LV-filling deficit and may reduce LV-filling even more [66, 168, 169, 184, 284–286]. If RV-D occurs, no further fluid administration is advisable, volume loading will be harmful [287, 288] in the failing RV: In case of increased RV filling pressures above 10–15 mmHg, fluid loading should be avoided because volume application may worsen the hemodynamic situation by enhanced pericardial constraint including a further shift of the interventricular septum towards the left ventricle [7]. Conversely, volume unloading will be beneficial and allows for an increase in SV/CO [287, 288].

As such, the pericardium plays a relevant role in acute RV-F pathobiology [9, 269].

Furthermore, compensated RV-D/RV-F quickly deteriorates (to end-stage) [9] through a vicious cycle of auto-aggravation which is unique to the RV [9].

4.3.2.3 Auto-aggravation

RV-dilatation (RVEDV ↑) and the alteration of the RV-geometry secondary to the increased RV-afterload or substantial volume loading leads to a tricuspid annulus

dilatation and functional tricuspid insufficiency (TR) [289–291] which is further aggravated by the increased RVEDP [9, 289]. The tricuspid regurgitation leads to congestion in the hepatic and renal vascular bed and to a fall in RV-SV [9, 289] which is, as per definition, RV-F. Less blood volume will be ejected into the pulmonary vasculature due to the fact that the PA-pressure is higher than that on the venous side and, due to the TR, ejection into the low pressure conduit is easier. The reduced RV-SV implicates a further (additional to the reduction of LV filling secondary to the DVI effect) reduction in LV preload via the so called series effect [194, 292].

4.3.2.4 Series Effect

The two ventricles are coupled in a row (series), one after the other, and thus their output necessarily is equal over time [169, 193]. Therefore, a reduction in right ventricular output results in less blood (volume) being transported to the LV [194, 292]. Less filling of the LV (less LV-pre-load) will result in a fall in LV-SV as per the Frank-Starling mechanism [262, 263]. 'The performance of the RV determines LV-preload' [193].

Due to systemic vasoconstriction the systemic arterial BP is usually maintained in the initial phase of acute RHF [293]; however, with a further, substantial decrease in LV preload causing considerable loss of LV-SV, a BP drop is inevitable [289, 294, 295]. RV-F is often accompanied by hypotension [251, 296]. Kerbaul [22, 160] and Bellamy [297] showed that, unfortunately in this situation, we cannot expect an increase in contractility to maintain or increase the RV-SV.

The combination of autoaggravation and the series effect can be summarized below:

Compensated RV-D with ↑ RVEDD/RVEDV and ↑ RVEDP (due to DVI)
↓ **Autoaggravation**
TR → ↓ RV-SV and thus RV-F
↓ **Series effect**
↓ ↓ LVEDV (↓ ↓ LV-preload)
↓
↓ ↓ ↓ LV-SV
↓
↓ ↓ ↓ systemic BP
[9, 30, 194, 251, 262, 263, 269, 272, 289, 292, 294–296]

4.3.2.5 Pulmonary Hypertension and Ischemia

An elevated PA-pressure puts the RV at risk of myocardial ischemia [33, 133, 298], with or without pre-existing coronary artery disease [299, 300] and RV-F may occur as a result of the ischemia [301]. RV-dilatation increases the likelihood that ischemia will develop because, at a certain point, a critical increase in wall tension and stress (secondary to RV enlargement) occurs, producing a significant mismatch between oxygen supply and demand [289].

With an increase in RV-afterload, the isovolumetric contraction phase and ejection time are prolonged and an increase in RV myocardial oxygen consumption results [9, 161, 221]. An increased oxygen demand would normally be compensated by a substantial increase in RCA-perfusion [221], but, in cases of low RCA perfusion, there is a risk that incipient RV myocardial ischaemia will further worsen the RV-function [221, 251, 284, 294]. As RV-F is often accompanied by hypotension, predominantly secondary to the reduction in LV-SV as described above, resulting in a marked reduction in myocardial perfusion [221, 296, 301, 302] a worst case scenario may occur, the combination of PH and ischaemia [221, 284, 294, 303].

However, recent study results fundamentally challenge the described role of ischemia in the context of PH and (acute) right heart failure, rather conceding ischemic cell destruction being the last and decisive step in the deleterious disease course only in special cases such as acute pulmonary embolism [304, 305]: The results are suggestive of myocardial stunning rather than true cardiomyocyte loss causing progressive contractile impairment [306]. Moreover, progressive contractile dysfunction may be even caused by non-ischemic issues as some authors suspect [81, 307, 308]. Moreover, it is not at least the RV pressure overload itself which is suggested to down-regulate and thus to contribute to the progressive deterioration of RV contractility [81, 307, 309].

Hence, the development of an ischemic right ventricular myocardium [30, 33, 284, 294, 301, 302] may be in some conditions, e.g. pulmonary embolism [304], the final step in the pathophysiological cascade of RV-F where life threatening heart failure will almost inevitably develop [30, 284, 294, 303].

Ischemia of the right ventricular myocardium occurs when RCA-perfusion pressure <25–30 mm Hg [301, 302]; in the case of PH, the RCA-perfusion pressure has to be >45 mm Hg in order to avoid ischemia [302] and, if a significant RCA stenosis is present, an even higher perfusion pressure is required [30, 236, 301].

4.3.2.6 The Interventricular Septum and the Apex

In critical situations such as acute RV pressure or volume load, and particularly when RV ischemia develops, the interventricular septum (IVS) 'behaves' as a functional part of the RV [310, 311]. In case of acute RV pressure or volume load, the IVS moves during systole towards the RV in a 'paradoxical' fashion. This 'paradoxical' septal movement is an active process of the interventricular septum at the end of systole allowing prolongation of the RV contraction phase, whilst the LV starts to relax [31], moving towards the RV-cavity and increasing the RV contractile force [31, 312]. The loss of the contractility of the septum under such conditions will markedly worsen the haemodynamic situation [251], but inotropic drugs in this situation may augment the RV systolic function by improving the contractility of the IVS [311, 313, 314].

Furthermore, the contraction of the apex of the heart contributes in cases of RV-D/RV-F to the net contractility of the right ventricle as well [311, 315].

Therefore if either the septum or apex fails, e.g., myocardial infarction, the decrease in LV contractility may result in RV-F [316].

The functional behaviour described above is in accordance with the anatomy. The shared pericardium and septum, the mutually encircling epicardial fibres, and the attachment of the RV free wall to the anterior and posterior parts of the septum allow the apex and the septum to make a contribution to systolic RV function [15].

4.3.2.7 The Left Ventricle

As described, the left and right ventricles are inter-related. LV dysfunction/failure affects RV-function, leading to RV-D/RV-F in several ways. LV-dysfunction may increase the RV-afterload due to pulmonary congestion [15], and/or because of a reduced MAP, the RCA perfusion may decrease, leading to RV-ischaemia [317]. However, LV-dysfunction also exerts an influence on lung mechanics and gas exchange [318], with a reduction in lung volume and lung compliance [319, 320], consecutively potentially affecting RV pre- and/or afterload [321].

Conversely, RV pressure overload may affect LV properties such that pulmonary congestion/edema, indicating LV dysfunction, may arise in a primary normal LV [32].

4.3.2.8 Mechanical Ventilation

Mechanical (positive pressure) ventilation [33, 42–44, 322, 323] and the application of PEEP [35–38, 47–50, 52, 324, 325] increase the intrathoracic pressure (pleural pressure). Artucio [326] and Brienza [327] demonstrated that the application of PEEP and/or positive pressure ventilation may lead to a rise in transpulmonary pressure and an increase in RV-outflow impedance [42–44]. Increasing tidal volumes raises intrathoracic pressure [42, 45] resulting in a marked elevation of the transpulmonary pressure with the potential risk to cause an acute cor pulmonale as found in a substantial number of patients [328]. Transpulmonary pressure directly correlates with RV-afterload [45] and since transpulmonary pressure rises in positive pressure ventilation and PEEP use, RV-outflow impedance will increase [46, 320, 329], which may promote the development of RV-D.

RV-function may also be compromised via another mechanism:

With increasing pleural (intrathoracic) pressure, we find an impairment of LV- and RV-compliance: RV-compliance decreases markedly with only small increases in pleural pressure whilst the LV-compliance decreases a significant amount only with higher increases in pleural pressure [46, 51]. As a consequence, the steep rise in RVEDP associated with only very small increases in RV end-diastolic filling [46] is accompanied by a parallel rise in PP with the potential to cause DVI (see Sect. 1.8 of Chap. 1 and DVI of this Chapter).

Pleural pressure is directly transmitted to the pericardial space [330] and so an increase in pleural pressure will increase the PP. Therefore, the normally low RVEDP and PP will rise markedly in mechanical ventilation, pneumonia, ARDS, etc. and so will contribute to an ↑ in the pressure surrounding the heart [331]. Any rise in pleural pressure will, via a concomitant rise in PP, limit the distending

capacity of the cardiac cavities and will exert a constraining effect on both RV and, to a lesser extent, on the LV [51].

Furthermore, with mechanical ventilation the venous return is compromised, reducing the RV-filling and function and will hence reduce the RV-SV [332].

However, positive pressure ventilation and PEEP are not always detrimental. There is evidence that relatively low PEEP levels (≤8–10 cm H_2O) have beneficial effects on the pulmonary haemodynamics and do not increase the RV-afterload significantly, even though the pleural pressure and thus the transpulmonary pressure are elevated [52]. Schmitt [333] found that the use of a low PEEP improved the blood flow through the pulmonary vessel bed, reducing the RV-afterload and the risk of RV-D. The reasons behind these beneficial effects are:

- Air (gas) trapping is often present in respiratory failure due to chest infection or ARDS and increases the pleural pressure, the trans-pulmonary pressure, and the pulmonary vascular resistance. Gas trapping is relieved by (low) PEEP, hence reducing transpulmonary pressure and improving blood flow through a reduction in pulmonary vascular resistance [51, 334];
- (Low) PEEP is beneficial in diseased and stiff lungs/lung compartments as it improves blood flow in the pulmonary vascular bed [51, 333–335]. Interestingly the PEEP-levels mentioned above, which are beneficial for pulmonary haemodynamics, correspond to those called 'best PEEP' described by Sutter in 1975 [335]. He found PEEP levels around 8 ± 4 cm H_2O resulted in optimal oxygenation transport in ARDS patients. So, these PEEP levels seem to be beneficial for both the treatment of the respiratory failure and the maintenance of a sufficient cardiac function. There is no doubt, however, that PEEP levels >10–12 cm H_2O exert a significant RV pressure load (increased RV-afterload) and cause a leftward shift of the interventricular septum [51];
- PEEP will decrease LV-afterload which will, in the situation of LV-failure through mechanisms described previously, have a beneficial effect on RV function [336–338]:

$$\text{PEEP} \rightarrow \uparrow \text{intrathoracic pressure} \rightarrow \text{transmural LVEDP} \downarrow \rightarrow \text{LV wall stress} \downarrow \rightarrow \text{LV afterload} \downarrow \quad [51, 323, 339]$$

However, it has to be stressed that, in case of pre-existing and/or manifest RV-D/RV-F, PEEP was found to increase RV-afterload in every case and may worsen the hemodynamic situation by its net effect [40].

Meanwhile, a balanced lung- and "heart" protective approach has been proposed, essentially limiting the plateau pressure within the airways to <27 cm H_2O, best complying with the necessary requirements [81, 340–343]. If needed, mechanical ventilation with low tidal volumes (6(−8) mL/kg predicted body weight [344–347]) and relatively low PEEP (8–12 cm H_2O) is appropriate in patients with pulmonary hypertension [21, 348].

4.4 Diagnostic Aspects

4.4.1 Clinical Features

Cardinal clinical manifestations of RHF are exercise limitation and fluid retention [7]. Exercise limitation is the earliest sign of RHF and is a strong predictor of survival [349–351]. Exercise limitation is related to a decrease in flow reserve during physical stress [352–354]. Further, a reduction in peripheral blood flow can increase lactate production, contributing to muscle fatigue. Supraventricular tachycardia may contribute as well [355]. Syncope is a less common symptom often indicating severe limitation in flow reserve. RV failure may further lead to chronic kidney disease and hyopnatremia [356]. Congestive hepathopathy is often observed in patients with RHF and PAH, cirrhosis is a late complication.

Hemodynamically, acute RV decompensation is characterized by enlarged RV size with enhanced end-diastolic filling volume attended by an increase in RVEDP (acute increases in filling volumes yielded higher filling pressures [157]), RV diastolic dysfunction [156, 185], and diminished and falling CO [185]. Some patients with severe and progressive RV-F may even expire normal pulmonary pressures due to marked reduction in CO [1].Thus, the interpretation of PAP has to consider CO and severity of heart failure.

Patients presenting with acute decompensations of chronic PH can often clinically be barely distinguished from those with acute RV-F attributed to acute PE, as clinical presentations are very similar [1].

As such, although there are a lack of specific clinical signs in acute right heart dysfunction or failure [357] but, nevertheless, the following features are suggestive of acute RHF and may be present [9]:

• Neck vein distension	• Hepato-/hepato-splenomegaly
• Positive hepato-jugular reflex	• Abdominal discomfort
• Renal impairment with oligo-anuria	• Hypotension
• Tachypnoea is present in up to 80% [358]	• Peripheral oedema[a]
• Atrial and ventricular arrhythimas [1, 93]	
• Evated lactate, disturbed coagulation and raised liver enzymes may by an expression of liver dysfunction due to hepatic congestion [357]	

[a]Peripheral oedema is not unique to RV-D/RV-F, it is secondary to hyperaldosteronism induced by hypercapnic acidosis, hypoxaemia and renal insufficiency [100, 359], and chronic venous insufficiency

The clinical presentation is furthermore markedly influenced and determined by the underlying source precipitating RV-F and existing comorbidities [83, 144].

To conclude, acknowledged clinical cardinal signs of RV-F include [1]

(a) Fluid retention potentially causing peripheral edema, ascites and anasarca,
(b) Limited systolic reserve or low cardiac output leading to and provoking exercise intolerance and fatigue,
(c) Atrial and ventricular arrhythmias.

4.4.2 Serum Biomarkers

BNP has a strong, positive correlation to PVR and RVEDP in patients suffering from primary pulmonary hypertension [360, 361]. BNP rises gradually with increasing severity of RV-D/RV-F [306, 362, 363]. However, the thresholds of when to diagnose RV-D (RV-F) are still in discussion and vary from between >50 pg/mL [364] and >100 pg/mL [365]. Furthermore, elevated BNP levels may be present in chronic RV-D and chronic PH [208, 361, 366].

Troponin I > 0.1 µg/L (pathologically elevated) was found only in severe RV-D caused by pulmonary embolism [364]. Its occurrence is associated with early mortality [367, 368]. In the case of pulmonary embolism, patients with a negative serum troponin and normal ECG are at the lowest risk [369].

Both, Troponin and BNP have excellent negative predictive value and tend to exclude a complicated hospital stay when negative on admission [370, 371].

However, as both cardiac markers are not specific for right ventricular issues at all, the interpretation of their results can only be done in the clinical context they occur [2].

4.4.3 Electrocardiography

ECG ST-elevation (>0.1 mV) in VR3 and/or VR4 in patients with inferior ST-elevation acute myocardial infarction is highly specific for RV-ischaemia due to a proximal RCA-lesion (sensitivity 83%, specificity 77%) [64, 74]. Involvement of the RV, as a complication of acute inferior myocardial infarction (ST-elevation in II, III, aVF [372]) is to be expected in approximately 50% [70].

4.4.4 Echocardiography

Direct pressure and volume measurements can be made using a Swan-Ganz-conductance catheter [373]. Although right heart catheterisation has previously been the method of choice, echocardiography, due to favourable comparisons to the catheter results and as the less invasive method, is now widely used [374]. An echocardiographic assessment is essential in establishing the diagnosis of RV-D/RV-F [2, 31, 365, 375–378]. Vieillard-Baron [379] requires only the finding of RV-dilatation with a leftward shift of the septum in order to make a diagnosis of RV-D; however, there are many other echocardiographic features of RV-D/RV-F which can be used to confirm the diagnosis:

- The RV is clearly dilated when the RV size ≥ LV size [358, 375, 376, 380]. The most common criteria with which to diagnose RV-dilatation is the RV/LV-ratio (assessed in the four-chamber view), but there is disagreement about the thresholds indicative of significant RV-dilatation, ranging from a ratio of 0.6–1.0 [381–383]; recent publications definitely assume the RV being dilated if RV basic diameter, measured in the 4-chamber-view at the RV base, exceeds 41 mm, or if the ratio RVEDD/LVEDD > 1.0 [2, 384].

- The IVS becomes flat and bows towards the left ventricle in end-systole in case of predominantly pressure (over) load, thus, the right ventricle becomes circular at end-systole while the LV becomes eccentric in shape [31, 375, 376]. In end-diastole a countermotion is found [385]. This dyskinetic/paradoxical IVS movement, which is an effect of ventricular interdependence [2, 385], is indicative for RV pressure overload [2, 365, 384, 385]. Paradoxical septal movements may generally be a sign of an acute increase in RV-afterload [304]. In case of RV volume overload, a constant flattening of the IVS is seen leading to the so-called D shaped LV configuration [384, 385].
- The tricuspid annular plane systolic excursion (TAPSE) is an easy to use and very valuable parameter in assessing right heart function [305, 386]. It is merely the AV-displacement of the tricuspid valve.

TAPSE shows a good inverse correlation to the pulmonary vascular resistance (TAPSE ~ 1/PVR) representing pulmonary hypertension in cases of elevated resistance [305]. TAPSE is afterload dependent and pathological values indicate an elevated RV-afterload [305]. It is an excellent measure of the systolic RV-function [387–389] as it has a direct correlation with RV-EF (TAPSE ~ RV-EF) [307, 309, 386, 388]. TAPSE is a highly sensitive and specific parameter of depressed RV-SV [390] as RV-SV indirectly correlates with PVR [391].

Additionally, a good correlation is established between the severity of the tricuspid regurgitation (TR) and TAPSE (TAPSE ~ 1/TR) [305]. A normal TAPSE value is >22 mm [305, 392, 393], while 15–19 mm excursion indicates a moderate depression of TAPSE [305] and when < 15 mm the outcome is very poor [305]. However, TAPSE < 17 mm indicates a RV-LV disproportion reflecting the series and interdependent (DVI) effects of the failing RV on the LV-filling [2, 170];

- Hypokinesis of the free RV wall [365];
- A TR-jet velocity of >2.8 m/s is suggestive of pulmonary hypertension [2];
- Inferior vena-cava diameter (sub-costal view) > 21 mm during maximal) expiration (in spontaneously breathing patients) provides evidence for pathology [2]; if the amount of collapse is <50%, a pathologically high pressure is present, indicating pressure and/or volume (over)load [2, 394]. In mechanically ventilated patients the venous flow to the right heart is markedly reduced during inspiration secondary to the positive intrathoracic pressure reducing the amount of vena cava and hepatic vein collapse [395];
- Furthermore, the newer Doppler-tissue imaging derived parameters such as tricuspid annulus S′ velocity or longitudinal strain of the free RV wall may be used for assessment [2, 384]
- The pulmonary vascular resistance (PVR) may be calculated using echocardiographic parameters. PVR is calculated by the ratio of transpulmonary pressure (Δp) to transpulmonary flow (Qp):

$$PVR = \Delta p/Qp;$$

  - TR (maximal tricuspid regurgitant velocity) and TVIRVOT (time-velocity interval of the right ventricular outflow tract) can be used as a correlate to Δp (TR) and Qp (TVIRVOT) [396, 397]:
  - PVR = TR/TVIRVOT.
  - Due to the Bernoulli equation, TR will increase as systolic PA pressure increases [396, 398, 399];
  - Abbas [308] found a very good correlation between PVRcath (measured invasively) and TR/TVIRVOT with a correlation coefficient r = 0.93, CI 0.87–0.96:
  - TR/TVIRVOT < 0.2 is most likely to be normal with PVR < 150 dyn × s × cm (80 dyn × s × cm^{-5} equals one Wood unit [400]):
- **The combination of a small and well contracting LV and a big, dilated and poorly contracting RV is pathognomonic for 'acute' right heart failure** [401];
- Interestingly, McConnell [304] has described severe hypokinesia of the mid free wall of the RV, but with a normally contracting apex, as pathognomonic of pulmonary embolism.

Features indicating possible de-compensation of RV-F are [15]:

- Rising RVEDP;
- Worsening diastolic RV-dysfunction [185] (becoming obvious by an inadequate increase in RVEDP);
- ↓ LV-SV and markedly LV diastolic dysfunction (induced by an ↑ in RV-size and ↑ RVEDP [197, 198]).

Special clinical settings and their echocradiographic correlates [2]:

(a) Acute decompensation of chronic PH

• RV hypertrophy	• RV dilatation, spherical shape
• Paradoxical septal movement, systolic/diastolic septal shift	• RA enlargement
• Peak systolic velocity of tricuspid regurgitation >3.5 m/s	

(b) RV-AMI

• RV enlargement	• Global and/or regional hypokinesis
• Abnormal septal motion	• TAPSE ↓
• Congested (dilated) V. cava (even if RV-pressures are normal or low)	

(c) Acute pulmonary embolism

• RVEDD/LVEDD ratio >1 (>0.9 [402])	• McConnell's sign
• Tricuspid regurgitation velocities of 2.8–3.5 m/s	• Thrombi in the central pulm vessels
• Systolic/diastolic spetal shifts: paradoxical septal movement; LV D-shaping	

4.4.5 Invasive Hemodynamic Assessments

Invasive hemodynamic assessments (and monitoring) are recommended in case the diagnosis is unclear or in therapy-resistant patients [2].

At rest, CVP normally equals 0 mmHg [403], and the CVP/RA-P are only elevated in disease states [404, 405]. Elevated (>8–10 mmHg) right atrial pressure/CVP is highly suggestive for acute right heart failure in a typical clinical setting [93]. A CVP ≥ 10–12 mmHg has already to be considered high, and will exert considerable constraint on LV filling [273, 278]. Thus, RA-P/CVP pressures ≥9–10 mmHg are always pathological and indicate that fluid application is highly unlikely to be successful [406] and that DVI will relevantly impact left ventricular filling, RV and LV filling pressures and the overall hemodynamic situation [273, 278].

4.5 Therapy

It has been emphasized that RV-afterload (PH) and altered myocardial perfusion/ischaemia are decisive factors in precipitating RV-F and the ability to therapeutically ameliorate these factors will determine the prognosis [1, 2, 27–30, 33, 135, 251, 284, 294, 301]. Thus, reduction of the elevated RV-afterload and avoidance or reversal of RCA-hypoperfusion are essential issues which therapy must address [1, 2, 133, 251, 407–410]:

- Critical reduction of the increased RV-afterload
- Avoidance/treatment of right ventricular myocardial hypoperfusion/ischaemia

Acute RV-F/acute exacerbation of RV-D/RV-F are reversible if the cause of the increased afterload can be treated [9, 33].
Furthermore, the hemodynamic consequences of RV-D/RV-F are the result of a

- Critical interaction between both ventricles [72, 167, 168, 251, 252, 254] which has to be addressed thoroughly.

Other crucial targets are:

- Treatment of underlying disease [1, 2, 9, 33]
- Improvement of RV contractility to overcome critical acute situations [143, 173, 174, 179, 410, 411]

4.5.1 Specific Measures (Overview by [1–4, 9, 16, 20, 30, 33, 93, 98, 106, 107])

- Thrombolytic therapy/PCI in case of acute coronary syndrome [412–417]
- Thrombolytic therapy/catheter fractioning or embolectomy in pulmonary embolism [106, 107, 418–420]
- Specific treatment of broncho-pulmonary diseases
- Treatment of systemic sepsis
- ARDS: Therapy of underlying disease
- Correction of valvular heart disease, and left heart failure

In acute myocardial infarction with involvement of the RV early reperfusion by primary PCI is essential [412–417]; read more about this issue in Chap. 3, cardiogenic shock.

Right heart dysfunction/failure and pulmonary embolism:

RV-F is the most common cause of death within 30 days following PE [110, 421] and RV dys-function is known to cause an increased mortality [110, 422, 423].

50% of all patients with pulmonary embolism present as clinically stable, without hypotension or circulatory failure, although suffering from RV-D [110, 365, 424]. They are at high risk of haemodynamic instability or even death during the first days after admission [425, 426].

The Shock Index is a sensitive parameter which can easily be used in daily practice in order to assess the potential outcome of patients with pulmonary embolism [289].

$$\text{Shock Index} = \text{HR} / \text{sBP} \geq 1 \rightarrow \text{mortality} + +$$

Thus, patients with a positive (≥1) shock index should be treated by thrombolysis (Evidence level A, Class I) [427–431].

Although not all studies give convincing evidence about the predictive and prognostic value of RV dysfunction [422, 423], Kucher [424] established that RV dysfunction is an independent prognostic predictor by analysing the data of the famous ICOPER study [110]. Patients with a systoli blood pressure ≥90 mm Hg (and thus classified as being hemodynamically stable/with preserved BP) but with RV-dysfunction had almost double the risk of death (16.3%) in comparison to those without RV-dysfunction (9.4%) over the first 30 days. Thus, although initially haemodynamically stable, all patients with RV dysfunction are at a high risk of death [424]. These results are consistent with those reported by Figulla [256], who found a 5–8% mortality rate in patients with normal BP but with RV dysfunction, while the prognosis of all patients without RV dysfunction was excellent (mortality rate 0–1%). It should be noted that the level of blood pressure taken as normal (sBP of >90 mm Hg versus >120 mm Hg respectively) was different in both studies and that the blood pressure on admission has a substantial impact on the patient's prognosis [422] (see Table 4.2).

Not all studies have concluded that thrombolytic therapy reduces the mortality significantly when administered to clinically stable patients with RV-D but preserved BP [422, 423]. Nevertheless, the haemodynamic situation clearly improved and

Table 4.2 Impact of blood pressure on patient's prognosis

Clinical scenario	Mortality during hospital stay (%)
Normal BP, without RV-dysfunction	0–1
Normal BP, with RV-dysfunction	5–8
Hypotension, without signs of shock	15
Hypotension and shock	Up to 35

stabilised immediately after the patients received thrombolytic agents [110, 423, 426, 432–434]. Furthermore, the first prospective study assessing the long term outcome after first-time 'submassive' pulmonary embolism in previously healthy patients treated by heparin and warfarin found 41% of the patients either with persistent or subsequently (weeks to months after PE) developed RV abnormalities or functional limitations [435]. The authors suggest that first-time pulmonary embolism is able to cause persistent right heart damage or to initiate a process which damages the RV over time. The main pathological mechanisms involved appear initially to be ischaemia of the RV subendocardium followed by an inflammatory response [303, 436, 437].

The results by Kucher [424], Figulla [422] and Woods [289] suggest that patients in shock and those with hypotension need thrombolytic treatment, but it would also seem more than wise—based on the current evidence—to consider patients with established proof of RV-dysfunction on an individual basis for thrombolysis as well.

More recent studies and trials still demonstrate roughly 7% hospital and 32% overall mortality in hemodynamically unstable patients with PE [438]. Even RV-D and elevated cardiac biomarkers are indicative for increased risk of in-hospital death and clinical deterioration [439]. All studies and metanalysis substantially support the application of thrombolytic therapy in hemodynamic unstable patients with massive PE (defined as hypotensive patients or patients presenting with syncope, cardiogenic shock, cardiac arrest, or respiratory failure due to acute PE [215, 420, 440]). On the contrary, hemodynamically stable patients with submassive PE (defined as patients with acute PE being normotensive but with signs of RV dysfunction [441]), there still is an ongoing controversial discussion whether a clinically significant benefit can be achieved by thrombolysis [440–442], even though those patients also suffer from an increased risk of early mortality and adverse outcome [441]: The largest study on systemic thrombolytic therapy in patients with submassive PE in fact revealed that thrombolysis in that condition is preventive for circulatory decompensations, but at the expense of an increased ratio of intracranial bleedings [440]. Marti et al. found in their metanalytic study a reduced overall mortality and PE recurrence rate, and further a reduction of PE associated death, if thrombolytic therapy was given to patients with acute PE. However, in hemodynamically stable patients the benefit was statistically insignificant. Moreover, thrombolysis in PE was in general associated with a considerable risk of major intracranial bleedings [420], and the mortality reduction found resulting from thrombolysis is basically offset by the risk of fatal, particularly intracranial bleedings in hemodynamically stable patients with submassive PE [420]. Thus in hemodynamically stable patients with submassive PE, initiation of thrombolysis has furthermore to be based on thoroughly individual evaluation.

4.5.2 Adjunctive Therapy [2, 9, 33, 358, 443]

4.5.2.1 Fluid Management and Optimization of Preload, Diuretics

The recommendations regarding *fluid management* in acute RV-D and RV-F have completely changed in recent years following a large amount of discussion [9, 193, 391, 443, 444]. RV filling above the physiological limit is accompanied by RV-dilatation [445].Thus, although some patients with RV-failure may respond to volume loading, fluid administration in acute right heart failure bears a high risk of further RV dilation/RV-chamber "overdistension" with its deleterious effects of increased RV wall stress, ensuing or worsening DVI, and reduced RV systolic power, diminished systolic LV support, the onset of tricuspid regurgitation or worsened TR, reduced LV filling and finally compromised CO and ischemia [446]. On its own, fluid administration in case of acute or acutely exacerbated right heart failure should basically be avoided because a beneficial effect of volume expansion can generally not be expected, even if there is a low LV-preload [193, 288, 290]. This is in particular the case if CVP exceeds 10–12 mmHg [406, 446]. Volume administration in this situation will not increase RV-SV and hence CO; in a depressed RV or in manifest RV-F only volume unloading will increase CO [287, 288]. Therefore, in the vast majority of patients suffering from acute RV-D/RV-F, volume loading has no benefit at all [9, 72, 168, 169, 193, 290, 391, 444].

On the contrary, diuretics are often the therapy of choice, since RV failure is usually associated with or even caused by RV volume overload, and diuretics may be safely applied in patients with venous congestion as long as the arterial blood pressures are maintained [2].

Diuretics are indicated in volume overloaded patients who have a dilated RV with leftward shifted septum and DVI following initial stabilization (maintenance of appropriate BP) of the circulation [348, 447]. Diuretics may induce metabolic alkalosis and thus aggravate hypoventilation and hypercapnia and, as such, should be used judiciously [448]. Moderate peripheral oedema should be tolerated in compensated chronic states [449, 450].

However, there are some exceptions to this rule. In the (few) cases of RV-F with normal PVR volume loading may be beneficial and increase preload, leading to an increase in RV-SV and LV-SV [444]. A well monitored (by CVP) and cautious volume loading may be further appropriate in case of systemic hypotension in the presence of normal right-sided filling pressures [2, 451–455]. Moreover, probably also patients suffering from acute myocardial infarction with significant involvement of the right ventricle are the group who will benefit most from controlled and balanced volume loading [251].

Ideally in daily practice, an echocardiogram to clarify the diagnosis, to assess the hemodynamic situation, and to guide therapy should be performed as soon as RV-D/RV-F and/or biventricular failure are suspected. However, as an emergency measure in shock or in haemodynamic instability [451–453, 456], as long as no clinical signs of fluid overload are present, a careful and well monitored fluid challenge is acknowledged to be always appropriate [451–455].

4.5.2.2 Vasopressors: Treatment and Avoidance of Ischaemia

Vasopressors directly increase the systemic blood pressure and thus improve the perfusion pressure of the RCA [301, 457–460]. Ghignone [461] and others [212] were first to establish that vasopressors may be the critical element in the treatment of acute right heart failure, as the administration of vasopressor drugs can break the pathological vicious cycle and avoid the manifestation of RV myocardial ischaemia [30, 212, 284, 294, 461].

Agents that increase the aortic pressure are able to reverse RV ischaemia and actually improve RV function. Vlahakes [301] demonstrated that an increase in RCA coronary perfusion pressure will directly increase the net perfusion of the myocardium, certainly for the right ventricle [301, 462] and probably for the LV myocardium as well [462]. As mentioned in Chap. 2, *noradrenaline* is the vasopressor of choice, as it is in hypotensive, life-threatening situations where vasopressor administration is essential [410, 463–468], not only restoring arterial pressure but improving RV-contractility as well [251].

For practical purposes, the coronary perfusion pressure (CPP) is determined for the left ventricle by the eq. [469]:

$$\text{CPP} = \text{diastolic blood pressure} - \text{LVEDP}$$

The right ventricle under physiological conditions is perfused continuously throughout systole and diastole. In PH the CPP depends on the difference between diastolic blood pressure and RVEDP [357]:

$$\text{CPP} = \text{diastolic blood pressure} - \text{RVEDP, or}$$

$$\text{CPP} = \text{diastolic blood pressure} - \text{CVP}$$

Ischaemia is known to occur in healthy persons if the CCP in the RCA is as low as ≤25–30 mm Hg [301, 302]. In PH, a CCP > 45 mm Hg is necessary to avoid ischaemia [302], but generally a CPP > 50 mm Hg is essential in order to provide basic perfusion of the myocardium [470], and coronary autoregulation functions from approximately 60 mm Hg to 140 mm Hg MAP [471, 472]. This means that in PH, and if the CVP > 10 mm Hg, a diastolic blood pressure >55–60 mm Hg is required and, in order to maintain coronary artery autoregulation, a MAP > 65–70 mmHg is essential. However, a MAP ≥75 mmHg in case of AMI in order to more or less guarantee a sufficient perfusion of the left ventricular myocardium and hence potentially preserved LV contractile performance, the latter being critical for RV systolic performance [14] is typically recommended [471–473].

4.5.2.3 Critical RV-Afterload Reduction

The reduction of the pulmonary vascular resistance (RV-afterload) is, alongside avoidance and reversal of ischaemia, the central aim of therapy in patients suffering from pulmonary hyper-tension and RV-dysfunction/failure [133, 135, 251, 407, 409, 410]. A reduction in RV-afterload will reduce RV O2 consumption and will reverse the pathophysiological processes described, breaking the vicious cycle [9].

It is the norm to treat the underlying disease and to attenuate pulmonary hypertension in patients suffering from COPD, in order to reduce airway resistance and vasoconstriction of pulmonary vessels (as well as v-a-shunts) [474–476]. Therefore a combination of *β-agonist* and *anticholinergic agents* (bronchodilator therapy), preferably in nebulized form, is strongly recommended [474–476]. In patients with COPD, methylxanthines (e.g. aminophylline) are effective in reducing the pulmonary vascular resistance, increasing RV-EF and RV-contractility [477, 478]. However, they are not recommended to be routinely added to the bronchodilator therapy [475, 476, 479, 480] (and some regard them obsolete [391]) due to the frequent and often severe side-effects, potentially causing deterioration of the overall cardiac function, malignant rhythm disturbances, worsening a-v-shunting (producing a further reduction in arterial oxygen content) and tachycardia increasing O2 consumption, risking ventricular ischaemia, and exacerbating the final step in the vicious cycle [479, 480]. They should only be considered in patients with an exacerbation of COPD [479, 480] who are RV-F resistant to all other therapeutic measures and where it seems reasonable to continue in patients who were taking them prior to the exacerbation [475].

In severe asthma, magnesium has a synergistic beneficial effect with β-agonists and should be considered [481].

Symptomatic Treatment of PH: Vasodilators

Systemic vasodilators are highly unselective and, unfortunately, will worsen the ventilation-perfusion mismatch resulting in reduced arterial oxygen saturation, as well as reducing RCA perfusion (by lowering the systemic blood pressure), resulting in or worsening RV myocardial ischaemia [482, 483]. Thus, although vasodilators such as GTN or nitroprusside may reduce the resistance of the pulmonary vasculature [9], they should normally only play an adjunctive role in therapy, but may be considered in normotensive patients who are fluid overloaded [30].

Inhaled pulmonary vasodilators exert highly specific and local effects: *Prostaglandins* (e.g. Iloprost, a synthetic prostaglandin I_2) and their analogues such as *nitric oxide* (NO) show vasodilating effects selectively on the pulmonary vasculature [484–487], thus NO and Iloprost are very effective in reducing PVR [488]. Nebulized prostaglandins exert beneficial effects in patients with primarily pulmonary hypertension (PPH/PAH) and acute right heart failure [489] as well as other situations with secondary pulmonary hypertension and acute RV-failure [490–492]. No significant toxic effects of prostaglandins are known and they lower the pulmonary arterial pressure more effectively than NO [493, 494]. Unfortunately a concomitant reduction of mortality rate when administered in acute cases has not yet been established [492]. In desperate, life-threatening situations prostaglandins should be considered, although they are currently not licensed in Europe, due to cases of acute RV-failure due to secondary pulmonary hypertension [495].

Inhalation of NO will only reach vasodilatation in ventilated areas. The reflex hypoxic pulmonary vasoconstriction (Euler-Liljestrand reflex) will act and thus an increase in v-a shunt volume will be avoided [495, 496]. Administration of NO improves RV-pump function and reduces RV-dilatation in patients with COPD and

ARDS [82]. Importantly however, NO exhibits a rebound phenomenon after stopping its administration [497]. Although currently only licensed for use in primary pulmonary hypertension (PPH) of the newborn, it may be considered in cases of severe acute RV failure refractory to conservative treatment strategies [31]. Exhibiting less side effects prostacyclin is used in many centers as first-line selective pulmonary vasodilator in acute right heart failure conditions [446].

Sildenafil (a specific phosphodiesterase-5 inhibitor, PDE-5-inhibitor) exerts beneficial acute and chronic haemodynamic effects by lowering the pulmonary pressure in patients with pulmonary hypertension [498–500]. It has been shown to reduce PA pressure and to increase CO alone, or in combination with nitric oxide in stable patients [501, 502]. The effect commences soon after administration, with peak haemodynamic effects occurring within 1 h and lasting 3–4 h. Sildenafil has the potential to lower systemic blood pressure, causing hypotension, and so caution is warranted in critically ill patients [348].

Although not investigated intensively in the acute setting, PDE-5-inhibitors may protect against rebound phenomena [503], and smaller studies revealed their beneficial effects (besides the established role in the treatment of idiopathic pulmonary hypertension, PAH) also in acute and chronic LHD caused and associated heart failure conditions [504, 505].

4.5.2.4 Improvement of RV Systolic Function/Contractility

As previously described, the contractile power of the LV and in particular of the IVS [14, 145, 171, 310, 311] (and the apex [163, 167]) plays a direct and significant, in disease states decisive [14, 150, 506, 507], role in maintaining RV function. The LV substantially contributes to RV performance directly by improving the contraction of the LV and thus the IVS [314] and indirectly due to its 'wringing' action [508, 509]. Poor LV systolic function may result in RV-F [316].

The RV contractility may be compromised [22, 23, 133, 159, 251] by a number of different conditions, including AMI involving the right ventricle [66, 251] and PH from PE [23, 31, 168], sepsis [153, 288], acute respiratory failure [39–41], and, of course, by left heart diseases [27–29].

Thus, in life threatening situations and particularly where initial therapy is unsuccessful [410, 451–455] the use of inotropic drugs must be considered.

Dobutamine has been (maybe, still is) the agent of choice [348, 407], since it is able to improve right (explicitly via promoted left) ventricular contractility [14, 96] and right ventricular compliance [510], which will subsequently reduce RVEDP and RV wall stress. "Low" dose dobutamine (up to 5 μg/kg/min [511]) reduces the pulmonary resistance and thus RV-afterload [512, 513]. However, it is important to keep in mind the possible harmful effects with potentially unfavourable outcomes of dobutamine as mentioned in Chap. 2 [514–517].

Levosimendan has recently been shown to be effective in the treatment of RV-F and seems to be superior to dobutamine [160]. Kerbaul showed a significant reduction in PVR, in mean and diastolic PA-pressure, PCWP, as well as a significant improvement of SV, CI and RV/LV-SWI. The main beneficial

mechanism identified was an unloading of the RV through pulmonary vasodilatation [160, 411]. Morelli [411] investigated the treatment of RV-F with levosimendan in patients suffering from ARDS and also showed that levosimendan induces a substantial dilatation of the pulmonary vasculature [518, 519], reducing the pulmonary pressure and hence the RV-afterload. Levosimendan also appears to be able to improve RV contractility [518, 520, 521] (aside from improving LV contractility) without increasing the myocardial oxygen demand and without impairing myocardial relaxation [522, 523]. Furthermore, there are two other beneficial effects that may have contributed to the favourable outcomes seen in the studies by Kerbaul [160] and Morelli [411]. Levosimendan improves the ventriculo-arterial coupling of RV and the pulmonary artery. The $E_{a\text{-}pul}/E_{es\text{-}RV}$ ratio of the RV to the pulmonary artery was normalised [160]. Levosimendan seems to be preferable also because it does not compromise (RV or LV) diastolic function, and in fact beneficial effects on relaxation have been found [524]. As such, by combining pulmonary vasodilatory and positive inotropic effects, levosimendan is found to favourably address the RV-pulmonary arterial unit [3, 411, 446] thereby substantially improving RV function.

Milrinone, a phosphodiesterase 3 inhibitor (PDE-3-inhibitor) enhances contractility while simultaneously lowering pulmonary vascular tone. Some authors assign milrinone first-line status in patients suffering from elevated pulmonary afterload and consecutively RV-F due to groups II–V PH, as long as mean arterial pressure is preserved [446, 525, 526].

However, if inotropic support is necessary, levosimendan would appear to be the preferable drug in RV-F, but it is important to reiterate that, due to its vasodilative effects, normovolaemia [527] and a sufficient blood pressure to guarantee a proper RCA perfusion are prerequisites before commencing levosimendan administration. If necessary, a combination with noradrenaline will be required [527–529].

4.5.2.5 Intra-Aortic Balloon Pump

One of the main benefits of intra-aortic balloon counter pulsation is the increase in diastolic perfusion pressure and coronary blood flow [530–532] which plays a key role in the therapy of RV-F [212, 301, 408, 457, 461–463, 465, 533].

Jacobs [251] states that the IABP is known to be beneficial in the treatment of RV-F but, unfortunately, the IABP is underused in this issue and should be used more frequently in cases of RV-F [410].

4.5.2.6 Hypercapnia and Acidosis

Hypercapnia and acidosis always induce an increase in pulmonary vascular resistance [534, 535] and thus affect the RV-function through an increase in RV-afterload [536, 537]:

$$\text{Hypercapnia / acidosis} \rightarrow \uparrow \text{PVR and concomitant} \uparrow$$
$$\text{PA-pressure} \rightarrow \uparrow \text{RV-afterload}$$

Respiratory balancing with the use of mild hyperventilation is an effective measure to protect the RV from high afterload [536, 538]. A reduction of pCO2 from 50 mm Hg (6.66 kPa) to 30 mm Hg (4.0 kPa) will reduce the PVR and thus the RV-afterload from 700 dyn × s × cm^{-5} to 400 dyn × s × cm^{-5} [536].

4.5.2.7 Oxygen Therapy

Regardless of the underlying pathology, oxygen administration reduces pulmonary pressure and increases CO in patients with pulmonary hypertension [539]. It is widely accepted that alveolar and systemic arterial hypoxaemia contribute significantly to vasoconstriction of the pulmonary vasculature, particularly in diseases such as COPD, ARDS, interstitial pulmonary diseases, pulmonary embolism and extensive pneumonia [37, 540] which result in an increased RV-afterload. Under conditions of systemic arterial hypoxaemia, oxygen administration will lead to vasodilatation of the pulmonary vessels, and as long as there is no manifest fixed pulmonary hypertension, a lower RV-afterload will significantly [75, 541] improve RV-function [75, 542]. Continuous application of oxygen is the only measure to have been shown to reduce mortality in this situation [75].

4.5.2.8 AV Sequential Stimulation

In order to optimise RV-filling (and RVEDP), maintaining or even improving RV-function, AV-synchronous stimulation is essential [310, 543, 544]. Therefore, it is pivotal to maintain or to restore sinus rhythm (cardioversion, Amiodarone, temporary two-chamber pacemaker), as a normal (physiological) atrial function is essential to optimise RV filling [544].

Furthermore, persistent bradycardia will have a negative effect on both LV and RV filling and, as such, atropine or temporary pacing should be used to prevent this [310].

4.5.2.9 Mechanical Ventilation

Mechanical positive pressure ventilation contributes to an increase in RV-afterload [46, 326, 329, 545] due to an increase in transpulmonary pressures [33, 42–44, 322, 323], potentially leading to a deterioration in RV-function [328, 484] (as described above). Mechanical positive pressure ventilation also increases the risk of DVI by raising the pleural and thus the pericardial pressure (PP) [331]. Therefore, intubation and ventilation with positive pressure support should be avoided in patients with RVD/RV-F, if possible [546]. If mechanical ventilation is essential, then the levels of the applied pressures need to be controlled. PEEP up to a certain level (~10 cm H_2O), although causing an increase in transpulmonary pressure [35, 47–50, 325] and thus a rise in RV-afterload [326, 327], may improve the blood flow through the pulmonary vasculature [51, 333–335], resulting in a net reduction of the RV-afterload [333], at least as long as RV-F is not manifest [40]. Hence, appropriate PEEP application may display, net beneficial effects, but has to be integrated into the overall ventilatory strategy: A balanced lung- and "heart" protective approach is essential, hence limiting plateau pressure within the airways to < 27 cm H_2O has turned out to best comply with these requirements [81, 340, 342]. If needed,

mechanical ventilation with low tidal volumes (6(−8) mL/kg predicted body weight [344–347]) and relatively low PEEP (8–12 cm H_2O) is appropriate in patients with pulmonary hypertension [21, 348]. However, Groeneveld [547] suggests that using high frequency oscillator ventilation avoids the problem of increasing afterload due to positive pressure.

4.5.2.10 Anticoagulation

In pulmonary hypertension, hypercoagulation in the pulmonary vasculature tree will always be present [548–550] and the development of micro-thrombi is highly likely [483]. Therefore, the use of heparin or LWMH, or oral anticoagulants in therapeutic dosage is indicated in general in pulmonary hypertension [549–553], and oral anticoagulants for long term treatment. The frequently present arrhythmias are a supplementary factor to anticoagulated [554].

4.5.2.11 Digoxin

Digoxin is potentially detrimental in two ways: inducing vasoconstriction in the pulmonary arterial system and altering venous return to the disadvantage of RV-SV [450], and therefore is not indicated in the treatment of RV-D/RV-F [555, 556].

4.6 Summary

(After-)loading the right ventricle will provoke immediate RV dilatation in case the homeometric adaption is deficient or even fails [1, 3, 107]. Particularly acute increases in RV afterload causing an acute afterload mismatch are predisposed to cause acute RV dysfunction or even failure [14, 27, 96, 135]. RV dilatation is accompanied by disproportionate increases in RVEDP [157, 159] and will substantially affect LV—size (and hence LV filling) and function [195, 197–199], predominantly attributed to pericardial constraint and DVI [1, 14, 72, 135, 167, 169, 170, 192], and series effects [193, 194]. Secondary, due to the affected LV systolic function, RV contractile performance (further) suffers [135, 145, 171].

RV dilatation and the attended, basically compensatory measures and reactions including neuro-hormonal and inflammatory-endothelial activation [1, 83, 91, 205, 207, 211] may, however, induce a series of potentially deleterious aftereffects subsequently leading to hypotension, a jeopardized systemic circulation with lurking organ and tissue hypoperfusion, and an even more compromised RV function, ending up with circulatory collapse and shock [93, 95, 96, 135]. While, until recently, accompanying and induced ischemic complications have been considered to be the decisive component in the (often abrupt [89]) final RV deterioration [107, 215, 217, 218], meanwhile other, non-ischemic features, like the excessive LV compression [2, 3, 83, 93], RV-PA-uncoupling [107], RV-LV dyssynchrony [7], myocardial stunning [215], and the “self amplification” of the RV malfunction by the pressure overload considerably affecting RV contractility [22, 223, 224], are recognized factors relevantly involved in the progressive deterioration of RV function [22, 93, 223, 224, 226, 228].

RV-dysfunction or even failure (decompensated state), most commonly caused by LHD [27–29], is clinically characterized by exercise intolerance and signs and symptoms related to fluid accumulation and oedema formation [2, 7, 24, 25, 246, 247], the latter often accompanied by organ, particularly renal, dysfunction [5, 24, 123, 246–248]. Hemodynamically, an elevated RVEDP (≥9–10 mmHg) indicates RV-dysfunction [25].

Essential therapeutic issues include treatment of underlying malady [1, 2, 9, 33], reduction in afterload and reversal/avoidance of hypoperfusion [1, 2, 251, 407–410], improvement of contractility [143, 410, 411], and the correction of malfunctional ventricular interaction [167, 168, 251]. As such, the following overview by Naeije and Manes [135] (see Fig 4.4) summarizes the measures constituting the essential therapeutic armamentarium:

(1) Coronary intervention in patients with acute myocardial infarction affecting the RV (culprit lesion of the RCA or RCX) [412–417],
(2) Thrombolysis in case of pulmonary embolism [106, 107, 418–420],
(3) Diuretics rather than fluids [193, 391, 444] to treat RV dilation and pericardial constraint/DVI effects [348, 447],
(4) Oxygen in case of pulmonary embolism and states of relative low SaO_2 < 90–92% potentially inducing hypoxic pulmonary vasoconstriction [539],
(5) Selective pulmonary vasodilators to reduce RV-afterload [489–493],
(6) Lung and heart protective ventilation strategy in mechanically ventilated patients [340–343],
(7) Noradrenaline if hypoperfusion and/or hypotension are present [457–470], and
(8) Intropic agents to improve RV contractility (via enhanced LV performance) [143, 173, 174, 179, 410, 411].

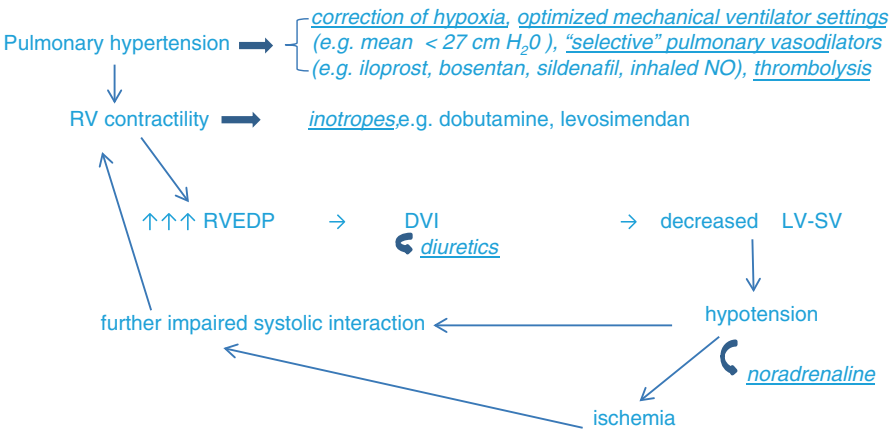


Fig. 4.4 *Overview of treatment* options, figure by Naeije and Manes [135] with permission

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Heart Failure with Normal Left Ventricular Ejection Fraction (HFNEF)

5

5.1 Definition and General Remarks

To diagnose heart failure with preserved ejection fraction (HFpEF), the following three criteria have to be fulfilled [1–8]:

1. **Signs and symptoms** generally present in **heart failure**, and
2. **Preserved left ventricular ejection fraction**, defined as LV-EF ≥ 50%, in the presence of a normal LV end-diastolic volume (LVEDV), defined as <97 mL/m^2 [1, 7, 9] and,
3. Evidence of **diastolic dysfunction** *and/or* **relevant structural cardiac alterations**

   (To fulfill criteon 3, the European Society of Cardiology asks for the following two to be present: elevated natriuretic peptides and either (I) proof of a relevant structural cardiac abnormlity (indicated by an enhanced LA size, LALVI, or a left ventricular muscle mass, LVMI, above the normal range), or/and (II) proof of abnormal diastolic properties, diastolic dysfunction [3]).

The criteria defining the syndrome used by authors based on the latest ACCP/AHA [4] and ESC guideline [3] have merged closer together, particularly the range of LV-EF. However, in the most recent, 2016 guideline, the ESC definition demands increased natriuretic peptide serum levels in addition to either diastolic dysfunction and/or signs of a structural heart disease [3], thus strengthening and appreciating the importance of biomarkers and structural abnormalities.

HFrEF (heart failure with reduced ejection fraction) is indicated by signs and symptoms typically present and constituting heart failure, and a **LV-EF < 40%** [2–4].

Furthermore, recently both the AHA/ACCP and the ESC introduced a *mid-range* (**HFmEF**) [3] or *borderline* [4] type, a group with a LV-EF between 40 and 49% (41–49% ACCP/AHA) but otherwise featuring all other HFpEF criteria.

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Specific *diagnostic criteria* (read below, Sect. 5.5) delineate exactly the findings and parameters indicative for a structural heart disease and/or suggestive for diastolic dysfunction.

HFpEF is a considerably complex malady [8, 10, 11] of broad phenotypic heterogeneity [12, 13], and multi-facet pathophysiology [9, 13–15], may potentially afflict various organs [13, 15], and mostly goes without a specific etiology but with miscellaneous pathogenetic underlying causes [13, 16–18]. Its clinical spectrum typically varies from dyspnea on exertion to even acute pulmonary edema [19–21]. Since diastolic dysfunction (DD) is a dominant, if not the dominant [9] feature of this disorder [11, 22–24], taking a key role in HFpEF pathophysiology [22, 25, 26], HFpEF has frequently been referred to as "diastolic heart failure" (in contrast to "systolic heart failure" or HFrEF) in the past [8, 27]. Indeed, more than 2/3 of all patients with HFpEF display DD at rest [28–30], during stress even up to 80–90% are found to develop abnormal diastolic properties [31]. Hemodynamically, DD impairs ventricular filling [32, 33] with a higher LVEDP for any given end-diastolic volume [34].

However, meanwhile it is quite clear that DD is not a unique finding in patients previously classified suffering from diastolic heart failure, but also occurs in patients with "systolic" heart failure (heart failure where the ejection fraction is reduced) [2, 33, 35, 36], is present in many asymptomatic elderly (60–80%) suffering from hypertension [37–40], and even more, altered diastolic properties are a very common and arguably physiological observation in elderly individuals associated with the aging process [37–39, 41–44]. Consequently, HFpEF is known to predominantly afflict older hypertensive patients [45].

Traditionally, DD has been considered to be an important intermediate step in the development of HFpEF, notifying, if displayed, that hypertension (HTN)/hypertensive heart disease (HHD) may progress to heart failure with preserved ejection fraction [46, 47], and chronic hypertension was thought to potentially turn into HFpEF [48, 49]. Meanwhile, "hypertension is neither necessary nor sufficient for HFpEF development" as Desai writes [48]. Many clinical conditions, myocardial as well as non-myocardial ones, are known to be associated with and may predominantly cause (acute) heart failure with normal ejection fraction, including valvular heart diseases, congenital heart disease, pericardial disease and primary (isolated) right heart failure with basically normal systolic LV function [50–52], whereupon abnormal diastolic function is the most common pathophysiology applying in these cases [51, 52].

Also, quite a number of other features have been acknowledged to be present and contribute to the pathobiology of HFpEF such as impaired LA-function [53], chronotropic incompetence [54, 55], right ventricular dysfunction and pulmonary hypertension [56–58], and even limitations in LV systolic capabilities are present in patients with HFpEF [59, 60]. Moreover, modifications and abnormalities of "extracardiac" features may arise in HFpEF patients being crucially involved, including altered vascular properties affecting LV afterload and ventricular—vascular coupling conditions [53, 54, 61–63], changes in preload circumstances (circulatory volume overload) [64], neuroendocrine activation [65], as well

inflammation/endothelial dysfunction [66, 67], and impaired peripheral vasodilator reserve [54, 68, 69].

As such, a very heterogeneous group of patients with different etiological features and several pathophysiological mechanisms applying and contributing may display the syndrome of HFpEF [70]. Consequently, recent findings and facts, recognizing that diastolic dysfunction is not the only underlying abnormality in this syndrome, have led to change the term diastolic heart failure, which implies a single operating pathophysiology [71].

Moreover, the initial consideration, HFpEF may be a precursor of HFrEF, being part of the same disease process, which may potentially step forward to HFrEF, and in which HFpEF and HFrEF indicate the two extremes within a continuum of a single disease [72, 73], has been abandoned due to a lack of evidence [9, 13, 15, 33, 74–76]. Of course, there may be overlaps as some patients with HFpEF are shown to lose up to 5.8% of their EF per year finally ending up with an EF < 50% (40%), while those with reduced EF may show improvements [74]. It is assumed and very likely that a transition from HFpEF to HFrEF may, in turn, occur due to additional adverse events, particularly intercurrent myocardial ischemia and infarctions causing loss of cardiomyocytes [77].

Nevertheless, all available evidence strongly suggests to consider HFpEF as a separate, distinct entity which has to be distinguished from HFrEF: The two syndromes differ in elementary issues of the pathogenesis and pathophysiology, in their etiologies, clinical and demographic characteristics, structural (cardiomyocyte hypertrophy [78] and myocardial fibrosis of varying degree [79]) and functional (cardiomyocyte stiffness [78, 80]) features, time to clinically overt malady, neuroendocrine response and biochemical parameters, associated co-morbidities and, of great importance, in their response to therapy [11, 14, 27, 66, 78, 81–84]. While HFpEF is basically attributed to endothelial dysfunction, HFrEF has to be considered as a disorder of the cardiomyocytes [27].

5.2 Epidemiolgy and Aetiology

At least 50% of all patients presenting signs and symptoms of heart failure have a normal or only minimally impaired global systolic LV function, thus suffer from HFpEF [34, 81, 85–89]. Moreover, Owan recognized that the occurence of HFpEF in all heart failure cases (HFpEF and HFrEF) increased from 38% to 54% within the last two decades [81]. Indeed, compared to HFrEF, the relative prevalence of HFpEF is increasing by 10% per decade [8, 81, 87, 90, 91], and the “true” prevalence of HFpEF in the general population is estimated at 1–5.5% [92].

HFpEF surely is a disorder of the elderly as its proportion is increasingly found with older ages [81, 85, 86, 88]. Although elderly women seem to be more afflicted in US [18] and Euopean surveys [93, 94], internationally a more balanced sex distribution appears to exist [95–97]. Comorbidities typically and highly prevalent in and associated with HFpEF (though also related to increasing age) include hypertension (60–80%), obesity (41–46%), diabetes mellitus (13–76%), coronary artery

disease (20–76%), atrial fibrillation (15–41%), impaired renal function (40–55%), and hyperlipidemia (16–77%) [81, 85–87, 91, 98–101].

Readmission rates add up to nearly 30% within 60–90 days after discharge [102] and to roughly 50% within 1 year [103].

Mortality rates recently reported in the literature describe in short term (30–90 days) 5–9.5% deaths [86, 87] , 29% deceased patients after 1 year since diagnosed and 68% (55–74%) after 5 years [87, 88, 91]. As such, the prognosis of HFpEF is definitely similar to, and as grim as, those found in patients with HFrEF (32% after 1 and 68% after 5 years) [85–88, 104]. However, in contrary to patients with HFrEF, the reasons of mortality in HFpEF are more often due to non-heart failure cardiovascular issues [18, 105, 106], reaching 40% of the causes of death [107, 108].

Consequently, in the majority of patients with HFpEF, a specific etiology cannot be determined [9, 13, 16, 83], rather, "HFpEF occurs most commonly in the elderly who have one or more co-morbidities like hypertension, obesity, diabetes, metabolic syndrome, chronic kidney disease, atrial fibrillation, and/or anemia" [109]. As such, the co-morbidities exert a considerable impact on the pathogenesis of HFpEF [9, 13, 17, 42], and HFpEF may be considered to be the "identical" clinical result of different diseases with diverse and miscellaneous underlying pathophysiologies [7]. Nevertheless, in some cases a (more) specific cause, usually provoking diastolic dysfunction and concomitant/consecutively HFpEF, may be identified as in case of hypertrophic, restrictive, infiltrative, or genetically determined cardiomyopathies as well constrictive pericarditis or cardiac fibroelastosis [50, 51, 83].

5.3 Aetiopathogenesis and Basic Pathophysiological Issues and Considerations

Heart failure with preserved ejection fraction, accounting for more than 50% of all heart failure cases [81, 89], is henceforth recognized as a separate and discrete clinical syndrome rather than a "milder form" and/or precursor of HFrEF as growing evidence clearly indicates [73].

Exercise intolerance with often severe dyspnoea on exertion and acute pulmonary edema are the key clinical pictures HFpEF patients present [19–21]. 2/3 of all HFpEF patients feature LV diastolic dysfunction at rest [28, 110], however up to 80–90% may display abnormal diastolic properties during stress [31]. Accordingly, LV diastolic dysfunction, as a central factor in the pathobiology and a pathophysiological hallmark of HFpEF [22, 24, 25], evokes, either alone or in combination with other pathophysiological features [1, 22, 25], the phenotypic, clinical appearances and the elevated filling pressures (a general finding in any kind of heart failure [111]) present in this syndrome [22]. The other features include combined ventricular-vascular stiffening (notably enhanced central aortic stiffening and (consecutively) blunted ventriculo–arterial coupling) [55, 61, 62, 68], impaired systemic vasodilator reserve [24, 54], systolic limitations [49, 112, 113], and extra-cardial causes like volume overload [114] and pulmonary hypertension [56, 58, 115] with subsequent ventricular, mostly diastolic interactions [41].

LV diastolic dysfunction underlying HFpEF is, in the absence of pericardial and endocardial disease [116], attributed to abnormal diastolic myocardial stiffness [8, 116, 117]. Diastolic myocardial stiffness is determined by (a) the composition, functional status and the amount of the extracellular matrix (ECM) and by (b) the cardiomyocytes, accurately the cardiomyocyte tension, respectively the cardiomyocyte stiffness which is largely defined by the functional and structural properties of the cytoskeletal giant protein titin [8, 118]. While originally the diastolic passive myocardial and the overall diastolic chamber stiffness have primarily been assigned to be predominantly determined by the collagen quantity and quality of the ECM [14] and by collagen crosslinking [119, 120], most recent study results revealed that cardiomyocyte stiffness alone has the capability to induce HFpEF without any involvement of the ECM [121]. This is in line with data demonstrating that 1/3 of HFpEF show normal collagen volume fraction although similar LV stiffness and end-systolic wall stress [80]. Meanwhile, several studies on HFpEF patients clearly relate enhanced diastolic LV stiffness to elevated cardiomyocyte stiffness [122–124].

Cardiomyocyte tension and stiffness are largely modulated by titin [125]. Changes in cardiomyocyte properties are reported to possibly occur in the acute setting attributed to alterations in phosphorylation status of titin (relative hypophosphorylation) and intramolecular disulfide bridging (both energy-consuming processes), associated and in conjunction with acute energy deficits [55]. As a result, an acute increase in passive LV diastolic stiffness ensues [126] causing acute cardiac failure [127]. In contrast, the collagen turnover and thus modification may take considerably longer with a known collagen half-life of 80–120 days [128]. Accordingly, increased myocardial stiffness and tension, predominantly caused by cardiomyocyte properties, may arise acutely, whereas alterations of the ECM indicate long-term and chronic changes.

The majority of individuals with DD will never develop symptoms [129], however, worsening diastolic function is identified to decisively contribute to the onset of clinical heart failure symptoms [130]. The transition from compensated conditions to overt HFpEF is reported to be related to profound myocardial stiffening [131, 132]. Drazner [133] recently illustrated in his paper on “the progression of hypertensive heart disease”, that both, (a) the progressive and adverse change of ECM composition and amount [106, 134, 135] enhancing myocardial stiffness [136] in patients suffering from hypertensive heart disease and (b) the (accompanying) increase in LV filling pressures [53, 130, 137], are causally responsible for the transition from HHD to HFpEF—indeed, ventricular passive stiffness substantially impacts LV filling pressures [22, 25]. However, other factors affecting LV-filling pressure such as PH and (subsequently influencing) ventricular interdependence, (consecutive) atrial dysfunction and vascular components, notably enhanced central aortic stiffness [21, 48, 62], may decisively contribute as well [56, 62, 138].

Intermittent or permanent increases in LVEDP potentially facilitating left-atrial dilatation and atrial fibrillation (thus atrial dysfunction) [138], and elevated pulmonary pressures are indicative for clinically relevant DD [31].

Traditionally, DD has been considered to be an important intermediate step in the development of HFpEF, occurring in patients with hypertension/hypertensive heart disease developing heart failure [46, 47], and chronic HTN was supposed to potentially turn into HFpEF [48, 49]: Hypertension has been viewed as being the "predominant factor in the development and the progression to and of HFpEF" [139]. HTN is found to be present in 60–80% of all patients diagnosed with HFpEF [81, 98]. Cellular and extracellular structural and functional changes as well as adaptions are demonstrated in the myocardial tissues and in cardiac function of HTN patients subsequently developing DD [78, 140] and HFpEF [98, 141, 142]. Even mild hypertension can result in DD [143]. As such, chronic pressure overload (e.g. HTN) is recognized to be a leading risk factor and cause of DD [92, 144] and of HFpEF [141, 145].

This prevailing mechanistic view of the syndrome of HFpEF based on classical, traditional knowledge and perceptions (mechanical/neuroendocrine model of heart failure [146]) received even more support by recent analyses and study results enlarging the existing concept by, notably, central and peripheral vascular and v-a-coupling issues ("HFpEF is recognized as a disease of abnormal v-a-coupling" [147]), consecutive and associated PH and ventricular interactions, all potentially influencing and contributing to the pathophysiology and pathobiology of acute heart failure [14, 21, 41, 56, 61, 148]. Furthermore, these features fit very well into the recently provided concept by Cotter, assigning acute heart failure either to a predominantly acute vascular or to a prevailing cardiac, acutely decompensating disorder [149, 150]. However, often both conditions are contributing with only one prevailing [149, 150]. These findings emphasize that the pathophysiology of heart failure is heterogeneous, the syndrome of acute heart failure complex and the disorder obviously of systemic dimension [18].

Anyhow, in recent years, a bundle of considerable evidence, strongly linking HFpEF to systemic inflammation, has been established [66, 67, 151, 152]. Significantly elevated, high levels of pro-inflammatory cytokines and other markers of activated inflammation including tumor necrosis factor alpha (TNFα), several interleukins such as IL-1, IL-6, monocyte chemotactic/chemoattractant protein 1 (MCP1), adhesion molecules such as intercellular adhesion molecule-1 (ICAM1) and vascular cell adhesion molecule-1 (VCAM1), and CRP, at least hsCRP (high sensity), released by immune-competent cells (neutrophil granulocytes, monocytes, macrophages, T cells), but endothelial cells and even vascular smooth muscle cells as well [141], are consistently laboratory-confirmed assured in blood samples (and thus within the systemic, peripheral circulation) of heart failure patients [153–156]. Being further of substantial prognostic relevance, these inflammatory mediators, and thus inflammation as such, are considered as being crucially implicated in the disease process [152]. Indeed, increased levels of inflammatory features are independently associated with asymptomatic diastolic dysfunction [157], and repetitive and progressive inflammatory episodes are demonstrated to be strongly associated with the progression of ventricular diastolic dysfunction to HFpEF [154, 158]. Furthermore, a recently published study provides distinct evidence that systemic inflammatory conditions are predictive of incident HFpEF [151], a strong sign of a causal impact of inflammation on the aetiopathogenesis of HFpEF [141, 159].

Moreover, HFpEF, a disease of the elderly [89, 144], is typically accompanied by a range of comorbidities including arterial hypertension, obesity, diabetes (as a rule type II), metabolic syndrome, coronary artery disease, chronic kidney disease, and COPD [85, 86, 142, 160]. All these disorders have been identified as being risk factors for, and precursors of, incident heart failure [161–164]. Furthermore, these maladies are independently associated with early development of diastolic LV dysfunction [165–168]. All these pathologies deploy low grade systemic inflammation [66, 141, 151, 169, 170]. "HFpEF is, compared to asymptomatic patients although as well suffering from obesity, diabetes, HTN, etc., characterized by an increase in cardiac inflammation" [66]. Moreover, metabolic risk factors are not only strongly associated with inflammation, but also with endothelial dysfunction, oxidative stress, impaired myocardial energetics, abnormal cardiomyocyte Ca-handling, reduced NO bioavailability, and maladaptive cardiac remodelling [171–173].

Inflammation per se is a protective response to physiological and unphysiological stimuli, injuries and insults of any kind, e.g. infection, and applies by interactions between cell surfaces, extracellular matrix, and pro-inflammatory mediators [174]. It is basically a vascular answer to any stimulation or threat [175, 176]. Although traditionally considered to be a local process, inflammation may potentially enlarge to a systemic condition [177]. Janeway and Travers state: "The inflammatory response has to be recognized as a systemic process rather than "purely" a local reaction" [178].

Inflammation is inevitably associated with endothelial activation and dysfunction: Endothelial cells are recognized to considerably participate in the initiation, maintenance, and amplification of inflammatory processes [179, 180] and as such, endothelial cells are an integral component of the early innate immune response (conditional innate immune cells) to injury of any kind [181]. The distinct and very close correlation between inflammation and endothelial dysfunction is well established [182]. Inflammation causes endothelial dysfunction [112, 183, 184], subsequently, the dysfunctional endothelial cells display a number of features contributing to and, in turn, amplifying the inflammatory process [181].

Endothelial dysfunction (ED) refers to an "activated" endothelium denoting a maladaptive response to pathological stimuli [185]. Thus, systemic inflammation potentially affects the whole body, more accurately is likely to activate the endothelium of the whole body including the coronary microvasculature and central cardiac endothelium, e.g. endomyocardium [66, 146].

Indeed, cumulating evidence indicates that the **inflammatory condition** and the **endothelial dysfunction** [182, 186] must be **central** and **crucial** features in the **pathobiology of HFpEF** [24, 66, 67]. Endothelial dysfunction is associated with cardiovascular diseases, e.g. coronary artery disease, hypertension, diabetes, chronic renal disease, and noticed as a systemic disorder [187–190]. As a result of accumulated co-morbidities, the unifying affection acknowledged and with considerable implication in the pathobiology of HFpEF is endothelial dysfunction (ED) [48]: Comorbidities present in HFpEF lead to ED [117].

Compared to age-matched controls, patients with HFpEF display ED, and ED is related to adverse outcome [67]. Thus, the endothelium takes a central position in

the (inflammatory) response, coordinating and "orchestrating" the reply and the reactions to the metabolic, biomechanical, and chemical threats provoked by the co-morbidities [179, 180, 191].

The cardiac endothelial tissue encompasses the endocardium, the intramyocardial capillaries, and the endothelial cells of the coronary microvasculature [117]. The central endothelium, comprising the vessel network of heart and the pulmonary blood flow path, constitutes the largest endothelial surface of the body [192], decisively contributing to the development of heart failure with preserved EF [192]. Endothelial cells are capable to communicate bidirectionally [193, 194]. The cardiac endothelium is demonstrated to modulate cardiac performance [195] since it affects, by autocrine/paracrine signalling (by releasing factors such as NO, ET-1, and natriuretic peptides), the contractile properties [196]. The acute cardiomyocyte function decisively depends on cardiac endothelial cell condition and function [195, 196]. Accordingly, the influence of the endothelial cells on different cardiac cells emphasizes the importance of ED in and the impact of ED on the pathobiology of HFpEF [192, 197]. The "systemic" ED and especially the coronary microvascular endothelial inflammation (see below the new concept by Paulus and Tschoepe, see Fig. 5.4) are not only important bystanders of HFpEF, but play a pathophysiologic relevant and causative role in that syndrome [159, 192].

Hence, the comorbidities commonly seen in patients suffering from HFpEF induce a systemic inflammatory state and as such will afflict the central endothelial cells of the coronary microvasculature and of the endocardium causing ED as clearly evidenced by histologic-bioptical studies [66, 123]: The systemic inflammation is suggested to gradually affect (inflame) the cardiac microvasculature [66], causing ED [197, 198] and subsequently impacts on the interaction between cardiac endothelium and the cardio-myocytes [66, 117, 199, 200], so that finally the myocardium may be inflamed [66, 199]. The expression of adhesion molecules [66] facilitates the recruitment, activation, and transendothelial migration of inflammatory cells into the vessel walls and the myocardium [66]. The conversion of fibroblasts into myofibroblasts, which significantly affect ECM composition, collagen synthesis and collagen deposition in the interstitial cardiac tissues, promoting myocardial fibrosis, is stimulated [201] and accompanied by DD [202, 203]. The amount of cardiac ECM and the collagen quantity and composition influence and co-determine chamber stiffness [103], and a correlation between both, myocardial collagen and the amount of inflammatory cells, and diastolic dysfunction could be established [66]. Activated myofibroblasts, for their part, provoke and maintain inflammation by producing chemokines and cytokines stimulating the inflammatory cell recruitment and ED, thus contribute to establish a vicious cycle maintaining and even fuelling the inflammatory and associated processes [204].

The most important biological consequence of ED certainly is the impaired NO bioavailability [117, 159]. Particularly caused by oxidative stress, hyperglycemia following insulin resistance (IR), components of the activated RAAS (namely A II)

and by TNFα [117, 205], the limited NO availability will lead to substantial consequences: The dysfunctional endothelial cells can offer the adjacent cardiomyocytes only a markedly diminished NO supply, this results in disrupted NO-cGMP-PKG signalling (more detailed in the paragraph on pathophysiology), leaving titin hypophosphorylated [78, 122, 205, 206] and facilitates disulfide bridging within the titin molecule [207]. Histologic-bioptic samples of patients suffering from HFpEF revealed reduced PKG activity and low cGMP concentrations in their myocardial tissues, associated with markedly enhanced cardiomyocyte stiffness [205]. Titin decisively determines the elastic properties of the heart [78]: **Myocardial and chamber** passive **diastolic stiffness**, crucially determining LVEDP, are **largely shaped** and assigned to the **properties of the giant sacromeric cytoskeleton protein titin** [125, 208], notably in normal sized heart chambers as typical in HFpEF [121, 209–211]. Elevated diastolic LV stiffness causing DD is basically attributed to elevated intrinsic cardiomyocyte stiffness as numerous studies reported [80, 122–124, 212]. We have substantial evidence indicating that "stiffened" titin alone is able to induce DD and HFpEF [210, 213], independent of ECM and thus myocardial fibrotic state [210].

As such, acutely altered titin stiffness as in energy deficit [55] following acute (myocardial) ischemia with subsequent increase in LVEDP [53, 126, 130, 137] causing acute cardiac failure [127], may be likewise understood as a (predominantly) *cardiac reason* for acute heart failure in terms of Cotter's concept [149, 150]. On the other hand, acute elevations of blood pressure predominantly acting on loading conditions [61, 62, 214] and consecutive (sometimes disproportionate) increases in LVEDP [61–63] may also precipitate acute heart failure, but as a result of primarily acutely changed *vascular properties* provoking an acute afterload mismatch [61, 149, 150].

Reduced NO bioavailability and disrupted NO-mediated signalling pathways and the increased formation of oxidative stress associated with the features activated, are well implicated in the pathobiology of heart failure [215, 216]. Oxidative stress of the coronary microvasculature reduces NO bioavailability, cGMP content, and PKG activity in the adjacent cardiomyocytes [17].

The metabolic syndrome, a cluster of metabolic factors, notably obesity, but even the principally physiologic aging process [217] are all strongly related to insulin resistance (IR) and enhanced oxidative stress, provoking adverse synergistic effects on myocardial structure and function [218]. Obesity, diabetes (type II), and IR are all reported to exert direct adverse effects on the myocardium independently of confounders like HTN or coronary artery disease [171–173]. These co-morbidities present in HFpEF are independently associated with early DD [165–168] and have been prospectively identified as precursors of incident heart failure [161–164]. Hence, metabolic disorders may contribute via enhanced myocardial inflammation, oxidative stress, downregulated NO bioavailability affecting the very important signalling NO-cGMP-PKG pathway, and limited bioenergetics to DD and HFpEF development [55, 127].

The joint detection of soluble ST2[1] and PTX_3[2] within the blood stream, indicative for a systemic vascular inflammation in the presence of myocardial wall stress, is reported to correlate well with DD and HFpEF, hence substantiating that indeed inflammation is potentially a causal feature of HFpEF [221].

The association between the soluble TNFα type 1 receptor, a marker of systemic inflammation, and incident HFpEF found in elderly individuals further contributes to assume a causal role of inflammation in that type of heart failure [222]. High grade evidence comes from a study by Kalegeropoulos [151] since the results verify that systemic inflammation, induced by the co-morbidities observed in HFpEF, reflected by high levels of inflammatory markers in the circulation including the classical agents TNFα and IL-6, is predictive for incident HFpEF (but not for HFrEF and as such likewise indicating that both disorders are different entities). As the correlation demonstrated persists even after correcting for known heart failure risk factors (co-morbidities, etc.), these study findings are highly suggestive for a direct, causal role of inflammation in the pathogenesis of HFpEF [151].

Hence, it has been inevitably and necessary that Paulus and Tschoepe implemented a novel paradigm of the pathobiology of HFpEF: Their concept applies systemic inflammation as fundamental in the pathophysiology of HFpEF [159, 199]. The common co-morbidities including HTN, diabetes, and obesity associated and observed with HFpEF, cause a marked systemic inflammatory state, thereby also severely affecting the endothelial layers of the cardiac vessel system and even the endocardium, and thus provoke coronary microvascular, endocardial and (consecutively) myocardial inflammation and dysfunction [66, 123]. ED ensues and as a result of inflammation [123, 180, 197, 198], cardiomyocyte stiffening with subsequent DD develops [80, 123, 126, 210, 213] and ECM remodelling arises, leading to myocardial fibrosis, accompanied by DD [66, 120, 202, 203]. Accordingly, ED and microvascular, especially coronary microvascular disease are not only important bystanders of HFpEF but play a pathophysiologic relevant and causative role [159]. For further details of this concept, please see paragraph on special pathophysiology. The results of several animal studies nicely fit and support this new view of inflammation-induced HFpEF [223, 224].

However, HFpEF is not merely a conglumerate of co-morbidities [75, 225]. A study by Mohammed revealed that HFpEF patients, compared to healthy and hypertensive controls, feature more cardiovascular abnormalities than the individuals in either control group (healthy individuals and hypertensive persons), even after adjusting for comorbidities, sex and age [75], a result which is comprehensible and coherent. Furthermore, the outcome of HFpEF is demonstrated to be worse

[1] Soluble ST2 is an inhibitor of the ST 2 receptor (**s**uppression of **t**umorigenicity **2** receptor), a receptor for IL-33, which is markedly induced in cardiomyocytes and released into the blood stream in case of mechanical cardiac stress/overload [219].

[2] PTX3 , pentraxin-related protein, is a strong marker of vascular pathology and notably expressed and released by several cells including fibroblasts, smooth muscle cells, and endothelial cells in case of inflammation [220].

compared to patients with various comorbidities but with no evidence for heart failure: The mortality rates in the HFpEF group added up to 53–76 per 1000 patient-years while in the matched (correcting for age, sex and comorbidity allocation) control groups without HF, the mortality rate ranged between 11 and 47 per 1000 patient-years [226]. However, *that difference was present although the burden of co-morbidities was lower in the HFpEF cohort* [226]. Hence, those findings strongly suggest that HFpEF is not simply a collection of co-morbidities, but rather an independent entity [82]. Moreover, the transition to and deterioration in symptomatic HFpEF is related to additional pathobiological issues affecting the functional and structural myocardial status, including v-a-coupling disorders, neuroendorine activation, energy deficits (deficits of high energy phosphates), PH and ventricular interaction, and likewise ischemia [14, 41, 55, 147, 227, 228]. Ischemia caused by coronary ED potentially causes angina symptoms and may affect systolic and diastolic heart function [228, 229].

The development of HFpEF is strongly influenced by aging, a systemic, basically physiological process principally affecting all organs [230, 231]. LV diastolic stiffness rises with increasing age, even when BP and LV-mass are in physiological ranges [232–234]. With aging, diastolic relaxation is blunted attenuating the effect of diastolic suction [235, 236] and subsequently potentially increases LVEDP. NO-dependent vasodilation is compromised [237, 238], and low–grade systemic inflammation with associated impaired NO bioavailability [199] potentially provoking myocardial fibrosis are typical findings. Chronotropic incompetence, limited systolic function, and shortened cardiac output response to exercise [239, 240] further characterize normal aging. Accordingly, aging predisposes for HFpEF, and comorbidities present substantially aggravate the typical "abnormalities" ensuing with increasing age [68]. Aging and hypertension are considered to be the main risk factors for the development of HFpEF [38, 103], as they are a sufficient cause of HFpEF [48, 75]. Moreover, the presence of HTN/HHD was until recently thought to be inevitable for transitioning from asymptomatic DD to HFpEF [139, 199]. Indeed, HFpEF may, in some cases, "simply" reflect predominantly synergistic effects of the risk factors of elderly individuals [48]. As such, if diabetes and HTN coexist, cardiac abnormalities are demonstrated to be more severe and profound than characteristic for and typically seen in each disorder alone [241]. However, *obesity*, *diabetes*, *HTN*, and *chronic kidney disease* are each associated with *unique* structural and functional alterations in the heart and vasculature of HFpEF patients [75]. Metabolic disorders like obesity, diabetes, and insulin resistance directly display adverse effects on myocardial structure and function and this independently of confounders like HTN or CAD, referred to as "obesity" [171], "diabetic" [173], and "insulin-resistant" [172] cardiomyopathy. In HFpEF related to diabetes, increased LV diastolic stiffness is reported to be primarily attributed to enhanced cardiomyocyte stiffness and to the hypertrophy of cardiomyocytes [123, 126]. As those diabetic patients did not suffer from HTN, cardiomyocyte hypertrophy was definitely not due to pressure overload, but rather a specific effect of the diabetes [146]. In diabetes and insulin resistance, oxidative stress, generated via several pathways including the accumulation of advanced

glycation end products (AGE), is markedly enhanced [146], further coupled with reduced oxidative defence, thus, an inflammatory milieu ensues [242]. Subsequently, NO bioavailability is substantially diminished (AGEs quench NO [243]) and endothelial function will be considerably afflicted and microvascular inflammation of the coronary vessel network and the endocardium occurs [159]. As a consequence of the critically limited NO bioavailability, hypophosphorylation of titin arises as Heerebeek demonstrated, displaying and/or contributing to cardiomyocyte stiffening [123] and cardiomyocyte hypertrophy—the latter typically eccentric [244]. Comparatively, in chronic pressure overload as in HTN and HHD, myocardial abnormalities, typically including concentric hypertrophy [133, 245], and excessive forms of collagen deposition, which will result in a marked increase in myocardial stiffness, are contributing to DD [136]. In obesity, the relative thickness of cardiomyocytes, indicative for concentric hypertrophy, increases [246].

Worsening DD is clearly shown to be independently **related to incipient HFpEF development** [129, 247]. DD is a prominent manifestation of diabetes [248], and in asymptomatic diabetic patients developing overt HF, *worsening* diastolic function was definitely related to subsequent incident HF [247]. Moreover, diabetic patients with DD have a significantly higher mortality rate [247]. The Relax-study results further emphasize the adverse role of diabetes in the progression to HFpEF [249].

Hence, HFpEF may be seen as a cardiometabolic disorder [146, 199]. Likewise, chronic pressure load as in HTN/HHD is associated with (1) substantial collagen deposition and changes in collagen composition of the ECM, stiffening the heart muscle [136], and (2) considerable enhanced passive cardiomyocyte tension, both verified in HTN patients who subsequently display DD [78, 140]. Further deteriorating diastolic function (which is usually associated with a (further) rise in LVEDP since abnormal diastolic properties require rising filling pressures to ensure appropriate LV filling [53, 137]) may lead to overt HF symptoms reflecting HFpEF [130, 133, 134]. Thus, various features are involved in the process with a transition from a asymptomatic pre-clinical condition (with likewise enhanced inflammatory markers including IL-6 and TNFα [130, 250, 251]) to overt HFpEF [49, 53, 130, 252].

As such, HTN and consecutively HHD have lost their accentuated role in the group of co-morbidities being necessarily present for the transition from asymptomatic DD to overt HF [75, 199]: Paulus and Tschoepe [199] view HTN as "merely one of many comorbidities fuelling systemic inflammation, oxidative stress, and endothelial dysfunction in this syndrome", and, "HTN is neither necessary nor sufficient for HFpEF development" as Desai writes [48] interpreting Paulus and Tschoepe.

However, even this example underlines the prominent heterogeneity of aetiologic factors and patho-mechanisms able to contribute to or even to induce HFpEF. The strong association between HFpEF and systemic inflammatory markers is well explained by (a) the inflammation created and induced by the co-morbidities verified *and* (b) by the hemodynamic-mechanistic features related to increased LVEDP, both causing inflammatory discharge, and as such further

substantially supports the diversity of reasons and mechanisms (inflammation may be seen as a vascular response to **any** threat) found in and characteristic for this type of heart failure [151, 251, 253].

Thus, HFpEF is a very complex disorder with considerable phenotypic heterogeneity, multifactorial pathophysiological pathways, miscellaneous potential etiological factors and multiorgan involvement [13, 117]. Various features are involved in the process of transition from the asymptomatic pre-clinical condition (with likewise enhanced inflammatory markers including IL-6 and TNFα [250, 251]) to overt HFpEF [49, 53, 130, 252]. Accordingly, a "simple" paradigm shift from the traditional mechanistic-hemodynamic (namely afterload excess and vascular failure) approach, which is accompanied by neuroendocrine activation [48, 146], to an inflammatory cardiometabolic disease as suggested by Paulus and Tschoepe [199] will not meet and represent all the facets present, typically assigned to and denoting the syndrome of HFpEF.

Correspondingly, Butler [83] and Tschoepe and vanLinthout [117] point out: HFpEF is a highly complex disorder caused by various etiological features, potentially interacting each other, and as such involves multifactorial patho-physiological pathways. Cardio-metabolic, inflammatory conditions (precipitated by physiological aging possibly amplified by a range of comorbidities commonly accompanying HFpEF) essentially go along with altered mechanical cardio-vascular properties, incited neuroendocrine activity, and altered pulmonary hemodynamics, thereby predispose ensuing overt heart failure.

However, even Butler's and Tschoepe's and vanLinthout's characterisation probably does not describe explicitly enough the wide spectrum of etiological and pathophysiological features verified to potentially contribute to the entity of HFpEF as their annotation does not literally refer to the most essential issue: Analyzing hemodynamic data at rest and when exposing patients with HFpEF to stress, HFpEF is precipitated by a bundle of *cardiovascular* disorders with heterogeneous underlying pathophysiologies [14, 25, 114]. These include diastolic dysfunction [22, 24, 25, 38] as the central and most common (but not exclusively [68]) pathophysiological hallmark, altered structural and functional systolic myocardial (impaired contractile function, particularly limited contractile reserve) and vascular properties (vascular stiffening and consecutively modified v-a-coupling), blunted (peripheral) vasodilatory response (largely a result of endothelial dysfunction), chronotropic and lusiotropic abnormalities, and the (consecutively) affected pulmonary circulation/RV-PA-unit [14, 21, 25, 56, 58, 62, 78, 114, 117]. **Altered LV filling mechanics** are the characteristic pathophysiological feature present in all HFpEF patients [254, 255]. They are the result of both "intrinsic structural and molecular alterations" [254], on the one hand attributed to cardio-metabolic, inflammatory aberrations thereby stiffening the left ventricle (heart muscle), and on the other hand assigned to an "increased vascular load imposed by a stiffened arterial vessel system" [254]. A stiffened ventricle and/or an altered vascular load affect ventricular–arterial coupling, and since the pulmonary circulation/RV-PA-unit is generally also afflicted, mainly through the elevated left ventricular filling pressures [254], HFpEF may indeed be considered as a *coupling malady* [254] (Fig. 5.1).

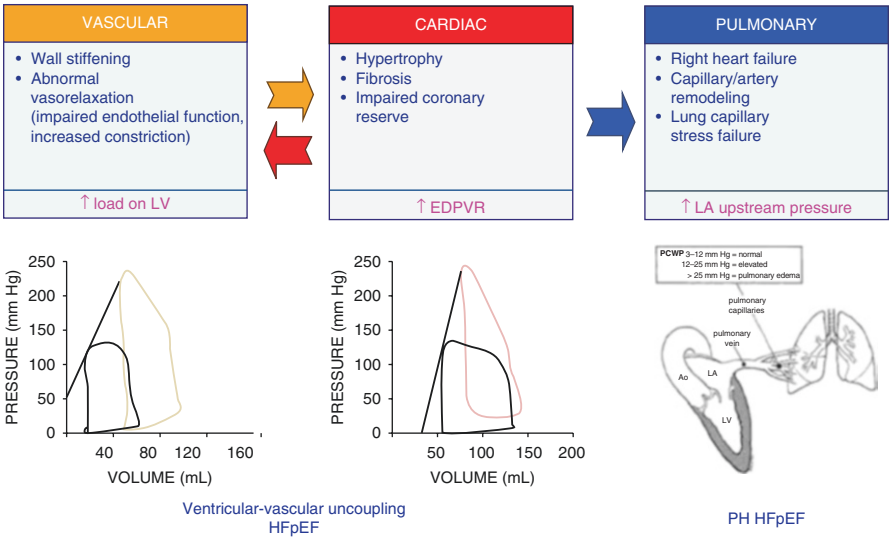

Fig. 5.1 Adapted from Guazzi Circ Heart Fail 2014, 7: 367–377 [254] with permission. The diagram sequence depicts that both, altered vascular (*left picture*) and structural cardiac (in the *middle*) properties affect LV filling mechanics resulting in elevated LV-filling pressures and modified systolic ventricular elastance. Consecutively, ventriculo–arterial coupling conditions change and coupling becomes derranged. These alterations, at the head the increase in LVEDP, are transmitted backward, impacting the pulmonary circulation. Subsequently, the pulmonary circulation and the right heart become involved (*picture on the right*), effecting the coupling between the RV and the pulmonary vessel bed, and ending up in pulmonary hypertension due to left heart disease (PH following HFpEF). As such, HFpEF may be viewed as a coupling disease.
Legend: EDPVR: End-diastolic pressure-volume relation

5.4 Special Pathophysiology

5.4.1 The Pressure-Volume Relation and the Filling Pressure (LVEDP) in HFpEF

Heart failure is basically associated with elevated LV filling pressures [256, 257], since it is defined as the inability of the heart to supply the bodies' tissues suitably with blood in order to meet their metabolic demand, *or to do so only at the cost of elevated filling pressures* [258, 259]. Hence, elevated left-ventricular end-diastolic pressures (LVEDPs) are a general finding in all heart failure patients [82, 111, 259]. Accordingly, elevated filling pressures are universally seen, at least during (physical) exertion [20, 24], in the syndrome of HFpEF [22, 130, 252, 260]. These elevated LV filling pressures are essentially attributed to diastolic dysfunction, the leading pathomechanism of HFpEF patients [22, 53, 78, 80, 130]. Diastolic dysfunction basically results from increased chamber and myocardial stiffness, subsequently displaying elevated filling pressures [25, 31, 130], the main physiologic consequence of diastolic dysfunction [261].

Diastolic dysfunction has been defined "as the inability to fill the ventricle to an adequate preload volume (end-diastolic volume, EDV) *at acceptable low pressures*" [262]. Myocardial stiffness and relaxation largely determine ventricular

diastolic function [263] and therefore ventricular chamber stiffness [264]. In the vast majority of HFpEF patients, a **considerable increase in chamber stiffness** (impaired LV compliance due to altered cardio-myocyte stiffness and modified extracellular matrix composition) is evidenced [22, 25, 55, 78], furthermore, a **delay in and hence an incompletion of myocardial relaxation** [22, 25] may be seen. The latter will become particularly evident (a) during tachycardia (e.g. physical stress), as a shortening of the diastole and thus of the LV filling period results [7, 260, 265], and (b) in case of an acute increase in afterload (e.g. acute rise in blood pressure/hypertensive dysregulation [62, 266]) since active relaxation is reported to be slowed and consecutively prolonged by acute elevations in LV afterload [266, 267]. Both conditions (shortened diastole and elevated afterload) are delaying and blunting the drop in LV-LA- pressure gradient during early diastole and thus impair diastolic suction [268] thereby contributing to the elevated filling pressures found in that syndrome [257].

However, it is mainly the LV stiffness as the predominant underlying abnormality, which induces and contributes to the elevated filling pressures [25, 130]. The increase in myocardial diastolic stiffness, reflected by a **leftward and upward** shift of the PV-relationship leading to a steeper slope [22, 260, 269, 270] (see Fig. 5.2), is largely attributed to cardiomyocyte stiffening (with an increase in cardiomyocyte stiffness as the disease inherent process), and, to a lesser extent, to an altered (active) diastolic relaxation [121, 209, 271, 272]: It is basically the giant elastic sarcomeric protein titin, regulating myocardial passive tension and stiffness [208], which determines

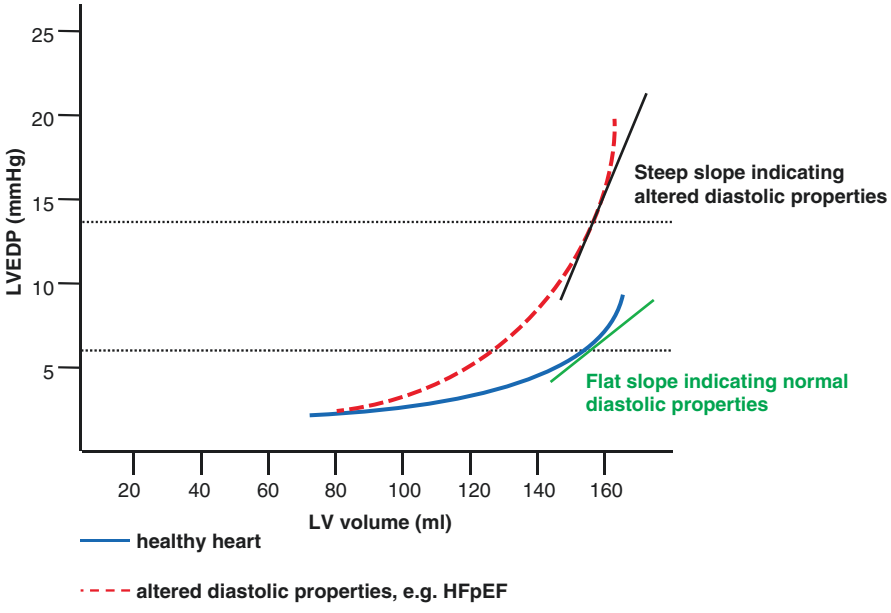

Fig. 5.2 Diastolic pressure–volume (P-V) relation—observe the different gradients of the slopes of the respective curves. Adapted from Borlaug BA. Circulation Heart Fail 2014;7:2–4 [273], with permission

myocardial and LV chamber stiffness as numerous studies have shown [78, 80, 122, 124]. Titin contributes roughly 80% to LV passive stiffness as long as sarcomere length ranges within the physiological band of 1.8–2.2 μm (as they indeed do in HFpEF), while the influence/contribution of ECM becomes more important in dilated sarcomeres of >2.2 μm [209, 211]—as in HFrEF. Furthermore, the impact of the influence of an altered relaxation on the magnitude and on the curvature of the relation has been challenged and significant increases in LVEDP resulting from slowed relaxation have never been clearly assured in studies and thus may be queried [121, 271, 272].

However, not all studies found a **steeper slope** (reflecting changes in diastolic properties) of the pressure-volume relationship underlying the increase in LA and LV filling pressures in patients with HFpEF [62, 114]. This is suggestive for reasons and mechanisms other than **primarily** altered **(intrinsic)** diastolic properties being responsible for, and/or contributing to, enhanced filling pressures consistently found in that patient group [262, 273]. Elevated filling pressures are verified to be caused also by parallel upward shifts of the P-V-relation (Fig. 5.3).

Parallel upward shifts of the P-V-relationship, but with no change in its slope and thus similar LV "intrinsic" diastolic properties (unchanged cardio-myocyte

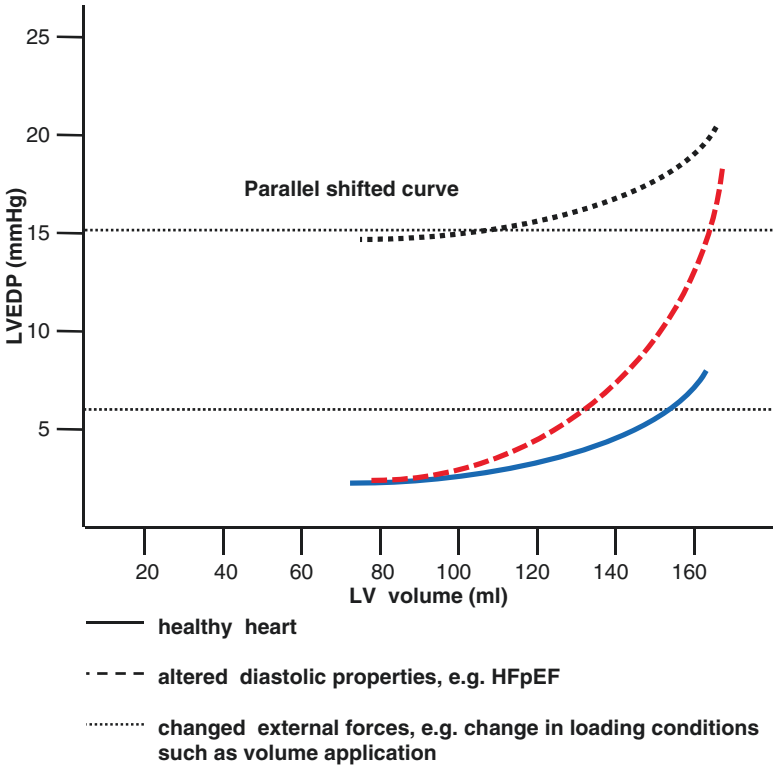

Fig. 5.3 Acute volume loading, but also acute increases in afterload, e.g. raised systolic blood pressure, may lead to a parallel upward shift of the p-v relation as they alter extrinsic conditions, while represents true changes in intrinsic diastolic properties. Adapted from Borlaug BA. Circ Heart fail 2014, 7:2–4, with permission

stiffness and extracellular matrix composition [262, 275]), are in general attributed to **"extrinsic" reasons** and altered **"extrinsic"conditions** [275–277], namely altered right ventricular loading conditions and changes in pericardial constraint with consecutive perceptible and enhanced diastolic ventricular interaction (DVI) [256, 273, 274]. DVI is found to be notably present in case of elevations in pulmonary pressures (PH) [278–280], potentially resulting from heart failure of any reason [281, 282]. Pulmonary hypertension is an exceptionally common feature in patients suffering from HFpEF [115, 283, 284], and enhanced diastolic ventricular interaction is common in patients with left-sided HF and PH [285]. Other "extrinsic" features include volume overload [114], endocardial diseases [116] and, of special importance, altered ventriculo–arterial coupling [62]. As explained elsewhere, changes in loading conditions may (subsequently) alter diastolic properties [38, 62, 114, 286, 287]. However, as already demonstrated by Alderman and Glantz, **acute changes** in chamber stiffness are largely caused by **external forces** and their associated effects [275], and are generally not able to alter intrinsic diastolic myocardial properties of normally oxygenated myocardium [275, 288] (Fig. 5.3).

This diversity of possible (patho)mechanisms and circumstances does indeed explain the divergent study results and appreciate the mechanistic heterogeneity found in the pathobiology of HFpEF [25, 256, 274].

5.4.2 Pathomechanisms

5.4.2.1 Diastolic Dysfunction

Diastolic dysfunction (DD) is a hallmark and central in the pathophysiology of HFpEF [22, 24, 25]. The vast majority of patients suffering from HFpEF display DD [29, 30], at least during physical activity (80–90%) [31].

In the absence of endocardial or pericardial disease, diastolic LV dysfunction results from increased myocardial stiffness [8], which is regulated by extracellular matrix (ECM) and the cardiomyocytes [8]. Furthermore, a change in the stiffness within one compartment (intracellular–extracellular) is also transmitted to the other compartment via matrix cellular proteins [8].

Diastolic LV dysfunction consists of prolonged isovolumetric LV relaxation, slow LV filling, and increased diastolic myocardial stiffness [289–292], whereupon myocardial stiffness has turned out to be by far the predominant feature [257, 293]. Furthermore, 1/3 of all HFpEF patients are found to have normal myocardial collagen volume fraction despite similar high LVEDPs compared to those with elevated collagen ratios [80]. Accordingly, elevated (passive) diastolic LV stiffness is basically attributed to elevated "intrinsic" cardiomyocyte stiffness, meanwhile confirmed by numerous study results [80, 122–124].

ECM

In HFpEF, an elevated total amount of collagen with an excessive collagen type I deposition (due to exaggerated synthesis and a depressed degradation, thus collagen turnover [119, 294]) and an intensified collagen-cross linking [8, 136] are contributing to diastolic

dysfunction [120]. Fibroblasts will be stimulated, mediated by TGF-β (transforming growth factor, a cytokine), which is released by inflammatory cells, to transdifferentiate into myofibroblasts, decisively involved in ECM collagen production fascilitating fibrosing [66]. Furthermore, reduced NO bioavailability (details read below) attributed to endothelial dysfunction contributes to the fibrosing of myocardium by affecting the cGMP-pathway, exerting direct fibrotic properties [295, 296]. NO deprivation promotes endothelial cells to transmit to mesenchymal cells which stimulate fibroblasts/myofibroblasts facilitating fibrosis [297]. Collagen per se is a stable molecule with a long turnover (80–120 days [298]), thus the fibrosing process is more a long term issue and not involved in acute disorders. Factors disrupting (myocardial) collagen balance include ischemia, enhanced wall stress, A II, and TGF-β, provoking altered collagen synthesis, composition and deposition leading to pathological tissue fibrosis [299], subsequently affecting chamber stiffness which is related to the cardiac amount of ECM [103].

Both, hypertensive heart disease and HFpEF are associated with excessive collagen volume, altered collagen composition and function, causing increased diastolic stiffness [136]. However, 1/3 of HFpEF patients have normal collagen volume fraction [80]. Myocardial inflammation is demonstrated to contribute to changes in ECM and to diastolic dysfunction [66], albeit titin's expression/composition (its isoform N2B) and titin's phosphorylation status predominantly determine cardiomyocyte tone and thus passive stiffness [122, 123, 209, 211].

Cardiomyocytes

Intrinsic cardiomyocyte stiffness has been found elevated in HFpEF patients [78, 80, 123]. This stiffness has been referred to as the cytoskeletal protein titin [122, 206, 209, 300–302]. Titin contributes to LV passive stiffness by roughly 80% as long as sarcomer length ranges within the physiological band of 1.8–2.2 μm, while the influence/contribution of ECM becomes more important in dilated sarcomeres of >2.2 μm [209, 211]—as in HfrEF. As such, elevated diastolic LV stiffness is largely/basically attributed to elevated intrinsic cardiomyocyte stiffness as numerous studies have shown [80, 122–124].

Cardiomyocyte elasticity is titin-based adjusted, transcriptionally and post-translationally [127]. Transcriptionally, the stiffer N2B titin (titin is obviously expressed in two isoforms) isoform is, to the disadvantage of the N2BA (more compliant) isoform, stronger expressed in patients with HFpEF [208], thus the ratio (normal hearts 35:65 [208]) of N2BA to N2B isoform is reported as having changed in favour of the stiffer N2B type [206, 209, 301, 302], causing elevated cardiomyocyte and LV stiffness [127]. Furthermore, post-translationally cardiomyocyte stiffening arises from alterations in the phosphorylation state of titin (stiffer if hypophosphorylated) [122, 206, 300], but may be further due to formation of disulfide bridges within the titin molecule, as the result of increased oxidative stress [207]. The phosphorylation is mediated by protein kinase A (PKA) and protein kinase G (PKG), both make titin more compliant while phosphorylating it, and hypophosphorylation of titin is reported as being the result of low PKG activity [9, 78, 127] in consequence of the deficient cGMP concentration [78]—cGMP activates as a second messenger intracellular kinases such as PKG and PKA [303]. This diminished cGMP content is attributed to the low NO bioavailability and the high peroxydinitrate level as both predispose a reduced cGMC production by soluble guanosine

cyclase [304]. The low NO availability is the result of endothelial dysfunction [192], in this case of the microvascular endothelium of the coronary vessels and intramyocardial capillaries, which have been afflicted as part of the vascular endothelial layers of the body by the systemic inflammation related to the "comorbidities" demonstrated in HFpEF patients such as hypertension, obesity, diabetes, metabolic syndrome, and COPD [75, 151, 199]. The, in that setting, released proinflammatory agents elicit endothelial production of ROS (reactive oxygen species) which cause high nitrosative/oxidative stress and subsequently limit NO bioavailability for the adjacent cardiomyocytes [9, 78, 127], as well as NO-mediated signalling [215, 216].

NO is known to enhance LV relaxation and LV distensibility through a number of mechanisms, some are dependent on an intact NO-cGMP-PKG pathway, like reduction of myofilament Ca sensitivity by troponin I phosphorylation and by enhancement of phospholamban—mediated sarcoplasmatic reticular Ca reuptake [305]. Moreover, as a result of the deficient NO-cGMP-PKG signalling pathway, vasodilator response of the coronary mircovasculature is substantially reduced [197].

Figure 5.4 by Paulus and Tschoepe summarizes the pathobiological processes within the heart muscle causing diastolic dysfunction and potentially precipitating HFpEF.

Furthermore, as the peripheral endothelium is, of course, afflicted as well (systemic inflammation), a systemic deficient/compromised vasodilator response exists and, as several studies emphasize, contributes to (explaining) the reduced exercise tolerance typical for HFpEF [68, 306]. Moreover, peripheral endothelial dysfunction is verified to be an independent predictor of outcome [67], accordingly further substantiating the **causal involvement of the endothelium** (of a dysfunctional endothelium) in the pathobiology of HFpEF malady [192].

This blunted vasodilator response correlates with LV diastolic dysfunction [197].

The disrupted NO-cGMP-PKG pathway is able to explain the increased cardiomyocyte stiffness (altered titin expression and hypophosphorylation of titin [300, 301]), the interstitial fibrosis (increased collagen volume and deposition of type I collagen) [78, 120], and the development of concentric LV remodelling with hypertrophied (concentrically thickened) cardiomyocytes [78, 82].

For the sake of completeness, further disorders and malformations may modulate the titin-based cardiomyocyte stiffness [212]: (1) disordered and blunted cross bridge detachment, resulting in bonding of disulfide cross bridges within the titin molecule due to an energy deficit [55, 307], (2) compromised NO signalling [308, 309], and (3) oxidative stress-induced formation of disulfide bridges within the titin molecule [212], leading to slowed relaxation [310].

The slowed relaxation as the second quality of diastole is related to persistent cross-bridging and diminished/altered sarcoplasmatic reticular Ca reuptake [310]. The compromised NO signalling pathway impedes through deficient cGMP content (cGMP reduces myofilamentary Ca sensitivity allowing cross-bridge detachment) cross-bridge detachment [308]. Furthermore, since detachment is an energy consuming process, the diminished ratio of ATP found in HFpEF patients may be a contributing factor [55, 311].

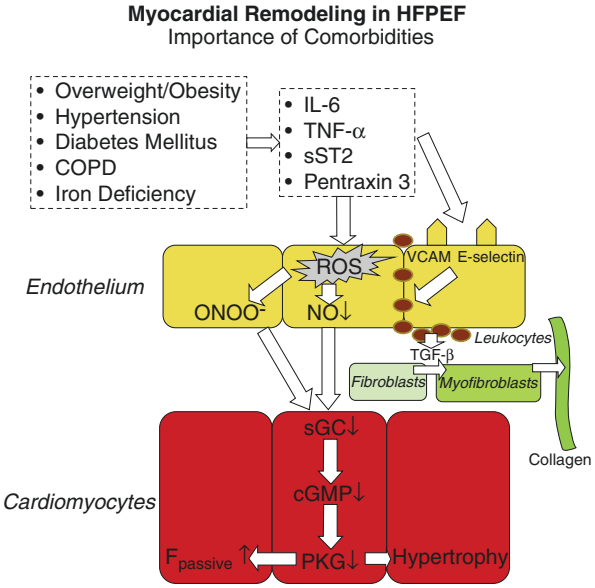

Fig. 5.4 Adopted from Paulus and Tschoepe [199] with permission. A (low grade) inflammatory condition (reflected by elevated serum levels of (pro-) inflammatory mediators, e.g. interleukin (IL)-6, tumor necrosis factor (TNF)-a, soluble ST2 (sST2), and pentraxin 3), induced by several co-morbidities, afflicts the coronary endothelium and the endocardium, and precipitates endothelial dysfunction (resulting largely in reduced NO bioavailability). Consecutively, cardiomyoyctes and the extracellular matrix (ECM) will be affected, precipitating alterations of cardiomyocyte stiffening (preferred expression of titin's stiffer N2B isoform) and fibrosing (change in collagen type and amount) of the ECM. Various signalling pathways and miscellaneous mediators are involved, of special interest is the disturbance of NO-cGMP-PKG pathway causing cardiomyocyte hypertrophy and (further) stiffening (hypophosphorylation of titin). *Legend*: *ROS* reactive oxygen species, *NO* nitric oxide, *VCAM* vascular cell adhesion molecule, *ONOO* peroxynitrite, *sGC* soluble guanylate cyclase, *PKG* protein kinase G, *F passive* cardiomyoyte resting tension, *TGF-β* transforming growth factor β

As such, DD is basically caused by altered diastolic myocardial stiffness [8, 116, 117]. Increases in diastolic myocardial stiffness result in increased filling pressures (higher pressures for the same filling volume) [22, 25, 38, 130, 269, 312]: **Increased filling pressures are the main physiologic consequence of diastolic dysfunction** [261]. Since these elevated left-sided filling pressures are transmitted backward into the pulmonary venule and venous network may pulmonary venous hypertension ensue [38].

Accordingly, ↑ diastolic myocardial stiffness → altered diastolic properties precipitating diastolic dysfunction → ↑ LVEDP → pulmonary venous hypertension [38].

The main (patho)physiologic consequences of these altered ventricular filling conditions [32–34, 38, 312] include:

(1) Ensuing pulmonary venous hypertension [38] and predisposition and facilitation of the onset of pulmonary hypertension and (consecutively) right heart dysfunction [14, 56, 115, 313].

↑ diastolic myocardial stiffness → altered diastolic properties precipitating diastolic dysfunction → ↑ LVEDP → pulmonary venous hypertension [38] → ↑ RV—afterload affecting RV-PA-coupling → acute right heart dysfunction [83].

(2) Small changes in filling volume are going along with significant changes in diastolic pressures [103, 314]. The stiffened ventricle is unable to accommodate increasing filling volume without marked increases in filling pressures [22, 315] and as such, little or even unrecognizable increases in filling volumes are accompanied by considerable changes in filling pressures [21, 26].

(3) A high vulnerability to acutely develop pulmonary congestion or edema [21, 22, 312, 316].

(4) Predisposition and facilitation of the onset of HFpEF, as *worsening* DD is clearly shown to be independently related to incident HFpEF development [129, 247].

(5) Diastolic stiffening leads to fluid redistribution [61] facilitating the development of fluid accumulation within the pulmonary vessel bed and tissue, causing pulmonary congestion/edema and, in general less clinically obvious, peripheral edema formation, thus incipient acute heart failure [317, 318].

However, other features than DD definitely contribute and may even be critical for acute decompensations [1, 14, 25, 61, 62, 114]: Chamber stiffness, and thus ventricular filling characteristics, although largely determined by myocardial stiffness [8, 25] and indeed in the majority of cases altered by changes in diastolic myocardial properties, DD [8, 29, 116, 117], may also be substantially affected by external issues stiffening the chamber [8]. Changes in "extrinsic" features, namely alterations in loading conditions, are in several clinical conditions the predominant factor causing an acutely altered chamber compliance [38, 61, 62, 319, 320].[3] *Acute* changes in chamber stiffness are clearly demonstrated being generally caused by altered external circumstances [275].

5.4.2.2 Vascular Stiffening and AV-Coupling

Vascular properties substantially affect cardiac properties and performance [38, 43, 61–63, 267, 322, 323]: "LV performance is influenced by arterial load [44] (since systolic wall stress reflects afterload as defined by the law of LaPlace [324, 325]), and arterial properties are in turn influenced by LV performance" [44, 326]. Vascular properties, specifically the vascular tone, play an essential role in the development and progression of HF [327]. Moreover, worsening vascular failure is considered to be a common precipitant for AHF [83].

Ventricular–vascular stiffening increases with aging, hypertension, and diabetes, and is abnormally pronounced in patients with HFpEF [53, 81]. This "increase in vascular stiffness has direct implications for the ventricular–arterial coupling" [287], and as such, HFpEF may also be seen as a disease of (altered) v-a-coupling [62, 147].

A physiological feature of aging is the increase in the stiffness of the arteries, particularly of the large elastic ones [39, 328, 329]. This age-associated rise in vascular stiffness, reflected by an increase in arterial elastance E_a [42], poses an

[3] Compliance is the inverse of diastolic chamber stiffness [38, 320].

enhanced load on the heart by increasing systolic wall stress [330]. In order to maintain a stable and matched v-a-coupling, ensuring that cardiac efficiency to transfer blood from the heart into the vasculature is maintained [331], the left ventricular elastance (ventricular end-systolic stiffness), E_{es}, has to rise proportionately in tandem with $E_{a.}$ [42, 43, 49, 130] Furthermore, an "optimized" chamber and coupling efficiency is inevitable and hence prioritized because only then proper and physiological hemodynamic conditions are guaranteed [42, 43, 332]. Consequently, the ventriculo–arterial coupling ratio remains roughly unchanged [43, 57, 62], is somewhat lower but still within the range where external work and efficiency are probably not compromised [331], although, in the elderly, "a stiffer heart is coupled to the stiffer vascular system" [70].

Of special note, the higher resting E_{es} is reflecting a higher end-*systolic* ventricular stiffness, compensating for increased vascular load attributed to "normal" aging, rather than indicative for a better, increased, contractility [37, 61, 230]. In contrary, systolic performance, respectively the systolic reserve capacity is impaired [333, 334].

Furthermore, increased vascular stiffness with subsequently enhanced LV afterload and concomitant elevated end-systolic ventricular stiffness also facilitates diastolic dysfunction [38, 43, 61, 322, 327]: Indeed, an increase in systolic ventricular elastance is associated with both, enhanced ventricular end-systolic but **also** diastolic stiffness [38, 43, 61, 335]. Petrie established an inverse relationship between diastolic relaxation and afterload in hypertensive and non-hypertensive humans indicating cross-talk between arterial load and diastolic LV function [336]. Moreover, an increase in arterial stiffness is associated with diastolic dysfunction [322, 337] and HFpEF [63, 338]. As such, augmented arterial stiffness is associated with both, systolic and diastolic dysfunction [335, 339, 340] at which increases in afterload generally cause a rise in LVEDP [21, 62, 341, 342].

Accordingly, v*ascular dysfunction definitely relevantly affects diastolic properties, implying diastolic dysfunction, augmenting LVEDP* [22, 78, 130].

The clinically most important consequence is that patients with high E_{es} (steeper E_{es} slope) and E_a, due to combined systolic ventricular and arterial stiffening, show an *enhanced systolic pressure sensitivity to changes in cardiac loading conditions* (changes in LV-afterload and changes in LV filling volume, preload) [43, 62, 124, 343]. Increases in afterload (e.g. application of vasoconstrictors) may induce dramatic, exaggerated increases in systolic blood pressure and LVEDP [62], while acute decreases in afterload (e.g. application of vasodilators) may provoke a substantial, disproportionate drop in BP and mostly SV, the latter due to the uneven decline in LVEDP and thus LV filling volume [124]. Likewise, even small changes in volume may be translated by the stiffened ventriculo-arterial system into amplified and disproportionate changes in systolic arterial pressure [43, 343]. Indeed, significant changes in filling pressure may even be seen with little or no detectable change in ventricular volume [21, 26]. In so far, diuretics given to those patients may result in significant blood pressure drops and may potentially induce hypotension and hemodynamic instability [37]. Conversely, application of only small amounts of fluids may provoke pulmonary

edema. The magnitude of the changes depends on the absolute values of E_{es} and E_a [256] and thereby are most pronounced in HFpEF patients since their absolute values of E_{es} and E_a are higher compared to healthy elderly and hypertensive patients/patients with HHD [130].

The enhanced systolic pressure sensitivity, characteristic of combined ventriculo-vascular stiffening, undoubtedly predisposes and is explicit co-responsible for the development of *hypertensive pulmonary edema*, the latter is, together with exercise intolerance, one of the two clinical key manifestations of HFpEF [13, 43, 62]. Gillebert [266] and Borlaug [344] report that "acute afterload elevation in the setting of ventricular–vascular stiffening causes a significant and disproportionate increase in blood pressure which may then feedback to (further) impair diastolic relaxation leading to dramatic increases in filling pressure during exercise". Indeed, every increase in afterload in the presence of ventriculo-vascular stiffening is consecutively attended by (1) a disproportionate upswing in end-systolic stiffness, E_{es} [38, 62] and (2) by a further diminishment of LV compliance [38], accordingly substantially enhanced LVEDPs ensue [38, 315].

Accordingly, for our daily practice with the elderly, hypertensive, and with patients suffering from HFpEF, the following consequences of the above described pathobiological alterations are of particular relevance:

1. A stiffer heart-arterial system displays a higher load-sensitivity, even if the coupling ratio is normal or near normal [70]. Accordingly, a clinically important effect of the combined increase in E_a and E_{es} is, due to the steeper slope of the end-systolic pressure volume relationship with a higher set point for any given volume [41, 70], a considerable lability in blood pressure with substantial fluctuations following even mild alterations in afterload (e.g. increasing BP due to changed sympathetic discharge) and marginal changes in volume loading (preload) [43, 62, 343], or mildest modifications in SV [62, 124].

   HFpEF patients, found to be highly sensitive to changes in loading conditions (volume and pressure load) [43, 61, 62], are especially predisposed to develop pulmonary congestion or actually flash pulmonary edema even in case of only mild, acute increases in BP [21, 62, 345, 346] or yet undetectable volume expansions [43].
2. The "physiological" aging process of the vascular system with consecutive increase in LV systolic and diastolic stiffness [42, 43] may potentially precipitate clinical symptoms (due to impaired hemodynamic performance) in case typical maladies such as hypertension, diabetes, and metabolic syndrome develop on top [44].
3. The systolic reserve capacity is limited in HFpEF patients since the resting E_{es} is already elevated [70]. Accordingly, net stroke work generation, and consecutively SV, increase only mildly during stress, thus blunting chamber emptying and leaving LVESV high, thus limiting cardiovascular performance capacity [43, 68].
4. Extended cyclic changes of arterial blood flow, resulting from enhanced pulse pressure attributed to arterial stiffening, cause larger pulsative pressures and may thereby affect microcirculation, subsequently provoking endothelial dysfunction which potentially spreads over the whole body facilitating end organ damage [37].

5. A heart which has to eject into a stiffened arterial system must generate higher end-systolic pressures to achieve the same net stroke volume [347]. Hence, for any given level of ejected blood, a greater energy requirement is necessary [348, 349]. This may acutely provoke energy deficits precipitating hypophosphorylizations of titin and thus stiffens the cardiomyocytes (even further) affecting diastolic properties [55].

To summarize, arterial stiffening (↑ E_a) affects both, ventricular systolic and diastolic properties [38, 322, 327, 335, 337, 339, 340]:

↑ E_a → concomitant, tandem **increase** in **end-systolic ventricular stiffness**, E_{es} [42, 43, 49, 130].
→ patients work on an already higher end-systolic pressure volume relation with a higher set point for any given change in loading conditions [41, 70]
→ limited systolic reserve capacity and the heart must generate higher end-systolic pressures for the same net stroke volume [347]. This necessitates a greater energy requirement for a given level of ejected flow [348]
→ affects diastolic properties by precipitating **increased diastolic stiffness** [322, 336, 337]:
→ ↑ **LV stiffness** → ↑**filling pressures** [38]
The presence of combined increased/elevated E_a and E_{es} allows for disproportionate increases in E_{es}
→ in case of an acute increase in BP (and thus E_a), a concomitantly exaggerated rise in LVEDP may occur [21, 38, 62, 315]
→ this predisposes for acute hypertensive flash pulmonary edema development [62, 268]
→ "dictates" high blood pressure lability [43, 62, 124, 343] and allows for dramatic blood pressure fluctuations for any given change in loading conditions or SV [62, 124].

5.4.2.3 Systolic Function and Cardiac Reserve

Study results assessing the systolic function of patients suffering from HFpEF have been controversial [24, 49, 60, 112, 269, 336, 350–352]. However, it depends on the method used to assess systolic properties and the question which feature and parameter really reflects systolic performance [49, 60, 112, 336, 353]. As such, although EF is widely used to characterize and to indicate systolic function [14, 60], it does, by far, not represent systolic properties: "EF is only a crude measure of LV systolic function as influenced by several factors beyond contractility per se including loading conditions and chamber geometry" [354]. Indeed, EF is highly dependent on loading conditions and little sensitive to subtle abnormalities [14, 269, 355–357]. Hence, if afterload increases, EF will fall and vice versa (afterload ↑ → EF ↓ and vice versa) [358, 359]. Differently, EF represents ventriculo–arterial coupling conditions and as such is a coupling parameter rather than indicating systolic performance [49, 262]. Nonetheless, by all means it makes absolutely sense that we use EF, as proper circulation and functioning of blood flow decisively depend on both balanced cardiac and vascular properties and their neat and smooth interaction [37, 61].

Meanwhile, due to overwhelming evidence, there is no doubt at all that patients with HFpEF display and show subtle altered, impaired systolic properties [57, 60,

112, 336, 351, 360, 361]. Applying load-independent parameters in tissue Doppler and strain based, as well as speckle-tracking echocardiographic and MR imaging, assessments clearly revealed a couple of systolic abnormalities, confirming diminished systolic performance and contractile power (the most specific feature of systolic function) in patients with HFpEF on the myocardial, but actually also on the chamber level [49, 60, 112, 269, 336, 352, 353, 361]. Particularly longitudinal and circumferential tissue fibre shortening are demonstratedly impaired [60, 353, 361]. The left chamber is reported to thicken in radial layers while it shortens in longitudinal and circumferential plane during systole [362]. Indeed, myocardial contractility, and as such specific systolic properties, are truly indicated and reflected by circumferential midwall fractional fibre shortening [244, 363, 364], and longitudinal strain in particular allows to assess for myocardial deformation, a specific systolic issue [60, 113, 365]. Moreover, long axis function is reported to be affected early on in HFpEF as the longitudinal subendocardial fibre layout is predisposed to ischemia in case of elevated filling pressures and wall stress [366, 367]. Most recently, although even more difficult to assess, subtle systolic issues such as torsion, twist and untwist [353, 368, 369] are found to be altered. Accordingly, substantial evidence clearly demonstrates impaired systolic longitudinal and radial, and compromised twist function in HFpEF patients [49, 60, 351, 353, 361, 370].

The gentle systolic abnormalities and deficiencies become clinically evident in most patients during stress conditions, e.g. physical exertion: The physiological and necessary increase in SV [20, 68, 258] and ejection fraction [68, 371] to adapt cardiac performance during stress fails to appear properly, predominantly as a consequence of the inability of the heart to empty the chamber appropriately (thus unable to reduce ESV,) rather than as the result of limited diastolic filling volumes [19, 68, 258]. This persistently elevated ESV impairs early diastolic suction and thus promotes LA-hypertension [336, 372] and consecutively pulmonary venous hypertension potentially precipitating pulmonary congestion or edema.

However, as Najjar states, “although impairments in contractility are verified, the deficit is only mild and diminished contractility is not the culprit lesion in the pathogenesis of HFpEF” [354].

5.4.2.4 PH and RV Dysfunction, DVI

Pulmonary hypertension is highly common in patients suffering from HFpEF; up to 83% develop PH [56, 285]. Elevated left-sided filling pressures are demonstrated to be transmitted backwards, precipitating congestion in the pulmonary venous system by passively provoking an elevation of the pulmonary venous pressure [111, 281, 373, 374]: Pulmonary venous or postcapillary pulmonary hypertension applies [56, 281, 375, 376]. These elevated filling pressures are related to several features including diastolic dysfunction [22, 25] and ventriculo-vascular stiffening [38, 61, 327, 335, 337], and may even be exaggerated during physical stress or augmented NHs drive (e.g. increase in BP), since physiological processes like “suctioning” are blunted in HFpEF individuals, driving the LA pressure up [138, 260, 353]. Although this (altered) “behaviour” may in principle make sense as the stiff ventricle can only

fill at the expense of elevated LA pressures [20, 260], acute further increases in left-sided filling pressures will add up to pre-existing pulmonary pressures [24], and concomitantly further enhance pulmonary pressures definitely precipitating clinical symptoms [345, 377]. Elevated pulmonary pressures (consequently with the rise in pulmonary venous pressure, pulmonary artery pressure (PAP) increases [378]) always precipitate and display an increased systolic load on the right ventricle, after-loading the right heart chamber [379–382]. However, as elevated LA pressures predominantly affect the pulsatile load, pulmonary vascular compliance will be impaired, consecutively increasing pulmonary vascular resistance [383, 384]. Thus, aside from the passive component related to backward transmitted elevated LVEDPs and LA-Ps causing PvH, elevated PVR indicates and reflects altered pulmonary vascular properties [374, 385, 386], probably a more substantial and lasting effect and contribution to pulmonary vascular impedance [373, 387]. This is more serious as vascular alterations are less likely to be reversed and as increased pulmonary vascular resistance indicates "pulmonary vascular disease" [373, 374, 386–388]. Furthermore, the increase in pulmonary vascular resistance (and PAP as well) markedly impacts on the impedance (rises) of the pulmonary artery and the RV outflow tractus, after-loading the right ventricle [379–382]. Particularly a rapid rise in PAP and/or PVR, causing acute pulmonary hypertension and concomitantly afterloading the right chamber enhancing RV wall tension, immediately leads to RV-dilatation [379, 389], which is accompanied by increases in RVEDV [380, 382, 389] and RVEDP [390, 391], compromised RV contractility [392, 393], and impaired RV-EF [389, 394]. Under these conditions, diastolic ventricular interaction (DVI) applies, compromising left ventricular filling and (thus even more) worsening global cardiac function and systemic circulation [41, 395, 396]. DVI, coming in general into effect with increasing RVEDP, as in case RV loading conditions change [273, 397], essentially contributes to acute right heart failure pathobiology and makes a crucial hemodynamic impact on right heart and subsequently systemic cardiovascular function [398].

Passively backwards transmitted elevated left-sided pressures may precipitate ultrastructural abnormalities indicating acute alveolar-capillary stress failure. However, these aberrations are fully reversible if PvP and thus the capillary hydrostatic pressure returns to normal values after a more or less short spell [399, 400]. Accordingly, patients suffering from LHD and consecutively *persistent* venous pulmonary hypertension may, although the increased pulmonary pressures are basically of backward transmitted, passive nature, develop functional and structural modifications of the pre-capillary, namely of the arterioles and the small arteries of the pulmonary vessel system [373, 401, 402]. These alterations cause an increase in PVR and concomitantly a further considerable rise in (mean) pulmonary pressure [373, 374, 387]. Indeed, vasoconstriction of functional nature and/or structural reductions in the area of the pulmonary arterioles and arteries inevitably provoke an "out of proportion" increase in the pulmonary pressures, hence display, in addition to the PvH, a pulmonary "arterial" constituent to the total PAP recognized [385, 386, 403, 404]. Pulmonary vascular disease, characterized by elevated PVR and reduced pulmonary vascular compliance [405], indicated by an enhanced

transpulmonary gradient (see Chap. 6), confirms the pre-capillary component contributing to PH in HFpEF [285, 406]. This 'out of proportion PH' is found in roughly 50% of all HFpEF patients [124, 285], necessitating further, different therapeutic measures.

5.4.2.5 Ventricular Dyssynchrony

Penicka et al. [407] demonstrated that significant LV dyssynchrony is able to evoke in hypertensive, so far clinically unremarkable patients, symptoms of heart failure. Considerable dyssynchrony is reported to be present in nearly up to 50% of patients with HFpEF [408–410]. Pathophysiologically, marked dyssynchrony impairs both, diastolic and systolic function [408]. However, there are conflicting results and opinions regarding the potency of dyssynchrony as being an additional factor able to provoke overt heart failure in the presence of relevant diastolic dysfunction [411, 412].

5.4.2.6 Left Atrial Dysfunction

The LA may be understood as a reservoir, conduit and pump, modulating LV filling [413, 414]. LA further complies with a kind of "watershed" function between LV and pulmonary circulation and as such buffers pressure and flow oscillations [415]. Its pump function is required even more in case of altered diastolic ventricular properties to maintain filling, and indeed its pump force has been demonstrated to increase in the presence of mild diastolic LV dysfunction, but unfortunately fails and even deteriorates if moderate or severe diastolic ventricular dysfunction apply [413, 414, 416]. As such, while in healthy individuals LV effectively "pulls" blood to fill in early diastole (suctioning) [372, 417], LV filling in HFpEF patients decisively relies upon a high LA pressure which "pushes" blood into the "stiffened" chamber [20, 24]. However, increases in LA-pressure are augmenting pulmonary venous pressures promoting venous pulmonary hypertension [281, 373], and increase the *pulsatile* RV load, even acutely during exercise [418]. Accordingly, LA dysfunction is associated with pulmonary vascular disease, promoting pulmonary vascular remodelling and PH [418, 419], and, consecutively RV dysfunction/failure [56, 418, 420, 421]: Due to increased PVR and pulmonary artery stiffening (following enhanced pulsatile load) the RV will be "afterloaded" [285]. Moreover, ensuing RV-dysfunction is affiliated with increased risk of death [57, 393].

Left atrial dysfunction is characterized by abnormal dimensions (dilatation), as well systolic (↓ systolic function) and diastolic (↑ stiffness) properties [415, 422–424]. LA dimensions, area and volume, are considered to represent global functional LA parameters [425], and LA dilatation is a marker of diastolic ventricular dysfunction [426]. Intermittent or permanent increases in LVEDP facilitate left-atrial dilatation and atrial fibrillation (thus atrial dysfunction) [138]. LA enlargement is linked to occurrent symptoms [53, 138, 427, 428] and disease progression [429, 430]. Moreover, LA dysfunction may be the initial mechanism to develop symptoms [431].

As LV filling is reliant on atrial contraction in that patient group [432], atrial fibrillation is poorly tolerated [433]. Actually, LA dilatation is associated with a loss of normal electrical activity promoting the development of atrial fibrillation (AF)

[434]. Moreover, AF leads to even lower exercise tolerance [53, 138] (even in case of similar chronotropic reserve [435]), is associated with more severe RV dysfunction [57], and increased risk of death [436].

5.4.2.7 Peripheral Factors

The majority of patients suffer from exercise intolerance [26] and largely develop symptoms during exertion rather than at rest [436]. Recent study results are now clearly indicative for a reduced ventricular-vascular reserve with vascular and peripheral muscular issues substantially contributing, in addition to cardiac limitations, to the clinical picture [54, 68, 258, 306, 438]. Namely, a considerably blunted peripheral vascular vasodilation is demonstrated to be a relevant issue and contributor to symptoms [54, 68, 371]: While in healthy persons the arterial resistance decreases during exercise (to accommodate the large blood flow with only mild pressure increase) [61], patients with HFpEF show a blunted exercise-associated vasodilation [68, 353, 371].

This compromised vasomotor function with enhanced vascular tone during exercise may be related to endothelial dysfunction [68], a well established feature in HFpEF pathophysiology [68, 439]. Also, an improvement in aortic distensibility, reducing aortic stiffness and subsequently attenuating afterload, is demonstrated to be missing [63, 315]. Thus, blunted vasodilation and missing improvement in aortic distensibility (as such an altered vasorelaxation in the presence of an attenuated contractile reserve) lead to dynamic limitations in ventriculo–arterial coupling during exercise [55, 61, 68, 371]. While in healthy humans the E_a/E_{es} ratio declines during exercise, since the increase in E_{es} (reflecting a true augmentation of contractility) exceeds the change in E_a [61], this drop in E_a/E_{es} ratio is markedly more blunted in HFpEF patients compared to hypertensive patients not suffering from HFpEF [55, 68].

Other peripheral issues suggested to contribute to the patients' exercise disability include deranged muscle microcirculation [438], limited lean total and leg muscle mass, and altered muscle fibre composition [440, 441].

Cardiac features applying, disturbing, and restricting reserve function are chronotropic incompetence, depressed systolic function, and possibly diastolic filling abnormalities [15, 19, 20, 25, 442]. Patients with HFpEF show at least a limited peak chronotropic reserve [54, 55, 68], up to 50% even fulfil the criteria for chronotropic incompetence while exposed to stress [443]. The contractile reserves are attenuated in persons with HFpEF [55, 68, 371]:

The contractile reserve is mitigated by a high basal E_{es} as typical in this patient group and a further increase in E_{es}, due to positive inotropic effects displayed during exercise, will only gently augment net contractility [62]. The systolic restriction may further be related to ischemia, oxidative stress, disturbed energetics, passive stiffening, and abnormal Ca handling [49, 55, 60, 272, 336, 351, 444]. Therefore it is important to note that the increase in end-systolic ventricular elastance during exercise is highly likely to be mainly related to passive myocardial stiffening rather than indicating a true increase in contractility. This evidence is further supported by the trend that the increase of E_{es} in HFpEF patients is higher compared to hypertensive individuals (2.42 mmHg/mL vs. 2.3 mmHg/mL) [49].

Although limited diastolic filling has, without a doubt, a significant impact on exercise intolerance, the study findings are quite controversial:

The preload reserve seems to be shortened as no relevant increase in LV end-diastolic filling (LVEDV) could be observed in HFpEF [26]. However, the study results are somewhat conflicting and a recent trial found a mild increase in LVEDV [61]. Other authors have demonstrated an attenuated preload reserve (diminished increase in diastolic filling despite marked elevations in filling pressures) [25, 445], while some did not find relevantly diminished diastolic filling volumes [54, 68] in HFpEF patients during stress. Anyway, end-diastolic left ventricular filling volume is obviously not the crucial factor of stress intolerance [19, 68, 258].

5.5 Diagnosis and Clinical Issues

5.5.1 Symptoms and Signs of Heart Failure

Dyspnoea on exertion and exercise intolerance, although being functional hallmarks of heart failure in general, are together with acute pulmonary edema key clinical pictures HFpEF patients typically present [19–21, 446]. The typical patient suffering from HFNEF is the elderly woman [437, 447] with arterial hypertension (with or without LV-hypertrophy), and often additional co-morbidities commonly present in patients with HFpEF, particularly diabetes mellitus and obesity [5, 50, 85, 89, 276]. However, early on in the disease course, the symptoms of heart failure may be really discrete and signs of overt heart failure like fluid retention and/or edema formation may be missing [407, 448]. Accordingly, other causes (differential diagnosis) of exertional dyspnoea may be looked for [449]. Since in addition the signs and symptoms of heart failure are generally non-specific, thus not really discriminating between HF and other causes [450–452], HFpEF may be an under-diagnosed disorder [6, 20]. Particularly in HFpEF the prevalences of typical symptoms and signs of heart failure are usually lower compared to HFrEF [103]:

Prevalence of clinical feature	HFrEF/systolic heart failure (%)	HFpEF/diastolic heart failure (%)
Orthopnoea	73	60
Paroxysmal nocturnal dyspnoea	50	55
Peripheral edema	46	35
Jugular venous distension	96	85
Hepatomegaly	40	30
III. heart sound (S_3)	65	45
Rales or crepitations	70	72
Chest X-ray consistent with		
– Pulmonary venous hypertension	80	75
– Cardiomegaly	96	90

Breathlessness, orthopnoea, paroxysmal nocturnal dyspnoea, reduced exercise tolerance, fatigue, tiredness, increased time to recover after exercise, and ankle swelling are considered to be more typical symptoms and signs of heart failure, while elevated jugular venous pressure, positive hepato-jugular reflux, and the presence of a III. heart sound are probably more specific [452–454]. Rales, crepitations, III. heart sound, and peripheral edema may be more common in case of acute decompensation, but rarely found in chronic heart failure [455].

However, the diagnostic evaluation always commences with the history and the physical examination [446].

An ECG may reveal signs of LV hypertrophy or concomitant conditions like arrhythmias (particularly atrial fibrillation), however, a normal ECG in the setting of suspected *acute* heart failure virtually rules out this diagnosis [456], but not HFpEF [446]. An abnormal ECG simply increases the likelihood that heart failure exists, but its specificity is really low [454, 457, 458].

Differential diagnostic considerations (adapted from Wachter and Edelmann [7] and modified) include

- Pulmonary maladies:
  - Chronic obstructive lung disease
  - Pulmonary embolism
  - Pneumonia
  - Pulmonary fibrosis
  - Pneumothorax
  - Pleural effusion
  - Lung cancer
- Cardiovascular:
  - HFrEF
  - Pulmonary hypertension (for other reason than HFpEF)
  - Valvular heart disease
  - Constrictive pericarditis
  - Hypertension and hypertensive crisis
  - Arrhythmias
- Neuromuscular maladies
- Adipositas and obesity associated hypoventilation syndrome
- Varia: medication, anemia, deconditioning

5.5.2 Ejection Fraction

In order to assess the systolic function of the heart and thus **the second criterion** of the definition of HFpEF, in the vast majority of cases an echocardiogram will be performed. Echocardiography is anyway the main tool in the diagnostic work up [3, 4, 449, 459], playing a pivotal role in the diagnostic process [3, 4, 449, 460].

EF is the most common parameter used to assess the systolic function of the left and right ventricle [355]. EF succeeds due to its easy application, is well understood, and its reliability to detect any abnormalities in contractility is at least reasonable [355]. The level of EF that defines a normal systolic function is somewhat arbitrary [461], but, nevertheless, in the (joint) American and European echocardiography guidelines on the diagnosis of HFpEF [462–464] and the most recent European and American guidelines on HFpEF [3, 4], a LV-EF ≥ 50% determines a normal or only mildly impaired LV systolic function, as previously proposed by other authors [1, 5, 6, 293].

However, EF is far from an ideal parameter to assess the contractility, and a preserved EF does not automatically imply normal systolic function [62, 336, 465]. Being dependent on afterload, preload and on heart volume and mass [356, 357, 466], EF will fail to report excess afterload [467], in cases of augmented preload [468, 469] and when concentric LVH is present [470] (see Chap. 1, paragraph 6).

As such, EF may be, by all means, seen as a coupling parameter, describing fundamental aspects of ventriculo–arterial coupling rather than truly reflecting contractility [471, 472]—for more information see Chap. 1, paragraph 6.

Often misinterpretation and a failure to detect an impaired systolic function can be avoided by assessing the longitudinal fibre shortening. The longitudinal shortening may be reduced but the EF appears to be normal, or nearly normal, secondary to an increase in the radial shortening, compensating the longitudinal weakness [46]. Thus, the longitudinal shortening must be assessed separately in order not to miss a compromised systolic function [46]. A decrease in longitudinal shortening is an early sign of LV (RV) systolic dysfunction [473, 474].

This can easily be done by assessing the systolic atrial-ventricular (AV) displacement of the mitral valve (systolic mitral valve annulus displacement) [336] or tricuspid valve (TAPSE), respectively. AV displacement reflects systolic LV (mitral valve annulus) and systolic RV (tricuspid valve annulus) function [475, 476]. Assessing the motion of the mitral valve annulus, the subendocardial longitudinal muscle fibres are examined [477]. Unfortunately, this element of contraction is not assessed by examining the ventricle in the conventional way [478], measuring the overall (global) performance in M- or 2D-mode, expressed by EF (or FS) [479]. The contribution to the global systolic function of the longitudinal fibres is normally greater than that of the circumferential fibres, which are usually assessed [480, 481].

Yip [478] showed that a significant number of patients with a normal EF, and therefore classified as suffering from HFpEF (in his study termed diastolic dysfunction), indeed have a reduced systolic function when assessing the longitudinal fibres by the mitral valve annulus displacement method.

The measurement is not only technically easy but is shown to be markedly more sensitive than cardiac catheterisation and older echocardiographic parameters in detecting subtle systolic dysfunction [465], overview [336, 477, 482–484].

Normal displacement amplitude of the mitral valve annulus is 12–14 mm [336, 482, 484]. A displacement of <10 mm clearly indicates impaired systolic function (overview by [336]) as well as an unfavourable prognosis [482].

It should be mentioned that the velocity of the *septal* annulus site is usually lower than the one of the *lateral* site, thus an average value of the measurements of both septal and lateral displacement is recommended for evaluation and decision making [1].

It was previously recommended that all patients should undergo echocardiography within 72 h after onset of symptoms [5] in order evaluate the systolic function, and in order to diagnose or exclude HFpEF because rapid improvement may be seen in a short time period. This appears redundant now as Ghandi [21] showed that no improvement of LV function can be expected in the days following hospitalisation, and thus there will be no change in systolic function on admission in comparison to a few days later. Expedient echocardiography is of course desirable for other reasons previously defined.

5.5.3 Diastolic Dysfunction, Structural Changes and Bio-markers

The **third criterion** required to meet the definition of HFpEF is "diastolic dysfunction" which may be evaluated by echocardiography, more precisely Doppler-echocardiography, cardiac catheterization and/or by measurement of plasma natriuretic peptide concentration [89].

5.5.3.1 Natriuretic Peptides

The most recent ESC guideline [3] requires **elevated levels of natriuretic peptides**, defined as BNP > 35 pg/mL or NT-pro BNP > 125 pg/mL, as one "sub"-criterion of the third benchmark of the definition of HFpEF. In acute conditions, higher values (>100 pg/mL for BNP and >300 pg/mL for NTpro-BNP) should be used [3, 485]. The ACCP/AHA guidelines and most of the publications still use "older" BNP/NT-pro-BNP cut-off levels of >220 pg/mL NTpro-BNP and >200 pg/mL BNP [1, 7, 449, 486].

Indeed, the release of BNP/pro-BNP will be induced by myocardial wall stress reflecting myocardial stretch and thus indirectly elevated filling pressures [449].

The importance the ESC attributes to the biomarkers is somewhat striking as up to 30% of all patients with HFpEF do not exhibit elevated BNP or pro-BNP serum levels, although filling pressures are elevated [487]. In HFpEF patients, BNP (and its biological inactive form pro-BNP) levels tend to be lower anyway, compared to patients suffering from HFrEF [487, 488]. This may be due to a lower BNP expression associated with obesity and insulin resistance [489–491], furthermore, concentric remodeling (hypertrophy) reduces both systolic and diastolic wall stress following the law of LaPlace [492]. On the other hand, proBNP levels rise with age and are higher in women than in men [493], increase with deteriorating renal function (as soon as GFR < 60 mL/min) [494, 495], and in case of tachycardic

arrhythmias such as atrial fibrillation or in myocardial ischemia [496] and may be affected by comorbidities such as liver failure [497] and sepsis [498]. Accordingly, BNP, respectively pro-BNP plasma concentrations, are to some extent non-specific [496] and with limited sensitivity. This is at least of relevance in patients with milder forms of HFpEF who merely exhibit elevated filling pressures on exertion [407]. Furthermore, the natriuretic peptides may not reach the level as a stand-alone parameter providing sufficient evidence of functional and/or structural alterations satisfying criterion 3 of the definition.

Of note, a normal ECG and/or a BNP/pro-BNP level of <35 pg/mL respectively <125 pg/mL rules heart failure (HFrEF, HFmrEF, and HFpEF) actually out [3, 129].

5.5.3.2 Functional and Structural Alterations

Confirmation of altered diastolic properties/function by tissue Doppler (TD) assessment or invasive hemodynamic measurements gives by itself sufficient evidence to fulfil the third criterion [3, 4, 89, 446, 449]. As such, *diastolic dysfunction* (functional alterations) may be indicated by the E/e′ ratio determined by tissue Doppler echocardiography, or by the invasively measured/calculated left ventricular filling pressure (pulmonary wedge pressure respectively), or by calculation of the relaxation constant τ, or the constant b of the pressure/volume slope [1]:

1. An E/e′ ratio ≥13 [3, 16], respectively ≥15[4] [2, 4]
   or
2. A LVEDP >16 mmHg or a PCWP >12 mmHg, *or* a prolonged relaxation constant $\tau > 48$ ms *or* a pressure/volume constant of >0.27

   [1, 3, 4, 7, 8, 446, 462–464].

The ESC [3] further proposes in its most recent guideline that a mean velocity of e′ < 9 cm/s on septal and lateral mitral wall may be equally qualified as a stand-alone parameter to indicate abnormal relaxation and thus diastolic dysfunction, a proposition based on the results of echocardiographic assessments and research [462, 464, 500, 501].

5.5.3.3 E/e′ Ratio

The E/e′-ratio is a marker of LVEDP and LV stiffness [7] and is considered to reflect LV-filling pressure [3, 8]. E represents the peak flow velocity of transmitral blood flow in early diastole, a well established element in the assessment of mitral blood flow profile [449]. A reduced early transmitral blood flow velocity,

[4]As the displacement velocities are greater at the lateral mitral annulus side than at the septal side, different cut-offs have to be chosen [498].

characterized by the E-wave, indicates impaired relaxation [446] while an increased velocity may reflect a reduced compliance (e.g. due to increased LV stiffness) [446]. The tissue Doppler assessment of the velocity of the mitral annular longitudinal myocardial fibre shortening and lengthening, characterized by the e-Wave and called e′, has been a big step forward in the assessment of the diastolic properties of the LV: e′ reflects the recoil and the active phase of diastolic relaxation, and is shown to correlate well with τ [502, 503]. The lengthening velocity of the lateral and septal mitral annulus myocardial fibres in early diastole is considered to be a sensitive and reliable parameter, reflecting diastolic properties [504, 505]. e′ is less influenced by loading conditions and other variables as compared to E [504, 506], and a reduction in e′ to <8.0 cm/s [504, 507] clearly indicates a slowed relaxation [508]. Again, the combination of E and e′ is of special value and their ratio is an even more accurate estimate of ventricular filling pressure (LVEDP) with good accuracy over a wide range of EFs [503, 509–511]. Thus, with the ratio of the velocities of the E-wave of the mitral inflow pattern to the velocity of the e′ wave of the tissue Doppler assessment of the myofibres of the mitral valve annulus region, we are able to estimate the end-diastolic intraventricular left ventricular pressure (LVEDP) [503]:

- E/e′ ratio > 15 → LVEDP > 15 mmHg, and thus clearly elevated [503]
- E/e′ ratio < 8 → LVEDP < 8 mmHg (normal LVEDP) [503]

It must be remembered that in cases of severe MR, the E/e′ ratio is not a reliable parameter with which to estimate LVEDP [512]. Furthermore, although ventricular compliance predominantly influences the LVEDP [513], extracardiac factors may affect the LVEDP as well:

- Pulmonary pathologies, such as pneumonia or malignancy, can change the intrathoracic pressure and/or pressure in the pulmonary vascular system [514].
- Rising intra-abdominal pressure will increase the intraventricular pressure as well [515].

Unfortunately, there is ongoing criticism and this parameter (E/e′) is again and again questioned, as the correlation with invasively determined PCWP in the setting of acute decompensations of patients suffering from HFrEF [516], or in symptomatic patients with hypertrophic cardiomyopathy [517], was found to be weak. Furthermore, the E/e′ ratio may not be sensitive enough to detect early stages of HFpEF, and as “only” roughly 25% of HFpEF patients fulfill the current definition, and a substantial number of controls (up to 40%) show borderline values, hence specificity and sensitivity of the E/e′ ratio seems to be low [407].

However, the comparison of E/e′ directly with invasively measured filling pressures (conductance catheter) in acutely decompensated patients revealed a really

good correlation between the two parameters as a 83% sensitivity, a 92% specificity and an area under the ROC curve of 0.907 for E/e′ > 8 [516] is in fact a more than reliable measure of high-stiffness modulus in HFpEF patients [518]. This finding may imply an E/e′-ratio > 8 could be considered as providing sufficient stand-alone evidence of diastolic dysfunction without the necessity of further additional or surrogate parameters for all patients where the E/e′ ratio ranges between 8 and 15 (8 < E/e′ < 15) [519]. The results would allow the use of the E/e′ ratio even in the current "gray" zone as a stand-alone parameter trustworthy indicating diastolic dysfunction if the ratio exceeds 8 [8].

5.5.3.4 Inconclusive E/e′ Ratio, Surrogate Markers

However, as long as the E/e′ ratio is inconclusive as defined by the range 8 < E/e′ < 15, additional, surrogate or second line, minor parameters are demanded necessary in order to diagnose HFpEF [8, 129, 446]:

Surrogate markers indirectly suggestive for diastolic dysfunction include structural abnormalities such as LA enlargement or increased LV-mass, further atrial fibrillation, and elevated natriuretic peptide plasma levels (as BNP/NT-pro BNP plasma levels cannot stand alone so far!) [8].

However, the most recent ESC guideline requires the existence of at least one of the two predominant structural abnormalities (LA enlargement and LV-mass) in order to fulfil criterion 3 of the diagnostic requirements of HEpEF [3]. This denotes an upgrade of these two markers, as until now they are ranked as second line, or additional clue, by many authors [7, 32, 446, 449, 486], and are still further endorsed as second line indicators by ACCP/AHA [4] and other societies [486]. Decisive structural abnormalities (indirectly providing evidence of diastolic dysfunction) may be indicated by:

1. An enlarged left atrium, defined as LA-volume index LAVI > 34 mL/m^2 [3, 16] determined by echocardiography (other authors including ACCP/AHA use an cut-off of LAVI > 40 ml/m^2 [4, 7, 486])
   and/or
2. An increased LV-mass index (LVMI), defined as LVMI ≥ 115 g/m^2 for males, ≥95 g/m^2 for females [3] determined by echocardiography (values currently widely used by the ACCP/AHA and other authors are LVMI > 149 g/m^2 for men and >122 g/m^2 for women [4, 7, 446, 449]) [1, 463, 464].

Enhanced left atrial volume (and thus enlargement of the LA) is considered to be a morphological marker of chronically increased diastolic filling pressures [28, 520], but may occur in atrial fibrillation or mitral valve disease as well [276]. Accordingly, LA enlargement has to be interpreted in the context of the clinical condition present and the other echocardiographic findings [501].

Concentric remodeling is a quite common structural finding in patients with HFpEF [28, 521].

Additional and supportive echocardiographic parameters suggestive for functional (diastolic) abnormalities are (1) the Ard-Ad difference (if >30 ms) and (2) the combination of an E/A-ratio < 0.5 together with a deceleration time (DT) >280 ms. [1, 4, 7, 522].

Ad (1) Difference between Ard time and Ad time

Diastolic dysfunction is suggested by abbreviated mitral inflow (A-) wave duration (Ad) (mitral inflow DT correlates well with PCWP when EF is reduced [523, 524]) and a longer duration of the flow reversal in the pulmonary veins (Ard) [51, 525, 526]. If the difference between Ard and Ad, is more than 30 ms, LV diastolic dysfunction can be reliably diagnosed [525–528].

Ad (2) the E/A ratio and deceleration time

The E/A ratio, a measurement of mitral valve filling velocities (early to late ventricular filling velocities), is directly dependent on the pressure gradient between left atrium and the left ventricle and is proposed to reflect both ventricular filling and pressure properties [449]. The combination of a reduced E/A ratio plus a prolonged deceleration time is highly suggestive for an impaired relaxation of the LV chamber [446]. Evidence of impaired relaxation has to be acknowledged as a really solid marker of diastolic dysfunction and with clear clinical relevance as Zile found LV relaxation to be virtually impaired in all HFpEF patients [22].

Mitral deceleration time of early filling is a measure of LV compliance and filling [529] and is practically measured as the time from the maximum E-wave velocity flow pattern (as determined from the Dopler mitral inflow pattern) to the flow reaching baseline.

As such, in case the E/e′ ratio is between 8 and 15 and thus inconclusive (as is still common sense), an additional parameter is necessary to fulfil criterion 3. An elevated BNP-level/pro-BNP-level requires additional evidence as well:

→ in case the *E/e′ ratio is inconclusive (8 > E/e′ < (13) 15)*, another second, minor parameter is necessary to substantiate the diagnosis such as:
– enlarged LA indicated by LAVI > 34 mL/m^2 (40 mL/m^2), or
– atrial fibrillation to be present in a typical clinical setting, or
– that the LV-mass index is bigger than 115 (149) g/m^2 (men) and 95 (122) g/m^2 (women), or
– E/A ratio < 0.5 in the presence of a deceleration time exceeding 280 ms, or
– the Ard − Ad difference exceeds 30 ms
→ in case of *elevated bio-markers* an
– E/e′ > 8 or one of the above mentioned parameters is required to meet criterion III [1, 7, 8, 446, 449].

5.5.3.5 Invasively Derived Parameters

Invasively determined diastolic parameters are still “gold standard” [5, 89, 446] in diagnosing HFpEF, and may be assessed at least if the diagnosis is unclear [8, 446, 449].

A prolonged relaxation constant ($\tau > 48$ ms) is indicative for impaired relaxation [445], and an increased slope coefficient reflects reduced LV compliance [446].

Interestingly, the highly quality clinical study by Zile [22] revealed that in virtually all patients with HFpEF, LV relaxation is impaired, and that even independent of LV hypertrophy (increased LV mass) and of increased stiffness.

The assessment of the diastolic pressure-volume (P-V) relation is the most accurate way to describe and evaluate cardiac diastolic properties [530]—but this invasive method is not feasible in daily practice as it involves fairly complex measurements of chamber stiffness at end-diastole with varying end-diastolic volumes [38]. The pressure-volume relation during diastole attempts to characterize the structural behaviour of the heart as a whole [530]. The relation is never linear, in general it is exponential [52].

A steeper slope at the same position of an upward shifted pressure-volume relation gives proof of altered diastolic properties [1, 22, 38, 275, 286, 312]. However, also "external" forces (shifting the p-v-relation upward in parallel, nonetheless increasing the pressures [275]) including cardiac constraining effects [114, 273, 276, 280, 285, 531, 532], changes in aortic stiffness [21, 38, 286] and ventriculo–arterial coupling [44, 62, 147, 287], (consecutively) affect diastolic properties [38, 62, 286] and LV performance supporting the considerable heterogeneity of this disorder [9, 13, 14, 256]—for details read the paragraph on "PV-relation and LVEDP" outlined above in this chapter.

5.5.3.6 Diastolic Stress Test

As a considerable number of patients may develop symptoms only during exercise (because of the limited sensitivity of markers), and the fact that the clinical course may be dynamic, and in case of clinical uncertainty, exertion-based assessment ("diastolic stress testing") is recommended in order to enhance diagnostic sensitivity and specificity [3, 24, 276, 533]. It may be performed by echocardiography or invasively assessed exercise hemodynamics [24, 534, 535]. Meanwhile quite a substantial number of publications could clearly demonstrate the value of diastolic stress tests in that heterogeneous group [24, 536–539]. Particularly as the occurrence of pathological pulmonary pressures developed during physical exercise are shown to be associated with increased mortality rates [535, 540], stress testing yields prognostic information which subsequently may inevitably demand therapeutic consequences.

As the findings of echocardiographic assessments during exercise are still challenged and suggested to be less robust than invasively derived ones [20, 449], invasively performed diastolic stress testing may be the preferred method [449]. Even more, since right heart catheterizations at expert centres are found to have extreme low complication rates, with 1.1% morbidity and a 0.055% mortality rate [541].

Accordingly, the algorithm to diagnose HFpEF can be summarized as follows (adapted from Wachter [7] and Paulus [1], with permission), see Fig. 5.5:

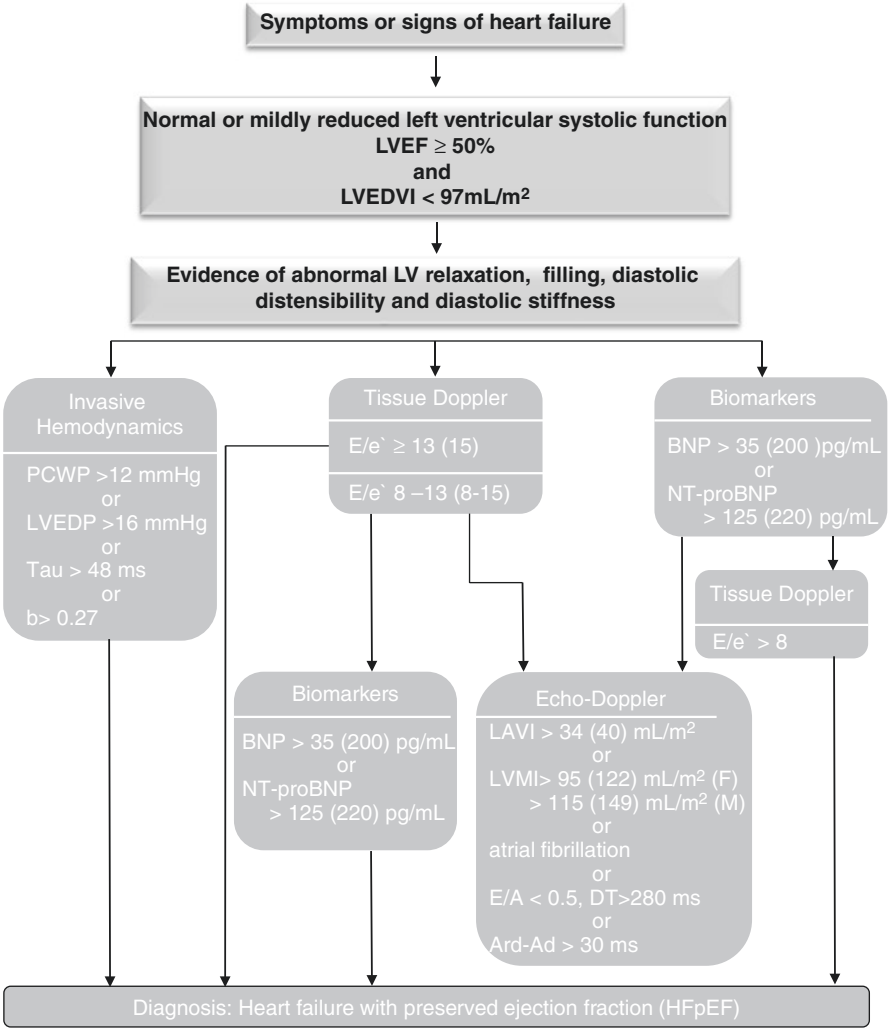

Fig. 5.5 Diagnostic algorithm

5.6 Therapy

No evidence-based specific therapeutic approach on how to treat HFpEF could be established until now [10, 11, 16, 32, 83, 542]. Clinical trials examining more or less the same drugs successfully applied in HFrEF have indeed all been really disappointing, since neither a survival nor a sustained symptomatic benefit could ever be demonstrated [3, 446, 449, 459, 542–543]. Reasons for this disappointing situation are explained by (1) the diversity in trial designs, (2) recruitment of patients without true HF, (3) inadequate diagnostic criteria used in HFpEF, but in

particular that (4) the disease mechanisms in HFpEF are still not fully understood, (5) the therapeutic approaches do not match the underlying pathophysiologies and that (6) there have been a considerable heterogeneity of patient groups with variable degrees of "different types" of HFpEF included in the trials [11, 16, 32, 446, 546].

As such, the therapeutic recommendations of ACCP/AHA [2, 4] and ECS [2, 3] are based on expert opinion rather than on evidence [3, 10, 11, 83].

The current therapeutic approach addresses the patients′ acute symptoms aiming to relieve the patients from congestion by alleviating hypertensive dysregulation or by slowing down acute tachycardic rhythm disturbances (as in case of new onset of atrial fibrillation) [547]. In a more long-term perspective, blood pressure, fluid status, and heart rhythm/heart rate need to be well controlled, ischemic events have to be prevented, and an "aggressive" treatment of the co-morbidities (a measure which is shown to be effective as it may obviate the development of HFpEF [547]), is paramount. However, all efforts are reported to possibly improve symptoms, quality of life and exercise capacity, hence represent a symptomatic pathway rather than a causal measure nor have any effect on mortality reduction [2–4, 16, 446, 542, 548].

Accordingly, (loop) **diuretics** are to be applied in case of (acute) pulmonary congestion and peripheral edema formation in order to relieve of dyspnea and volume overload associated symptoms [50, 85, 549]. The improvement of symptoms in case of fluid overload by diuretics is independent of LV-EF [550, 551], however, evidence from randomized studies are completely lacking [446]. Diuretics given in such circumstances definitely improve quality of life [549]. On the other hand, "overdiuresis" has to be avoided on all accounts, since altered diastolic ventricular properties imply that the heart is highly sensitive to even small changes in volume loading such that hypovolemia may immediately cause a fall in CO. [124, 446]

Spironolactone may be considered to be given in stable conditions instead of, or mostly in addition to, loop diuretics or thiazids in order to control fluid status, blunt fibrotic progression, and to take care of euvolemia: The so-called Aldo-DHF study in fact gave evidence that this mineralocorticoid antagonist may improve diastolic dysfunction [552], but neither the Aldo-DHF [552] nor the larger randomized TOPCAT study [545] found any improvement in outcomes when applied to patients with HFpEF.

Another essential issue to be treated is high blood pressure: Successful and ambitious BP control may indeed prevent the evolution of heart failure [553], and casual evidence suggests the treatment of hypertension could be critical in HFpEF/HFmrEF [553, 554]. Furthermore, a high proportion (61%) of patients with acutely decompensated HFpEF/HFmrEF present as hypertensive (defined as sBP > 140 mmHg [85], 12% even with uncontrolled hypertension [86]. **ACE-inhibitors and ARBs** are the preferred drugs to address hypertension in patients with heart failure, at least in those with HFrEF [3]. Unfortunately all the substances of these groups (ACIs and ARBs) failed to show any beneficial effect on mortality rate in HFpEF individuals [83, 105, 446, 542, 555]. A combination of enalapril and diuretics indeed led to a

significant reduction in LV mass and to an improved exercise tolerance [556], and the CHARM study in fact revealed that patients on candesartan had a reduced rate of hospitalizations due to heart failure [105]. Nevertheless the beneficial effect on mortality, as displayed in HFrEF patients, does not occur in HFpEF individuals at all if treated with these drugs [105, 555, 557–559].

Interestingly, a low-sodium diet has been reported to be associated with reductions in blood pressure and improved diastolic function [560].

Theoretically, **lower heart rates** may be beneficial in HFpEF patients since they extend diastolic filling time and reduce/avoid possible ischemic events (which impair relaxation) because of a prolonged coronary perfusion time [10, 50, 561]. As such, β-blockers, verapamil as well as ivabradine have been examined. No positive effect on mortality rate is reported in case of **β-blockers** [562–565]. Moreover, β-blockers may even worsen chronotropic incompetence, which is relatively common in HFpEF [10]. **Verapamil** is reported in several studies on hypertrophic cardiomyopathy to markedly improve LV diastolic properties, and thus LV filling characteristics, symptoms, and exercise tolerance [566–568]. The results of two smaller trials applying verapamil to HFpEF patients suggest verapamil may improve both, symptoms and diastolic function [569, 570]. Although these results are quite promising, unfortunately no larger studies have been done. The results regarding **ivabradine** are inconsistent, while Kosmala found an improved exercise capacity, Ashrafian found the opposite [571].

Atrial fibrillation with tachycardic chamber frequency is, besides hypertensive dysregulations, another common trigger for acute decompensations, 21% of acutely decompensated patients present with AF [85]. In patients with AF, control of ventricular rate is crucial [2, 32], and restoration of sinus rhythm would enable effective atrial contraction and aid filling of the LV [572]. Giving β-blockers in this situation seems to be ineffective, while digoxin has not been studied [3].

Exercise training has been assessed in several studies [305, 573–576] and the patients who typically trained three times a week for 30 min at an intensity based on previous exercise tests demonstrated improved symptoms, quality of life and exercise capacity. Two studies found an improvement of diastolic function [573, 577], none any change in neuroendocrine activity. Unfortunately, an evaluation regarding the rate of hospital (re)admissions and outcome (mortality rate) has not been done [16].

Sildenafil, although showing inconsistent results and no improvements in exercise capacity, quality of life, diastolic function and clinical status [58, 97], may nevertheless be considered in case of substantial pulmonary hypertension [446].

Statins may improve outcomes possibly due to anti-inflammatory and pleiotropic effects [578, 579], however a large study on rosuvastatin's impact on chronic heart failure was not able to reveal larger benefits [580].

Abbate [446] has summarized current treatment practice based on expert opinion in the following diagram, which the author of this book slightly modified (with permission) (Fig. 5.6):

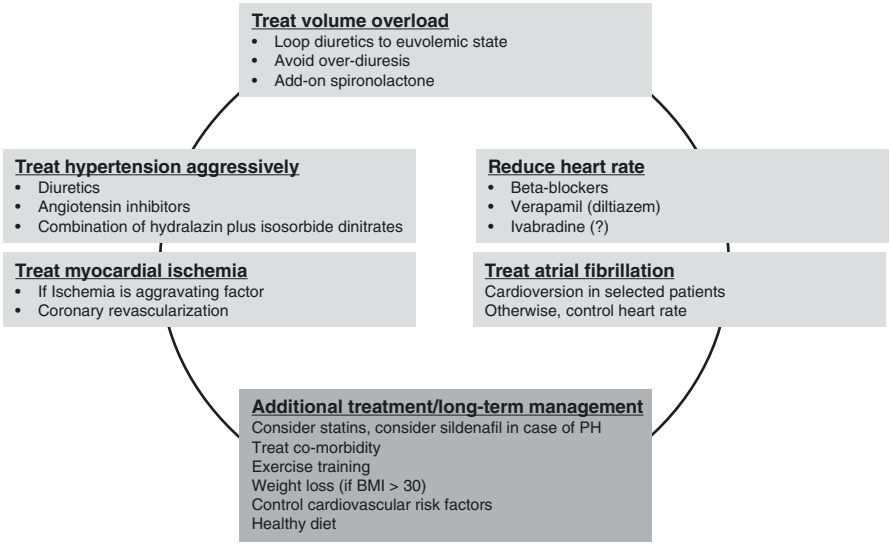

Fig. 5.6 Therapeutic options

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Pulmonary Hypertension in Left Heart Disease

6

6.1 Definition

Elevated left ventricular filling pressures are a general feature and hallmark of heart failure resulting from cardiac dysfunctions, essentially arising from and affecting the left ventricle [1, 2]. These disorders include heart failure due to diastolic and/or systolic malfunction, as such heart failure with preserved (HFpEF) and without preserved, reduced (HFrEF) ejection fraction; valvular diseases; congenital cardiomyopathies; and congenital and acquired afflictions of left heart inflow and/or outflow tract [2, 3]. Thereby, the pressure of the left atrium will be elevated, either subsequently due to the increased LV-filling pressure [1, 4], or even primarily in case of mitral stenosis [5]. In any case, left heart disease (LHD) is generally characterized by elevated left-sided filling pressures [4, 6]. These augmented left-sided filling pressures are transmitted backwards, downstream, thereby causing an increase in pulmonary venous pressures [1, 5–7], a condition "of passive or congestive nature" as associated with pulmonary venous congestion [6]. In the literature this issue has, in the past, been called *pulmonary venous hypertension* (PvH) [8], or *post-capillary pulmonary hypertension* [9] or *passive pulmonary hypertension* [10]. Consequently, with the rise in pulmonary venous pressure, pulmonary artery pressure (PAP) also increases [11].

Pulmonary hypertension (PH) is defined as a mean pulmonary arterial pressure **≥ 25 mmHg at rest** measured invasively by right heart catheterization [12–14], and **PH due to LHD** requires in addition a **PCWP > 15 mmHg** [5, 12, 13] **or a LVEDP > 15 mmHg** [5, 12, 13] (> 18 mmHg [15]) - group II PH.

In all other forms of pulmonary hypertension (groups I, III, IV, V—see below), PCWP is and has to be, per definition, ≤15 mmHg [12, 13], characterizing *pre-capillary PH* as the pulmonary veins remain basically unaffected [16–18].

Commonly, PH is applied equivalent to, and thus is supposed to be associated with, elevated pulmonary vascular resistance (PVR) [7]. However, PH simply indicates elevated pressures in the pulmonary circulation, rather than

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explicitly indicating pulmonary vascular alterations, which are reflected by an elevated PVR [7, 19, 20]. Moreover, in case of acutely elevated left-sided pressures [21, 22] and in the early phase of venous PH, with passive increase of the pulmonary venous pressure due to elevated LVEDPs and/or LA-pressures [22], PVR is usually pretty normal [13]. There is no evidence at all that this acute and non-sustained post-capillary rise in pulmonary pressure is accompanied by any kind of dysfunction inherent to the pulmonary vessel system [21]. Accordingly, although in most circumstances PAP enhancements are related to an increase in PVR, an increase in PAP is not inevitably coupled with an increase in PVR [23, 24].

6.2 Classification of PH

Pulmonary hypertension is classified in five categories [3, 12, 13].

Group I: Pulmonary arterial hypertension (PAH)

- idiopathic PAH
- heritable PAH
- Drug- and toxin-induced PAH
- PAH associated with connective tissue disease, HIV infection, portal hypertension, congenital heart disease, schistosomiasis
- pulmonary veno-occlusive disease and/or pulmonary capillary hemangiomatosis

Group II: Pulmonary hypertension due to left heart disease (LHD)
as classified by Simenneau [14] and modified by Rosenkranz [25]

- left heart systolic dysfunction/*HFrEF* (EF ≤ 50%)
  - ischemic cardiomyopathy
  - dilated cardiomyopathy
- left ventricular diastolic dysfunction/*HFpEF* (EF > 50%)
  - hypertensive heart disease
  - coronary heart disease
  - diabetic cardiomyopathy
  - hypertrophic cardiomyopathy
  - restrictive cardio, yopathy
  - constrictive pericarditis
- valvular heart disease
  - aortic valve stenosis
  - aortic valve regurgitation
  - mitral valve stenosis
  - mitral valve regurgitation
  - persistent/residual PH after effective valvular defect correction

– congenital/acquired left heart inflow/outflow tract obstruction and congenital cardiomyopathies including cor triatriatum, myxoma or left atrial thrombus

Group III: Pulmonary hypertension due to lung diseases and/or hypoxia

– chronic obstructive pulmonary disease (COPD)
– interstitial lung diseases
– other pulmonary diseases with mixed restrictive and obstructive patterns
– alveolar hypoventilation disorders
– sleep-disordered breathing
– chronic exposure to high altitude

Group IV: Pulmonary hypertension due to chronic thromboembolic disease (CTEPH)

Group V: Pulmonary hypertension with unclear/multifactorial mechanisms

– hematologic disorders like chronic haemolytic anemia, myeloproliferative disease
– systemic disorders like sarcoidosis, pulmonary histiocytosis
– metabolic disorders like thyroid maladies, glycogen storage disorders
– others like chronic renal failure, fibrosing mediastinitis

6.3 Epidemiology of Pulmonary Hypertension due to Left Heart Disease

Pulmonary hypertension ranks third, after coronary artery disease and arterial hypertension, in the number of incidences of cardiovascular diseases [26]. LHD is the most common cause of PH [17, 27], and accounts for 65–80% of all PH cases [17, 28, 29]. PH is far more common in patients suffering from heart failure (HFrEF and HFpEF), as traditionally assumed. In a study by Butler, who considers a PVR above 1.5 WU (130 dyn s cm^{-2}) to be elevated, 36% of the patient group, suffering from HFrEF, showed a mildly elevated PVR, 17% a moderate elevation, and 19% a severe one [24]—consequently 72% of the patient group was afflicted with a relevant PH associated with pulmonary vascular disease. Lam demonstrated in a community-based study of HFpEF patients, that 83% of patients had PH, defined as a systolic pulmonary pressure of >35 mmHg [8]. Schwartzenberg recently studied patients with HFrEF and HFpEF and found that 80–90% of the patients exhibit a PVR > 1.7 WU (about 136 dyn s cm^{-2}) and thus vascular inherent PH [30]. Bursi, defining PH as being present if the systolic PAP exceeds 35 mmHg, confirmed Schwartzenberg's results in a community-study, finding an incidence of PH in 79% of heart failure patients in his study (HFrEF and HFpEF) [31].

Accordingly, in both HFrEF and HFpEF, PH is frequently present: As study results demonstrate, PH occurs in roughly 80% of all patients suffering from primarily left-sided heart failure [24, 30–36], whereupon PH is even more present in HFpEF than in HFrEF. Moreover, diastolic dysfunction, as the central pathology in HFpEF, has been identified as being the predominant cause of PH in LHD [17].

Unfortunately, if PH is present, increased morbidity and mortality have been verified in both HFrEF [6, 21, 31, 37, 38] and HFpEF [6, 31, 34, 36]. It has been demonstrated, that systolic PAPs exceeding 35 mmHg are independently associated with decreased survival in both, HFpEF and HFrEF patients [8, 31]. Moreover, the presence of PH is even associated with poor prognosis and high mortality in the general population, not only in those with heart failure [34]. Up to 73% of patients suffering from primarily mitral valve disease develop PH as a complication [39, 40]. PH is also reported to be as high as 30–50% in patients with aortic stenosis [41, 42]. In valvular heart disease, the presence of PH indicates poorer survival after valve surgery [43]. Ensuing right heart dysfunction/failure in chronic LHD is shown to be predictive of clinical events and reduced survival [44–46].

6.4 Pathophysiology

Pulmonary hypertension in general results from increases in pulmonary vascular resistance (PVR), pulmonary blood flow, pulmonary venous pressure, or a combination of these features [2, 6, 19]. More specifically, and in differentiation to pulmonary venous hypertension (PvH), pulmonary arterial hypertension (PAH) with idiopathic arterial pulmonary hypertension (IPAH, formerly called primary pulmonary hypertension) as the classical disorder in this group of maladies, results from (a) vascular wall remodelling, (b) (micro)thrombosis, and (c) vasoconstriction [47, 48].

Elevated left-sided filling pressures are a fundamental and characteristic feature in patients with LHD [12, 13]. Since PH is verified to depend on elevated filling pressures (and on the degree of mitral regurgitation [49]), diastolic cardiac properties, rather than systolic LV function, are determining this disorder [50–52]. Increased LV—filling pressures are, in any case, passively transmitted backward, downstream, and thus have a substantial impact on LA pressure and on pulmonary venous pressure (PvP), facilitating the development of pulmonary venous hypertension [1, 5]. As such, elevated left heart filling pressures are recognized to cause PvH [53] irrespective of LV-EF [54]. Even milder elevations of LVEDP and consecutively or initially raised LA-pressures may display PvH, since, due to the anatomically serialised vascular structures, the transmitted pressure adds up to the resistive and flow-related PA-pressure [7]. Concomitantly with the rise in pulmonary venous pressure, pulmonary artery pressure (PAP) increases [11]. Moreover, downstream pressure has (compared

to the systemic arterial circulation) a marked impact on the pressure level within the pulmonary circuit, as it may contribute up to 50% (systemic circulation 5% to MAP) to total PAP [21].[1]

Acutely elevated and pathologically high pulmonary venous pressures may cause so-called "alveolar-capillary stress failure" [55], facilitating acute pulmonary edema formation [21, 22]. "Overt pulmonary edema is the clinical correlate of alveolar- capillary stress failure" [22]. This condition, histologically indicated by ultrastructural alterations of the alveolar-capillary unit due to an abrupt rise in pulmonary capillary **hydrostatic pressure**, is characterized by a disruption of the capillary endothelial and alveolar epithelial cellular layers resulting in endothelial cell dysfunction, capillary leakage and increased permeability of the alveolar-capillary barrier [22, 55], accordingly promoting acute pulmonary congestion [56] or even pulmonary edema onset[5, 21, 22, 57]. Acute pulmonary congestion or edema, arising from acutely increased left-sided filling pressures, are definitely caused by the raised hydrostatic capillary pressure, hence denoted hydrostatic or hemodynamic edema [58]. However, a rise in the permeability of the alveolar-capillary membrane, the predominant disruption in non-cardiogenic edema as described in the literature [58, 59], is supposed to contribute to the primarily cardiac initiated congestion/edema formation, and as such, both mechanisms, of course with quite different emphasis, may participate in the pathobiology of pulmonary edema development in LHD [5, 56, 60, 61]. Fortunately, there is good evidence suggesting that these ultrastructural abnormalities, indicating acute alveolar-capillary stress failure, are fully reversible if PvP and thus capillary hydrostatic pressure returns to normal values after a more or less short spell [62, 63]. Elliot [64] demonstrated complete restoration of the alveolar-capillary unit after normalized LA-pressure, indicating a quite impressive plasticity of this alveolar-vascular interface. Yet, acute alveolar-capillary stress failure may serve as a trigger for maladaptive processes ensuing, namely in the pulmonary vessel tissue structure [63].

On the other hand, if the elevation of the pulmonary venous pressure is sustained and PvH persists for a length of time, or pressure exacerbations occur repetitively [21], both the alveolar-capillary membrane [65, 66] and the pulmonary vessel network, including veins, arterioles and arteries [67], may suffer from an irreversible remodelling: The basement membrane composition changes and the membrane thickens, mainly attributed to considerable deposition of collagen (type IV) [65, 66]. These modifications may have a protective effect against further pressure damage and prevent edema formation [60], may substantially affect alveolar diffusion capacity (membrane conductance) and as such blunt gas exchange and remarkably limits exercise tolerance [21, 56, 68].

[1] Arterial pressure is generally determined by the integration of flow and vascular resistance, summed up with downstream pressure. Downstream pressure in the systemic arterial circulation is reflected by the CVP/RA-P, in the pulmonary circuit by LA-P/PvP [21].

This process of remodelling of the alveolar-capillary unit, caused by injury through elevated hydrostatic pressures in the capillaries of the alveolar-capillary unit, attributed to LHD with backward transmitted elevated left-sided filling pressures, is associated with and considerably influenced by an inflammatory response, decisively mediated and "orchestrated" by the endothelial cells [53, 69–71]. Vascular stretch is attested to possibly initiate an inflammatory response [72, 73], and hydrostatic pressure is known to be one of the highest potential biomechanical stimuli for endothelial cells to display a pro-inflammatory, pro-oxidant and vasoconstrictive milieu [74]. Of special interest is the impact of the endothelium on local hemodynamics, substantially regulating the vascular tone [75–77]. By communicating and interacting with the vascular smooth muscle cells, the endothelial cells try to provide a well-balanced vascular tone and blood flow, meeting cellular and tissue metabolic demands [75, 76, 78]. Imbalanced production and release of vasoactive agents, notably blunted NO synthesis in response to vascular pressure stimuli of the endothelial mechanoreceptors, and increased generation and release of ET-1, as occurring in endothelial dysfunction due to LHD with sustained PvH [79], implies impaired smooth muscles cell relaxation, and subsequently substantial increases in pulmonary microvascular tone arise, enhancing PVR [79–82]. PVR is crucially determined by the balance between these opposing mediator resources [79, 80]. Furthermore, a NO deficit results in the loss of the physiological oscillation in endothelial calcium handling, thus the cytoskeleton organisation will be considerably disturbed [83]. Alongside, a variety of local pro-inflammatory mediators including TNF-α, angiotensin II and endothelin-1 (ET-1), circulating immune competent cells, (myo)fibroblasts, etc., as well as hypoxia are also involved in the alterations induced, ending in a histological structural remodelling of the alveolar-capillary unit [22, 63].

Beyond this microcirculatory remodelling, pulmonary veins, arterioles and small and medium arteries are affected by the functional and structural remodelling [4, 53]. The imbalance between vasodilative and vasoconstrictive mediators, in case of *group II PH* in particular the blunted capillary and arteriolar NO synthesis in response to mechanical and receptor-mediated stimuli [79], favouring vasoconstriction, provokes a marked rise in the tone of pulmonary resistive vessels, significantly driving the PVR up [5, 27, 79, 80, 84]. Furthermore, media hypertrophy of the veins potentially leading to so-called pulmonary venous arterialization (histologically presenting as muscularisation of arterioles, hypertrophy of the intima and the media of the arteries) [5, 21, 67], are structural abnormalities inevitably resulting in increased PVR, due to a reduced area of the pulmonary vessel system [5, 85]. Noteworthy, these substantiated histological alterations are quite similar to those we come across in primary pulmonary hypertension [4, 86].

PVR increases, and pathologically high values are associated with and indicate, "pulmonary vascular disease" [5, 7, 20, 86, 87]. PVR may be considered to predominantly represent the functional condition of the coupled unit, composed of pulmonary endothelium and adjacent smooth muscles cells [88–90]. Increases in PVR indicate significant reductions of functional, or even

structural, capacity (diminished cross-sectional area) of the pulmonary vessel system, mainly of the small, resistive distal pulmonary arteries and arterioles [5, 85]. Moreover, at least in acutely elevated left-sided pressures [21, 22], and in the early phase of venous PH with passive increase of the pulmonary venous pressure due to elevated LVEDPs and/or LA-pressures [22], PVR is usually pretty normal [13]. Most patients suffering from HFpEF show some degree of PvH, but may have normal PVR, however, a substantial subset will develop pulmonary vascular disease [91].

Accordingly, patients suffering from LHD and consecutively **persistent** venous pulmonary hypertension may, although the increased pulmonary pressures are basically of backward transmitted, passive nature, develop functional and structural modifications of the pre-capillary, namely of the arterioles and the small arteries, segments of the pulmonary vessel system [5, 67, 79, 80, 82]. These alterations cause an increase in PVR and concomitantly, a (further) considerable rise in pulmonary pressures [5, 21, 85]. Indeed, vasoconstriction of functional nature and/or structural reductions in the area of the pulmonary arterioles and arteries, inevitably provokes an "out of proportion" increase in the pulmonary pressures, hence in addition to the PvH, a pulmonary "arterial" component to the (total) PAP is recognized [6, 19, 20, 47]. As such, study results reporting disproportionate PAP increases, clearly above of those expected from (measured) left atrial pressure/LV-filling pressures, are very well explained by this superimposed pre-capillary, reactive component contributing to the PH found in a substantial number of patients with LHD [4, 9, 92, 93]. Of course, not all patients are affected, and as such, the response and the consequences to PvH varies widely [4]. However, the majority of patients suffering from mitral stenosis [93], HFrEF [24, 38], and HFpEF [8] show a pre-capillary component to their pulmonary hypertension.

LA dysfunction characterized by increased LA size, interstitial LA fibrosis (causing increased LA stiffness), reduced LA compliance, and impaired LA contractility, contributes to the disease process by affecting left ventricular filling, enhancing LA and pulmonary venous pressures, provoking a rise in pulmonary vascular resistance and in PAP, amplifying the development and manifestation of "combined" PH [94–97]. Ensuing heart failure symptoms relate to LA dysfunction in patients with HFpEF [98]. Increased pressure and dilatation of LA are likely to be necessary adaptions to compensate for increased LV-filling pressures in order to maintain LV filling in HFpEF patients [99–101].

Furthermore, the development of relevant functional mitral regurgitation (MR), often exercise—induced and thus reiteratively occurring [50, 102–104], is demonstrated to augment LA pressure, since the pressure effected by the systolic part of regurgitation volume adds up to systolic LA filling pressure [103, 104]. The insensitivity of the pulmonary vasculature to vasodilators including NO and natriuretic peptides [6, 79, 93] and the neurohormonal activation are considered to potentially contribute to the disease process leading to combined PH.

In HFrEF, the extent of (functional) MR is considered crucial for the quantity of PH [50]. Hypoxemia related to congestion and obstructive sleep apnoea, often seen in patients with LHD, may also worsen PH [6]. Finally, even genetic factors

predisposing patients to maladaption of the pulmonary vessel network are being discussed [105].

This increase in pulmonary vascular resistance and PAP markedly impacts the impedance (rises) of the pulmonary artery and the RV outflow tractus, afterloading the right ventricle [106–109], with relevant consequences for RV-PA-coupling and RV-performance [5, 53, 106, 110, 111]. The dynamic interplay between pulmonary vascular resistance, the pulmonary vessel compliance, and the wave reflections determine RV-afterload [111]. Increases in PVR are the most common cause for increases in RV-afterload [112]. PVR reflects the resistive RV-load, however, vascular resistance and vascular compliance (representing the pulsatile load) are inversely related to each other in pulmonary circulation [113]. Consequently, a relevant decrease in vascular compliance will occur with increasing PVR [113]. This "special" relation is explained by the fact that in the pulmonary circuit, compliance is distributed over the whole vascular network, while largely located in the aorta within the systemic circulation [114]. Indeed, Stenmark [115] provides evidence that more than 1/3 of the increase in RV-load due to an increase in PAP is caused by pulmonary artery/large pulmonary arteries stiffening. Additionally, stiffening of the pulmonary artery/arteries is reported to increase while PH progresses [116]. Thus, large pulmonary artery stiffness causes significant increases in RV afterload [20, 111], notably in case of persistently high pulmonary venous pressure and in advanced stages of vascular remodelling [87, 111].

RV afterload is a major determinant of RV systolic function [117], and as the performance of the right ventricle crucially depends on its afterload, even more than the LV [106, 118], it is more than reasonable to consider RV and pulmonary vasculature as one unit: "PAH is a disorder affecting both the pulmonary vasculature and the right heart" [29, 119–121]. Accordingly, enhanced afterload effects RV systolic function and as mean PAP is inversely related to RV-EF [117], increasing PAP impairs RV-EF [122]. Therefore, in patients with PH, decreases in RV-EF generally reflect an increase in RV- afterload rather than a compromised RV systolic function/contractility [123].[2]

Furthermore, Di Salvo [124] and Ghio [37] both found that RV-EF provides, in addition to PAP, independent prognostic information, emphasizing the necessity to consider the RV-pulmonary circuit as a unit in patients with LHD and consecutive PH [119]. Several studies demonstrated that both, PH and the (subsequently) compromised RV-function, henceforth called the RV-pulmonary unit, considerably affect the prognosis of patients with LHD [31, 37]. Moreover, ventriculo-arterial coupling specifically refers to the relationship between ventricular contractility and

[2] LV systolic dysfunction is reflected by an increase in PCWP, and this, in turn, may result in an elevation of mean PAP and/or RV afterload [117]. Since an elevated mean PAP is coupled with a decrease in systolic RV-function [37], and RV afterload literally determines RV systolic function, thus a raise in mean PAP reflects an increase in RV afterload: mPAP ~ 1/RV-EF [117].

↑ PAP coupled to ↓ RV systolic function, and RV-afterload determines RV systolic function

→ ↑ PAP reflects an increase in afterload: mPAP ~ 1/RV-EF

afterload [113] and as such, ventriculo-arterial coupling, indicated by the $E_{a\text{-}pul}/E_{es\text{-}RV}$ ratio, is an important determinant of net cardiac performance [125] and cardiac energetics [126]. Only appropriate matching between the right ventricle and the pulmonary arterial system results in an optimal transfer of blood from the RV to the pulmonary circuit without excessive changes in pressure, an optimal or near-optimal stroke work, and energetic efficiency [127]. Interestingly, RV-PA uncoupling occurs in chronic pressure overload following PH due to LHD [128], while in idiopathic PAH RV-PA coupling is preserved [129].

As described in Chap. 4 in more detail, a rapid (and substantial) rise in PAP causing acute pulmonary hypertension with concomitantly enhanced RV wall tension, immediately leads to RV-dilatation [106, 130], which is accompanied by increases in RVEDV [107, 109, 130] and RVEDP [131, 132], compromised RV contractility [37, 108], impaired RV-EF [130, 133], RV pump failure and even cardiogenic shock may promptly ensue [134]. These hemodynamic alterations are largely a result of the thin-walled RV, which is physiologically coupled to, and ejects the blood into a low pressure highly compliant compartment [27, 85, 112], and therefore is only poorly capable to respond to, and suitably face, an acute increase in afterload [135]. Even mild acute PH, following an increase in RV-afterload, may lead to substantial RV-PA-uncoupling, indicating that the RV is not able to match the combined load of elevated PVR and augmented vascular/ventricular elastance [136]. Due to PH, which precipitates RV stiffening [137], and as such results in increased RVEDP [137] and RV-dilatation, tricuspid regurgitation [138] arises. Furthermore, diastolic ventricular interaction (DVI) applies, compromising left ventricular filling and (even further) deteriorating global cardiac function and systemic circulation [138–140]. DVI, coming in general and particularly into effect with increasing RVEDP, as for example when RV loading conditions change [141, 142], substantially contributes to acute RHF pathobiology and makes a crucial hemodynamic impact on right heart and subsequently systemic cardiovascular functions [143]. Beyond, RV-dilatation directly affects LV geometry, impairing LV filling [144], and subsequently compromises LV contractility with considerable effect on RV performance—as about 1/3 (20–40%) of systolic RV pressure generation and output results from LV contraction [143, 145, 146]. Furthermore, neurohormonal and endothelial—immunologic/inflammatory cascades acutely activated in cardiocirculatory challenge, markedly influence the acute pathology [119, 147–149]. As such, stimulated sympathetic discharge (including increased systemic catecholamines levels) and excited activation of the renin-angiotensin-aldosterone cascade, specifically angiotensin II, as well as enhanced endothelin-1 release, and all that in the presence of blunted and imbalanced counter-regulatory mechanisms such as natriuretic peptides, substantially co-determine the acute pathophysiology of right heart dysfunction [149–154].

In these circumstances, sufficient and consistent adaption may fail as the initial heterometric response may not be replaced by enhanced ventricular performance [155]: The so-called heterometric adaption (coping beat-to-beat changes) applies, when the ventricle is faced by an abrupt rise in afterload, using the Frank-Starling mechanism, and thus allowing to maintain SV at the expense of increased end-diastolic filling

volume [156, 157]. However, within a couple of minutes, ventricular elastance, and thus systolic performance, will match the increased load by full homeometric adaption, replacing the initial heterometric response [158]. This may not be the case in acute RHF thereby keeping the "compensatory" mechanisms activated and running.

In case of a gradual increase in PAP and PVR as is usual in LHD, so-called homeometric contractility adaption to afterload, according to Anrep's law [159], may ensue [155]. The homeometric adaption and remodelling is characterized by an increase in ventricular systolic function (e.g. contractility) without chamber dilatation, in order to meet the load the ventricle is facing [156]: The right ventricle adapts to the increased afterload by increasing its wall thickness and contractility [113]. Homeometric adaption is shown to be the predominant feature of RV to face increased afterload and to ensure preserved RV-PA-coupling [155, 160]. However, if the load rises further, becoming too high for too long a period, or if these compensatory mechanisms are insufficient to match the load imposed, RV-PA uncoupling, associated with a (further) increase in RVEDV occurs [155, 156], and a heterometric adaptive response, indicating RV dysfunction [113], or even RV-failure, rapidly ensues [155, 160]. Severe inflammatory conditions (e.g. septicaemia), long-term increase in PVR or advanced heart failure, are disorders predisposing RV-PA uncoupling and RV-dysfunction [155, 160]. Indeed, it is essential to mention that, for sure, further, supplemental features (in addition to the pulmonary vascular and pressure alterations and their consequences for the RV and the RV-PA unit) are involved and contributing to the complex pathobiology of (developing) RV-dysfunction/failure including persistent neurohormonal activation and inflammation, apoptosis, persistent oxidative stress, metabolic derangements, the results of remodelling like hypertrophy and fibrosis, and, not least, RV ischemia [113, 148, 161].

To summarise, in the first instance, LHD leads to pulmonary venous hypertension attributed to passive, backward transmission of the elevated left heart-sided filling pressures [1, 5, 7], mainly precipitated by LV dysfunction, many a time by LV diastolic dysfunction [162, 163]. Mitral regurgitation, often exercise-induced and thus occurring repeatedly, and the loss of LA compliance may amplify the pulmonary venous pressure increase and thus PvH [94]. Abrupt increases in left-sided filling pressures may cause alveolar-capillary stress failure [55], facilitating acute overt pulmonary edema formation [21, 22]. The main pathophysiological feature, and driving force precipitating pulmonary congestion or pulmonary edema, is the increased hydrostatic capillary pressure in the alveolar-capillary unit [58]. Alveolar-capillary stress failure is potentially fully reversible, as long as pulmonary venous pressures return to normal in good time [62–64]. However, persistent or recurrent elevated pulmonary venous pressures have been shown to cause functional and structural alterations not only at the alveolar-capillary unit [4, 65, 66], inducing irreversible remodelling, but also notably of the arterioles and the small and medium-sized pulmonary arteries [67] (the pre-capillary segments of the pulmonary circuit [5, 21]). Endothelial dysfunction, and the activated inflammatory cascade, decisively determine and integrate the incipient processes [53, 69–71]. This leads to both, functional alterations (mainly a significant rise in pulmonary vascular tone in microcirculation and resistive vessels, augmenting PVR [5, 27, 79]), as well

as to structural vascular remodelling (including intima and media hypertrophy of the pulmonary arteries and arterialization of the veins) [86, 164], reducing the area of blood flow and thereby driving the PVR up [4, 5, 27, 85]. Accordingly, PVR rises considerably [5, 7, 27], indicating pulmonary vascular disease [5, 87]. Subsequently, a further increase in pulmonary hypertension arises [5, 85], as the change in PVR is superimposed on the elevated PvP [86, 93]. Elevated PVR and the disproportionate (in excess to the left-sided filling and consecutively pulmonary venous pressures [162, 163]) rise in PAP, indirectly confirm a pre-capillary, pulmonary arterial component, superimposing the PvH and contributing to the considerable PH, recognized in a significant number of patients suffering from LHD [4, 27, 87]. As such, reactive PH displays and represents a complex reaction to chronically elevated filling pressures of the left heart side, including structural (pulmonary venous arterialization of small and medium-sized vessels [164]) and functional alterations such as ED associated imbalances between NO and ET-1 production fascilitating vasoconstriction [79, 80]. Consecutively, a marked load, largely attributed to the rise in PVR and to the stiffening of the large(r), central pulmonary arteries [115, 165], is imposed on the right ventricle (RV-PA unit) [106–109], crucially affecting RV-PA-coupling and RV function, potentially provoking RV failure [87, 113, 128].

6.5 Clinical Issues and Diagnosis

The symptoms patients with PH complain of, are non-specific and comprise amongst others, dyspnoea, fatigue, chest discomfort or pain, palpitations, syncope and peripheral edema [2]. Especially remarkable, and most common symptoms, are **exertional dyspnoea** and a noticeable **exercise intolerance**, which patients with PH suffer from, due to LHD [21].

The pathophysiology underlying exertional dyspnoea is complex and several mechanisms are interrelated and contributing [21]. However, the basic pathology may be that the pulmonary circuit in PH, due to LHD, is unable to accommodate the increased blood flows during exercise [166], and contrary to the physiologically expected PVR fall [167] and moderate increase in PAP [168], abnormally high pressures occur (rising PCWP, PAP and/or PVRs) [166]. One feature of the predominating pulmonary vascular pathophysiology is the impaired physiological dynamic pulmonary vasodilation, which subsequently imposes a considerable load on the RV during stress [169].

Exercise, provides a powerful tool to examine the response of the cardiovascular system to stress and to assess its functional reserve [170], and may reveal early stages of heart failure, especially in HFpEF [92]. Patients with normal filling patterns at rest may exhibit dyspnoea and PH during exercise [92, 166].

Ventilatory abnormalities, particularly oscillatory breathing patterns during exercise due to pulmonary vasoconstriction, compromised right ventricular performance and low total CO [171, 172], and the limited cardiac reserve and thus limited CO increase [85, 173], provoke a lower anaerobic threshold and contribute to dyspnoea [2].

Breathing alterations are common in group II PH, as such, periodic breathing is related to sympathetic activation [174], enhanced incidence of sleep apnoea, and especially patients with HFrEF and PH show inefficient ventilation with high expiratory volumes per time in relation to the carbon dioxide exhaled, hence are often hyperpnoic [175].

Syncope may appear due to exercise or arrhythmias. Chest pains, attributed to maladjusted coronary perfusion in the presence of elevated RV pressures [176], befall even more predisposed patients with coronary artery disease and/or RV hypertrophy, particularly if there is a low MAP (due to poor LV function) [2].

Peripheral edema formation may be the result of tricuspid regurgitation and RV dysfunction, leading to venous congestion, subsequently affecting abdominal organs, particularly incipient renal venous congestion which impairs renal function (called cardio-renal syndrome, see Chap. 7), will all complicate the malady [4, 11, 177, 178].

Moreover, Rosenkranz [28] even indicates that the clinical picture in patients with PH, due to LHD, may be completely dominated by signs and symptoms typical and characteristic for (acute) right heart failure. The spectrum of the clinical presentation of this patient group is broad, ranging from a more or less `pure` decompensated left heart phenotypic picture, to an appearance which is dominated by features representative of an acutely decompensated right heart [28].

Chest X-ray may indicate pulmonary vascular congestion or even pulmonary edema and pleural effusion in or without the presence of cardiomegaly. Of note, co-existence of pulmonary edema and signs of right heart failure is rare, possible due to that fact that the vascular alterations of the pulmonary vessel network protect against pulmonary fluid transudation [21]. Computer tomography may denote ground-glas opacities and mosaic perfusion patterns consistent with chronic interstitial edema [21].

ECG signs are unspecific, but may include LH hypertrophy and atrial fibrillation [21].

Lung function tests may reveal restrictive ventilatory patterns and disturbed gas diffusion [179].

Echocardiography is an essential tool and the method of choice to detect PH [4, 13] and thus is an indispensable procedure in the assessment of patients suspected of PH [2, 6, 13]. Systolic pulmonary pressures (sPAP) become assessable, if tricuspid regurgitation is present [180]. Systolic pulmonary pressures > 35 mmHg are suggestive for PH [181]. Both, under- and overestimations (if pressures are normal or only mildly elevated) are not infrequent [182], and estimated sPAPs between 35 and 45 mmHg need careful interpretation [183] and should only be apprised in the clinical context. Echocardiographically calculated sPAPs between 35 and 45 mmHg are considered to indicate mild PH, pressures between 46 and 60 mmHg represent a moderate and those above 60 mmHg a severe PH [184]. PH and its severity are determined by elevated filling pressures which can be echcardiographically evaluated by the severity of diastolic dysfunction [50–52]. As such, E/A-ratio and the E/e'-ratio are reported as the echocardiographic parameters which most reasonably reflect end-diastolic filling pressures [49, 50, 185]. Restrictive filling patterns (E-wave deceleration rate) and the degree of mitral regurgitation turned out to be the strongest independent predictors of PH [49, 186].

Furthermore, the presence of LHD/LV dysfunction may be assessed, or even recognized, by echocardiography. Signs suggestive of LV dysfunction include LA dilatation, LV hypertrophy, more severe mitral valve regurgitation, and indicators of elevated LV filling pressures [187–189]—further details see Chap. 5 HFpEF. As RV-function encroaches upon the prognosis in patients with LHD and PH, assessment of the right heart is absolutely essential [2, 190, 191].

The gold standard in diagnosing PH is right heart catheterization (RHC), and the current guidelines even require RHC in order to reliably diagnose PH [10, 13]. Clinical and/or echocardiographic evidence for PH should lead to RHC [2, 6].

Importantly, invasively derived pressure measurements should be registered only in end-expiration as the pressures recorded may significantly differ between inspiration (lower) and expiration (higher) while PH definition and specified limits are standardized to end-expiratory measurements [28, 192, 193]. Furthermore, LVEDP depends on loading conditions [28], and changes may induce a considerable modification of hemodynamics and thus the magnitude of pressure values recorded: especially patients suffering from PH caused by HFpEF are highly sensitive to even small changes in volume and/or BP [30, 127, 194, 195]. As such, after diuretic therapy, the presence of elevated left sided filling pressures, and subsequently PH, may be missed, just because the patient has been volume unloaded [196]. Volume depletion can underestimate left heart filling pressures [197]. On the other hand, in balanced fluid conditions, a standardized fluid challenge (500 mL normal saline infused within 5–10 min) may unmask a post-capillary, venous PH component present in patients with PH, clearly identifying LHD as the cause for PH [197–199]. If a PCWP of >18 mmHg can be recognized in response to the fluid applied, a left heart dysfunction, whether systolic or diastolic, should be assumed [198]. Extraordinarily and remarkably, Fujimoto [198] showed that even in healthy volunteers, a transient but significant increase in filling pressures (right and left sided) can be observed when infusing fluids rapidly (1 L of normal saline within 5 to 10 minutes): mean PAP, PCWP and RA-P were all significantly raised in all groups, young, old and HFpEF patients, but increased the most in patients with HFpEF. Causative, pericardial constraint was demonstrated to be largely responsible for the increase in filling pressures, indicating that non-myocardial structural changes caused the elevation in pressures [198, 200, 201]. Thus, no change in myocardial stiffness occurred [202, 203]. Accordingly, the results of fluid infusion in order to identify occult venous pulmonary hypertension need superb interpretation!

PVR—defined by [PVR = mean PAP – PCWP]/CO [85], which equals PVR = TPG/CO, is a commonly used parameter in daily practice [87]. Increased PVR represents pulmonary vascular disease, and as such, pulmonary arterial hypertension [24, 204]. PVR is found to be sensitive to both, changes in flow and filling pressures, however PVR may not sufficiently indicate changes of the pulmonary circulation at rest [162, 205]. PVR values of ≥3 Woods (240 dyn s cm^{-2}) are highly suggestive of pulmonary vascular disease [10, 206].

The new recommendations based on the 5th Symposium on PH in Nice, France, in 2013 encourage practitioners to include PVR in the characterization of PH—with an elevated PVR (>3 WU) in the presence of a mean PAP ≥ 25 mmHg and a

PCWP ≤ 15 mmHg (normal left heart-sided filling pressures) is indicating pre-capillary PH—but PVR should not be part of the general definition of PH [12]. In case of combined PH, attributed to LHD, PCWP > 15 mmHg and PVR > 3 WU are required.

High mean PAP, PCWP, PVR, and reduced PA compliance are indicative of poor survival and as such provide prognostic information [37, 207, 208].

Of *special note*, in case of RV failure, PAP may decline despite considerably high PVR and thus may underestimate the extent of pre-capillary PH [21].

The so-called transpulmonary pressure gradient (TPG), the driving pressure across the pulmonary circulation [27] (defined as TPG = mean PAP – LA-P, respectively PCWP [162]), has been shown to rise "out of proportion" to wedge pressure PCWP (left-sided filling pressure), concomitantly accompanied by disproportional increases in PAP [209], in patients with LHD suffering from combined post-and precapillary PH [24, 204]. As such, an elevated transpulmonary gradient (defined as calculated values exceeding 12–15 mmHg [41, 52]), reflects pre-capillary contribution to pulmonary hypertension in LHD patients [1, 21, 91]. Accordingly, in case of LHD, reflected by a mean PAP ≥ 25 mmHg and a PCWP > 15 mmHg:

- TPG < 12 mmHg may be suggestive of isolated post-capillary PH
- TPG ≥ 12 mmHg may be suggestive for combined, post- and precapillary PH

Elevated TPGs, *in the presence* of heightened PVR and impaired pulmonary vascular compliance, confirms significant pulmonary vasculopathy [21, 91].

In recent years, diastolic pressure difference or gradient (defined as DPG = diastolic PAP – PCWP [87]), is the preferred parameter used to identify a pre-capillary component contributing to PH in patients with LHD [87]. Diastolic PAP is, compared to mean PAP and systolic PAP, less influenced by changes in loading conditions, for example by PCWP (≈LA-pressure) and SV [28, 162, 163]. This effect is even more evident when SV increases, such as during exercise [162, 163]. Changes in mPAP consecutively have an impact on TPG. Therefore, TPG is affected by all determinants of mPAP including flow, resistance, and left heart filling pressures [162, 205]. Accordingly, mPAP, TPG and PVR may be "too" unspecific as indicators of pulmonary vascular remodelling [210]. Furthermore, the prognostic impact of TPG is poor [211]. As a consequence, DPG is considered to be the most reliable approach to identify pulmonary vasculopathy and hence pre-capillary input to PH in LHD patients [87, 162, 212]. In a landmark study, Gerges and co-workers [212] investigated the role of DPG in predicting outcome and, using a receiver-operating analysis, identified and determined cut-off points for DPG: They established "mixed" PH to be present, if DPG ≥ 7 mmHg or TPG > 12 mmHg. Patients with PH due to LHD and with a TPG > 12 mmHg and a DPG ≥ 7 mmHg, had an inferior outcome after 78 months than those with a TPG of >12 mmHg, but a DPG < 7 mmHg [212]. However, the study has a couple of limitations including: being retrospective in nature; having a bias in the population (patients presented a negative DPG, further a number of patients with a TPG of <12 mmHg had a DPD ≥ 7 mmHg); the patient group had been a selected

population (referred to a tertiary centre for their PH); they had a burden of ischemic heart disease; and the patients suffered from severe heart failure. Nevertheless, the cut-off ranges found their way into newly published diagnostic recommendations [162, 212], as such:

- isolated post-capillary PH: PCWP > 15 mmHg and DPG < 7 mmHg and/or PVR ≤ 3 WU
- combined post- and pre-capillary PH: PCWP > 15 mmHg and DPG ≥ 7 mmHg and/or PVR >3 WU [87, 213]

However, a very recent study challenged the value of the newly introduced DPG: In a study by Tampakakis [214], investigating in a retrospective analysis the John Hopkins Cardiomyopathy Database, DPG failed to provide sufficient prognostic information, and a correlation between DPG value and survival could not be established. They found that in patients with PH, increasing TPG and PVR were significantly related to a higher all-cause mortality, even after adjustment for standard variables.

As such, the DPG parameter, relatively independent of influences from varying CO and elevated filling pressures on pulmonary arterial compliance [87, 162], has not withstood real world scrutiny, and its implementation in the standard diagnostic may be premature [210]. Moreover, as discussed above, the pulmonary vessel system, with its properties, and the right heart and its performance, have to be considered and have to be seen at as a unit because they substantially interact and influence each other [1, 215]. Insofar, the metric DPG parameter may preferably and uniquely refer to and indicate pulmonary vascular disorders [212], but does not reflect right heart properties and function in the setting of pulmonary vascular pathology. Thus, an integrated approach relating pulmonary vascular pathology, indicated by PVR, TPG, DPG, etc., to RV-PA function and performance, e.g. RV-PA-coupling ratio, is potentially able to translate into prognostic significance [210].

However, clinical assessment and judgement remains crucial: Thenappan et al. have demonstrated in a study on "clinical characteristics of pulmonary hypertension in patients with heart failure and preserved ejection fraction" [91], that clinical, echocardiographic, and hemodynamic features are able to distinguish PH in LHD from PAH, and from patients with HFpEF but without PH.

Characteristics	PAH	PH due to LHD	HFpEF
Age	Younger	Older	Younger
Comorbidities	Rare	More frequent	Frequent
RA—dilatation	More frequent	Less frequent	**Absent**
LA enlargement	**Absent**	Frequent	Frequent
Aortic systolic pressure	Normal	**Elevated**	**Elevated**
RA-pressure	Normal to high	High	Normal
CO	Low	Normal	Normal
PVR	Markedly elevated	Moderately elevated	**Normal**

Notably:

1. If right heart failure ensues in patients with PH due to LHD, low CO may result in a fall in PCWP, making diagnosis difficult [10].
2. In patients with HFpEF, the presence of morbid obesity, chronic obstructive lung disease (COPD), atrial arrhythmias, particularly AF, dyspnoea on exertion, and mPAP ≥ 25 mmHg are suggestive of PH [216].

Accordingly, combining the study results of Thenappan [91] and of Guazzi [22], PAH may be clinically-hemodynamically distinguished from PH due to LHD by the following issues suggestive of PH-LHD:

– older age
– typical co-morbidities like coronary artery disease, hypertension, obesity, diabetes, obstructive
– sleep apnoea, COPD, etc.
– dilated left atrium
– left ventricular hypertrophy
– substantially elevated right atrial pressure
– elevated systolic aortic pressure
– evidence for pulmonary congestion/edema on X-ray/thoracic CT/ultrasound

To summaries:

1. A mean PAP ≥ 25 mmHg in patients with LHD, the latter hemodynamically indicated by a PCWP > 15 mmHg, confirms the presence of PH
2. A TPG > 12–15 mmHg and/or a PVR > 3 WU is suggestive of a mixed form of PH, which means aside from the post-capillary (venous hydrostatic component due to passive backward transmission of the elevated left-sided fillings pressures), a pre-capillary reactive superimposed component, due to congestive pulmonary vasculopathy, has to be determined
3. A TPG < 12 mmHg and/or a PVR around 3 WU is most likely indicative of a "pure", isolated venous pulmonary hypertension (PvH)
4. Using the newly introduced metric parameter DPG, *isolated post-capillary PH* is characterized by: PCWP > 15 mmHg and DPG < 7 mmHg and/or PVR ≤ 3WU, *combined post-capillary* and *pre-capillary PH* by: PCWP > 15 mmHg and DPG ≥ 7 mmHg and/or a PVR > 3 WU [27, 87, 213].

6.6 Therapeutic Considerations

Substantial and evidence based data on how to manage PH due to LHD are scarce at best, more often than not they are missing [5, 28, 87]. Current guidelines are based on expert opinion and provide only very limited treatment suggestions [5].

However, common sense is to treat the underlying malady(ies) and co-morbidities [13, 22], to address volume status [10, 196], and to keep attention on PAP, due to its clinical importance, since lowering elevated pulmonary pressure will reduce dyspnoea and hospitalization rates in both HFrEF and HFpEF [217, 218]. PH due to LDH will improve by unloading the left ventricle and thereby lowering LV-filling and pulmonary pressures [27].

Accordingly, *an optimized volume status* is crucial and of utmost importance [13, 53, 87]. *Diuretic therapy* is the conventional approach to control fluid status, applied in case of congestion, diuretics reduce mean PAP, PVR, and PCWP. Subsequently, the clinical situation of the patient will significantly improve [28, 53, 196, 219]. Functional mitral regurgitation, particularly in HFrEF, may not only play a marked role in inducing PH, but worsens prognosis [220]. Proper *repair of mitral valve regurgitation* (for example using a mitral clipping or cardio-band) even in asymptomatic patients [221] is demonstrated not only to improve pulmonary hemodynamics, but to markedly alleviate symptoms, ameliorate quality of life, increase exercise tolerance and to reduce hospitalizations [222, 223]. However, clinical outcome studies are still not available.

Additionally, cardiac resynchronization measures may result in improved cardiac output and reduced PAWPs in selected patients [224].

The approach for group II patients is based on pathobiological considerations, and simply applies PAH therapies by targeting the pulmonary vasculopathy. However, the results have been quite diverse and are in general not very positive [22, 87]. Only the treatment with the *phosphodiesterase type 5 (PDE 5) inhibitor sildenanfil*, applied to patients with LHD of miscellaneous etiology, has yielded encouraging results in both, HFpEF and HFrEF individuals [225–235]. Several observational trials (sildenafil was given in acute situations [225–228] and as long term therapy [229–231]) as well as diverse, mostly smaller, single centre studies [232–235] indeed revealed some beneficial molecular, hemodynamic, and clinical effects: *Phosphodiesterase type 5* activity is recognized to be significantly increased in the systemic (including renal), as well as pulmonary, circulation in heart failure patients [235–237]. Sildenafil leads to increases in NO-bioavailability and hence NO-mediated vasodilation [238]. Additionally, it has been demonstrated to improve endothelial function [238], to lower arterial stiffness [239] and LV afterload [240], to attenuate sympathetic activation [241], and to ameliorate myocardial contractility in general [27]. Decisively, while not lowering mean arterial pressure, despite SVR declines [27], sildenafil is recognized as a "selective" pulmonary vasodilator [242, 243]- of course, the high expression of *phosphodiesterase type 5* in the lungs substantially co-constitutes this selectivity [243]. Sildenafil was, in general, well tolerated, blunted PH and RA hypertension, reduced PCWP, PVR and RV dilatation [232, 235, 238, 244, 245]. LV mass was regressive, RV contractile function improved, as were LV and RV compliance, renal and neuroendocrine function and gas exchange [232, 235, 238, 244, 245]. Of note, fluid shift into the alveolar interstitium was diminished [242, 246]. It is supposed that *PDE 5* inhibitors, by ameliorating the cGMP—dependent phosphorylation of titin, exerts directly beneficial effects on LV diastolic stiffness [247].

Unfortunately, the randomised controlled RELAX- study failed to show any clinical or hemodynamic improvements in HFpEF patients, however PAH, and consecutively affected RV function, was not present in this study group [248]. Indeed, this result is not surprising, since sildenafil is a selective vasodilator, targeting the pulmonary vasculature, and thereby unloads the RV [236]. Moreover, neither post-capillary, nor combined PH, have been specified entry criteria. Strictly speaking, the Relax - study did not intend to assess the effects of *PDE 5* on pulmonary hemodynamics and RV function [22]. As such, these results do not preclude application of sildenafil in patients with *LHD and PH* [22, 249]. Nevertheless, the use of *PDE 5* inhibitors is anything else but definitive [28].

Sildenafil is initially given in a dosage between 3x 25 mg, but can be titrated up to 75 mg tds, on average 50 mg tds was used [228, 232]. Acutely 40 mg may be applied [245]. Noteworthy, acute reductions in PVR carries the subsequent risk of abrupt increases in left-sided filling pressures, as blood flow increases with PVR reduction [250].

To conclude, therapeutic approaches in LHD and PH are currently not evidence based at all, particularly not in patients with PH due to HFpEF. As such, careful consideration is essential and an individualised approach is necessary.

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Cardiorenal Syndrome (CRS)

7

7.1 Definition

To express and to outline the special relationship observed between the heart and the kidneys in health and in malady, several characterizations and definitions have been proposed [1]. The knowledge of a specific interrelation between these two organs dates back as early as the seventeenth century BC, where in the Egyptian "Book of the Dead" one can find: "Homage to thee, O my heart! Homage to you, O my kidneys" [2]. In any case, traditional Chinese medicine already recognized and described a disorder termed "heart and kidney failing to link", suggesting a close connection between kidney and heart dysfunction [3].

As such, the most recent and currently used definition is actually based on Ronco [4], who elaborated the most operational and practical determination of that interaction. The consensus conference of the Acute Dialysis Quality Initiative (ADQI), held in September 2008, compiled the following definition and characteristics of *cardiorenal syndrome (CRS)* [5]:

Cardiorenal syndrome, a complex disorder of both, the heart and the kidneys [6, 7], may be defined as "disorders of the heart and the kidneys whereby acute or chronic dysfunction in one organ may induce acute or chronic dysfunction of the other" [5].

To fulfil this definition, both organs must display or develop structural and/or functional alterations [8]. Furthermore, we can distinguish between five subtypes [4, 5]. *Type 1* (acute CRS) refers to an *acute worsening of heart function leading to acute kidney injury and/or dysfunction* [5].

7.2 Epidemiology and Prognostic Issues

Type 1 CRS is found to arise in up to 45% (incidence between 19 and 45%) of patients admitted with ADHF displaying acute kidney injury (AKI) [9–12]. The occurrence of AKI, attributed to AHFS, is indicative of an even worse

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prognosis, as it is associated with higher all-cause and cardiovascular mortality in both the short- and long-term perspective, and a prolonged hospitalization [10, 13–17]. Risk factors to develop AKI due to AHF include: a history of diabetes mellitus, severity of cardiac dysfunction on admission (the more severe heart failure the higher the risk to develop AKI) [14, 18], use of high dose diuretics (frusemide dose >100 mg/24 h, or use of high dose thiazides), vasodilator therapy or application of higher radiocontrast volume [9, 16, 19, 20]. Most cases of AKI occur and develop within 3–5 days after admission [9, 10, 21].

7.3 Clinical Issues and Diagnosis

Rapid worsening of renal function in the setting of AHF, resulting in volume overload, low CO and poor response to diuretic treatment (the latter known as "diuretic resistance"), are characteristic features of CRS, *type 1* [4, 22]. Typically, signs and symptoms of fluid retention are present in the clinical picture with pulmonary (rales) and systemic congestion [9, 10, 23], while laboratory findings indicate elevated creatinine and nitrogen urea plasma concentrations [4]—see Chap. 2, BUN with prognostic validity [24].

Of note, patients with worsening renal function more often suffer from hypertension and complain about fatigue [9, 10, 23].

Following and applying the definition, the diagnosis of CRS *type 1* requires incipient or worsening renal function attributed to, and induced by, primarily acute heart failure [7, 25]. Several tools to assess, to recognize and to classify renal dysfunction have been proposed and used in studies. I recommend to follow the definition of the RIFLE [26], respectively the AKIN classification [27], rather than to apply surrogate markers like the ratio of urine production to diuretic dose applied [28], or even newer biomarkers like NGAL or cystatin C (the latter arguably being a suitable indicator of high risk patients) [29–31]. The newer markers are not yet common daily practice, are not generally accepted by practitioners, and may need further evaluation in the context of cardio-renal syndrome [32, 33]. Applying AKIN allows for greater standardization of data, future (epidemiologic) studies and embeds CRS, *type 1*, into "the broader context of AKI" [34].

Impaired renal function, in the presence of AHF, is basically suggestive of altered renal perfusion [35], unless proven otherwise. Subsequently, either low cardiac output, and/or particularly the much more common increased renal venous pressure, has to be considered and the patient should be examined for this [36]. Renal venous congestion may distinguish acute CRS, *type 1*, from other etiologies of AKI [37]. Specifically, drug-induced renal functional alterations need to be taken into consideration in a differential diagnosis [38].

The poor response to diuretics (diuretics are the cornerstone and standard therapeutic approach in CRS *type 1* [39, 40]) has diverse aetiologies [4, 41, 42], and the persistence of signs and symptoms of heart failure, despite suitable and increasing dosages of diuretics, is referred to as "diuretic resistance" [43].

Unfortunately, there is no generally accepted definition of diuretic resistance. The most commonly cited definition of diuretic resistance is: "a failure to decongest despite adequate and escalating doses of diuretics" [42]. The pathomechanisms involved and responsible for the poor effect of diuretic medication include: compromised renal blood flow (RBF) [43], altered enteral drug reabsorption [44, 45], reduced glomerular filtration (as loop diuretics act best from the luminal site) [46, 47], low albumin concentrations (impair uptake and secretion of active frusemide) [48, 49], and increased levels of urea nitrogen and other organic acids competitively hampering diuretic availability on the site of action [50, 51].

AKI related to AHF is most common in up to 60% of all patients with preexisting renal dysfunction [11, 17], as is diuretic resistance in patients with preexisting (chronically) impaired renal function [41, 52]. Predisposing issues to develop AKI due to AHF are: obesity [53, 54], diabetes [9, 55], hypertension [55–57], anemia [58, 59], and of course nephrotoxic drugs and even the medication applied to treat AHFS [4, 34, 38]. As such, particularly contrast agents, as given in case of coronary angiography, are a frequent precipitant of *type 1* CRS [60–62].

7.4 Pathophysiology

The close interrelation and the interactions between the heart and the kidneys have been traditionally related to hemodynamic issues [63–65], as cross-talk between the two organs is physiologically necessary to regulate and to care for physiologic circulatory conditions and fluid and electrolyte homeostasis [1, 5, 65–68]. Cross-talk between organs is, in general, essential and indispensable to assure and maintain in vivo homeostasis, physiological and smooth functioning of the organism [5, 69]. The communication between the heart and the kidneys is of bidirectional nature, using several pathways available to notify, give feedback and impact on each other [43, 66, 69]. In the setting of malady, the injured, dysfunctional organ, may affect the other via various complex humoral, metabolic, and cell-mediated pathways [69]. As such, acute heart failure has a direct impact on kidney function (and vice versa in case of acute renal dysfunction) [4, 5, 7], by immediate precipitation of disrupted and toxic cell signaling promoting distant organ malfunction and/or structural alterations [70].

In detail: immune and somatic cell signaling may be substantially altered; the inflammatory cascades including augmented cytokine release and features associated with endothelial dysfunction are activated; enhanced

neurohormonal (sympathetic and renin-angiotensin-aldosterone) drive and modified heart- renal reflexes (e.g. Henry-Gauer reflex) are described; neutrophil migration, leukocyte trafficking, enhanced oxidative stress and disturbed redox homeostasis are verified; non-osmotic release of arginine vasopressin (disturbed hypothalamic-pituitary axis), and cell apoptosis are all potentially able to markedly affect distant organ function and structure, particularly the renal tubular epithelium and the renal vascular endothelium [1, 8, 22, 36, 66, 71–73].

As a main result, **intrarenal and intraglomerular hemodynamics** are substantially altered, affecting GFR [4, 5, 8, 36, 74–76], and fluid and electrolyte homeostasis [8, 71, 77, 78], and thus renal dysfunction, AKI, may apply. Accordingly, it is not astonishing, that traditionally cross-talk between heart and kidneys has been exclusively considered to be a hemodynamic feature [63–65, 79]. The attenuated GFR, and the fluid and electrolyte derangements are a consequence of altered renal hemodynamics, attributed to acute or chronic heart failure [8, 77, 80, 81], as Guyton explained: "Combined heart and renal failure in terms of interactions between cardiac filling and contractility, renal function, blood pressure and blood and extracellular fluid volumes" [67]. Indeed, altered renal function can, by all means, be related to changes in renal blood flow, and renal and glomerular perfusion pressures arising from incipient AHF [82]. As such, *renal dysfunction related to AHFS has been attributed to renal hypoperfusion following low cardiac output* [4, 22, 66, 74, 75, 83].

Renal blood flow, and subsequently the glomerular filtration rate (the latter being a hallmark of renal function which is decisively depended on renal perfusion/perfusion pressure and RBF respectively [84, 85]), are regulated by a very complex interplay between renal and systemic vascular resistance, CO and effective circulating blood volume, and intrarenal and intraglomerular hemodynamics. Thus, conditions determined, modulated and affected by miscellaneous factors and features including: renal autoregulation (with its two components, tubuloglomerular feedback and myogenic response of renal vasculature [84, 86, 87]), circulating and local hormones, paracrine factors, as well as endothelial and renal neurohormonal (sympathetic and renin-angiotensin-aldosterone system, baroreceptor-mediated neuronal) effects and replies [86, 88–94]. Impaired renal perfusion activates at least some (depending on the severity of hypoperfusion) of these mechanisms to compensate for hypoperfusion, largely facilitating renal and systemic vasoconstriction, and sodium and water retention in order to restore renal and systemic (as there will be, in turn, macrocirculatory effects [88, 95]) perfusion pressure, systemic perfusion in general and as such renal blood flow [4, 7, 74, 83, 96]. However, in case of mild to moderate reductions in CO and/or intravascular volume (the effective circulating blood volume), basically renal autoregulatory mechanisms (autoregulation is considered being primarily a pressure-mediated mechanism [97]), will promote *a gradual vasodilation* (mediated by myogenic response and vasodilating agents, such as

prostagalandin I_2 and NO) of the afferent, preglomerular arterioles, atoning for the diminished blood flow offered to the kidneys, by adapting the renal perfusion to the altered conditions and thus maintaining RBF [88, 90, 98–100]. Tubuloglomerular feedback (TGF) fine-tunes renal perfusion and GFR by co-adjusting the tone of afferent arterioles (vasodilation) via local mediators such as NO or adenosine [86, 89], and of vas efferens (*mild vasoconstriction in order to maintain or restore glomerular filtration pressure*), largely mediated via local renin release (of the macula densa due to diminished chloride concentration there), and thus concomitantly, locally generated angiotensin II [89, 93, 101], thereby contributing to restore and/or to preserve GFR. Additionally, salt and water retention ensues [102, 103] substantiating the adjusting measures. Myogenic response and TGF may be modulated by neurohormonal effects via paracrine and endocrine paths, as well as neurally-mediated reflexes and responses [86, 93, 104–108].

The circumstances are clearly different in case of severe AHF with markedly reduced CO, often accompanied by significant hypotension, and/or if compensatory mechanisms cannot resolve the compromised renal blood flow: Markedly reduced CO and thus effective circulating blood volume, or otherwise diluted effective circulating fluid volume, diminishes renal blood flow and will subsequently reduce renal perfusion pressure [98, 107]. This affects and substantially blunts, or disrupts, autoregulation, as soon as renal perfusion pressure drops below the autoregulatory threshold [98, 109]. Renal autoregulation is acknowledged to be attenuated, disturbed or even disrupted in heart failure, due to hemodynamic changes, but also related to endothelial dysfunction (see below) [8, 22, 37, 110–112]. As a response, a marked activation of the neurohormonal systems arises with a perceptible effect of an elevated sympathetic drive, and a strongly stimulated RAAS with substantially increased levels of angiotensin II (A II) [113, 114]. This is the result of attenuated and reduced stretch of the baroreceptors of the renal vasculature (e.g. vas afferens), due to an attenuated renal blood flow, consecutively considerably stimulating the neurohormonal systems [6, 43, 65, 80]. Its response (neurally/reflectory-mediated release of mediators like A II, NA, endothelin-1, vasopressin-arginine, etc.) promotes combined constriction of vas afferens and vas efferens, increasing their tone and total intra-renal vascular resistance [71, 93, 107]. Increases in the tone, and thus resistance, of vas afferens, and (general) increases in renal vascular resistance, are associated with reduced renal blood flow and glomerular filtration pressure, and subsequently a fall in GFR [93, 115–118]. Furthermore, changes in the tone of vas afferens and efferent are discordantly in those circumstances, as the afferent arterioles constrict *relatively* stronger than the efferent ones, since vas afferens had been initially dilated and is also more densely innervated by sympathetic nerves (three times more) compared to vas efferens [119]. However, as the effective filtration pressure is mainly affected by the ratio between the tones of afferent and efferent arteriole [76, 88, 90, 120], this ratio shortens as the tones of both arterioles approach each other. In

consequence, a generalized vasoconstrictive environment within the renal vascular bed is engendered [88, 118, 121], and renal function evidently affected. Furthermore, subsequently a considerable volume expansion, namely due to the effects of the sympathetic nervous system, aldosterone and arginine vasopressin, applies [80, 108, 122–125], which may, in turn, restore renal perfusion [102, 103]. However, this volume expansion is basically achieved at the expense of a substantial fluid overload, and in any case, the enhanced renal water, and particularly sodium reabsorption, provokes extracellular fluid expansion, as well as systemic and pulmonary congestion [71, 78, 80, 122]. Therefore, these hemodynamic alterations cause a bidirectional coupling, as renal failure due to AHF causes fluid retention which aggravates heart failure, and thus may provoke further reductions in arterial blood pressures thereby worsening renal perfusion even more [1].

Moreover, if GFR cannot be restored by the applied compensatory mechanisms, the kidneys are at high risk of ischemia and ischemic insults [107]: As with reduced glomerular capillary pressure, the post-glomerular vessel network may be under-perfused, thus tubular ischemia potentially applies and if evoking structural tubular injuries, acute tubular necrosis (ATN) may arise [126]. Furthermore, local differences in the intensity of the increase in renal vascular resistance are observed, resulting in diverse regional perfusion within different kidney areas [85, 95, 127, 128]. Endothelial dysfunction arises, and with limited NO bioavailability, endothelial-dependent vasorelaxation is mitigated [128], thus, microcirculatory failure applies. As such, substantially altered intra-renal microcirculation ensues [95, 129, 130], creating disproportionally modified, diverse local intra-renal blood flows [100, 131–134], promoting hypoxia/ischemia in predisposed areas, particularly the outer medulla [95, 132, 135, 136]. Subsequent reperfusion injuries may ensue [90, 132, 137].

Autoregulation, in general, refers to the ability of a vascular bed to adjust its tone to maintain a constant blood flow during changes in perfusion following variations in arterial perfusion pressure [138, 139]. “Autoregulation is largely and essentially a local mechanism of control of blood flow” [140]. Thus, autoregulation, as a crucial component determining microcirculatory hemodynamics [110, 141–143], provides a rather constant blood flow, and particularly, an appropriate blood flow distribution over a wide range of different perfusion pressures, ensuring that oxygen and nutrient supplies meet actual metabolic demand of each organ, region and tissue area [144, 145]. A well performing autoregulation is obviously a critical element in a proper renal perfusion arrangement, as altered and affected renal autoregulation applying in the context of AHFS has a substantial impact on renal function [8, 76, 97]. Even in case of **adequate CO**, as found in the **vast majority of AHF patients**, **GFR reductions are demonstrated** in quite a number of patients, arguably **attributed to impaired renal autoregulation** [76]. Indeed, renal autoregulation is basically mediated by changes in the tone of vas afferent [97]. As such, uneven renal blood flows are considered to be due to attenuated or impaired autoregulation [76], and CRS *type 1* is suggested to at least partly develop secondary to autoregulatory dysfunction [76].

Lowering elevated BPs in acutely decompensated heart failure patients may affect autoregulation and renal function, although BPs are therapeutically “only”

reduced to normal ranges [146, 147]. Drugs affecting renal autoregulation may contribute to blunted autoregulatory effects, including loop diuretics, renin blocking agents or non-steroidal anti-inflammatory agents [148]. Hence, GFR remains stable, unless renal autoregulation is attenuated or impaired, like in case of severe hypotension and/or markedly reduced CO, or in case renal autoregulation is afflicted, as in the setting of AHFS [8, 76, 97, 98]. Accordingly, only as long as renal autoregulatory capacity is uninterrupted, GFR will be maintained, despite reduced renal perfusion, resulting from mild to moderately impaired CO, reduced effective circulating volume or otherwise diminished intravascular filling [97, 98, 146, 147].

Renal autoregulation is closely related to, and dependent on, endothelial cell function: Endothelial cells are acknowledged to play a central role in the regulation of the microcirculation [149–151]. They exert relevant influence on vasomotor tone [143, 152] (via a dedicated collaboration and cross-talk with the vascular smooth muscle cells [150, 153, 154]), show cross-talk among themselves (communicating upstream information about the hemodynamic situation and constitution in the downstream areas (backward communication)), and as such, modulate and adopt local blood flows [110, 155, 156]. Accordingly, they decisively contribute to and arrange for a well-functioning microcirculation [149–151]. In low flow conditions, pro-inflammatory and pro-thrombotic properties are expressed [157]. It is crucial for flow adaptions that endothelial cells align with actual conditions and any disordered alignment, as may be present in case of disturbed blood flows, leaves the inflammatory pathways activated [150]. A compromised endothelial function is known to impair local vascular autoregulation and to provoke perfusion mismatch [158–161]. Unfortunately, endothelial cell function is reported to be afflicted in AHFS [112, 162–164]. Correspondingly, a well-performing autoregulation is closely related to, and also markedly dependent on, endothelial cell function, because the endothelium plays an obligatory role in cardiovascular homeostasis by regulating vascular tone (and cardiac function as influencing ventricular load by vascular stiffness [162, 165] and coronary and myocardial perfusion and thus ventricular function [166]), adjusting vascular permeability, preserving blood fluidity [167], and is particularly central to functions of the microcirculation [149].

However, by far the vast majority of patients admitted due to AHF are adequately perfused, with an at least reasonable CO and fair blood pressures caring for preserved renal blood flow and autoregulatory capacity—in fact, far less than 10% of all AHFS exert compromised organ perfusion [168–175]. As such, this traditional view of renal hypoperfusion being mainly responsible for incipient renal dysfunction in AHFS has been warrantable challenged [37, 176, 177]. Indeed, no correlation has been found between baseline renal function and CO/CI [19], an improvement in cardiac index does not translate into improvement in renal function [174, 178], and even patients with relatively normal systolic function (those with preserved ejection fraction and/or preserved CO) are often presenting with, or develop, impaired renal function [171, 179, 180]. Moreover, worsening renal function can be found in a similar range in patients with preserved and those with reduced systolic

function [181], and most AHFS patients are admitted with elevated BPs rather than being hypotensive [41]. Recent trial results present convincing evidence, that in those patients predominantly **venous congestion** is the main **reason for** (and cause of) **renal dysfunction** [169, 174].

That elevated renal venous pressures may affect kidney function has already been described more than 75 years ago [79, 182]: In a dog model, Winton [79] recognized a deterioration of urine generation with renal venous pressures above 20 mmHg and even a suspended urine formation at pressures ≥25 mmHg. Furthermore, he expressed a relationship between elevated central venous pressures and reduced renal blood flow, indicating that renal blood flow decreases with the decline in pressure gradient between vas afferent and vas efferent, probably induced by an increase in vas efferent tone [79]. Later on, extrinsic compression of abdominal veins due to intra-abdominal hypertension were also reported to compromise renal function [183, 184], which has in the meantime be confirmed by several studies [185, 186]. Firth showed a direct transmission of elevated central venous pressures to the renal veins, attenuating GFR, as increased renal venous pressure was accompanied by a drop in glomerular perfusion pressure—a dysfunction that may recover, if enhanced pressures are resolved [187]. Gottschalk and Mylle [188] demonstrated that in case where renal venous pressure exceeds 15 mmHg, a linear increase in peritubular capillary and intratubular pressures arises. However, every increase in intratubular pressure directly diminishes net ultra-filtration pressure, as enhancing the pressure within the Bowman's space, which opposes glomerular filtration pressure, and subsequently attenuates GFR [1, 76, 97, 189]. Raised systemic and renal venous pressures, with concomitant congestion of the renal venous system, are thought to cause extravasation and congestion of the kidney [82, 177]. Since the kidney is surrounded by a tight non-distensible capsule [82, 177], subsequent interstitial intra-renal pressure increases in case of elevated renal venous pressures [190–193].

Consecutively, renal parenchymal hypoxia, tubular dysfunction, due to tubular obstruction, or even collapse concomitantly opposing glomerular filtration pressure [97], and activating the RAAS may apply, promoting a decrease in GFR [97, 191–193]: Elevated venous pressures, in any case, reduce the trans-renal perfusion pressure (a decrease in arterio-venous pressure gradient occurs with increasing venous pressures within the renal vessel system), will provoke a diminished renal blood flow [22, 97], and may distend the venule network surrounding the tubules of the distal nephron, causing tubular compression, obstruction or even collapse of the tubules (at least as long as the pressure of the ultrafiltrate does not exceed venular pressure [79]) ensue [107, 177]. Subsequently, net glomerular filtration pressure is lowered, and backleak of the ultrafiltrate into the interstitium may occur, the latter potentially leading to an increase in the interstitial pressure [107, 177].

With increasing renal venous pressure, neurohormonal activation ensues. As such, increasing renal and systemic angiotensin II concentrations are demonstrated to accompany increasing renal venous pressures [190, 194], leading to (further) decreases in GFR, enhanced proximal tubular sodium and water reabsorption

(aggravating heart failure and renal venous and intra-renal interstitial pressure elevation and congestion), and stimulated sympathetic drive [71, 125, 192, 195]. Angiotensin II and sympathetic activity affect arteriolar tone and thus, impact on perfusion and afferent and efferent glomerular pressures [125, 190].

This concept is further considerably supported, and profoundly substantiated, by results demonstrating an association between increased central venous and right atrial pressures, attributed to acute decompensating or chronic heart failure, and worsening renal function. Moreover increasing central venous pressures go along with an increased mortality rate in that patient group [174, 196, 197]. Beyond this, elevated central venous pressure is reported to be associated with higher baseline createnine serum concentrations [197] and tricuspid regurgitation, attributed to heart failure, and shows a relationship with renal dysfunction [198]. Damman finally verified that in heart failure patients, venous pressure is an independent determinant of glomerular filtration [169].

It is not definitely known how autoregulation responds to the increased renal venous pressure, however, renal autoregulation is considered to be affected by the above described hemodynamic alterations (renal hypoperfusion and renal venous hypertension), impairing autoregulatory effects and efficacy, or even provoking complete breakdown of autoregulation [8, 22, 76, 97]. It seems, and it is suggested that, due to the increased renal venous and interstitial pressures, not only the RBF will be attenuated, but that the myogenic response is strongly affected (while TGF is not relevantly impacted) and thus autoregulation impaired [199, 200]. Meanwhile, "systemic venous congestion" (and thereby renal venous congestion) is acknowledged to be "the major driver of acute cardiorenal syndrome (CRS, *type 1*), especially in severely elevated central venous pressure from RV dysfunction and/or tricuspid regurgitation" (associated with (acute) heart failure) [35, 76, 169, 174].

Haase [76] summarized the hemodynamic alterations potentially displayed, and to be anticipated in, CRS *type 1* patients with respect and related to the clinical-hemodynamic profile assessed by physical examination at bedside as proposed by Stevenson [201] (and later resumed and established by Nohria and co-workers [202, 203]). This is currently the widely used and even endorsed (by AHA/ACCP and ESC) approach [204] to evaluate the predominant clinical-hemodynamic condition of AHF patients and seminal for the initial therapeutic approach and prognosis [202, 204–206]: Source [76].

Warm and dry	*Warm and wet*
Discordantly ↓ RBF Intra-renal microvascular dysregulation	Discordantly ↓ RBF **Impaired** intra-renal **autoregulation** ↑ renal venous pressure
Cold and dry	*Cold and wet*
↓ RBF **Impaired** intra-renal **autoregulation**	Discordantly ↓ RBF **Impaired** intra-renal **autoregulation** ↑ renal venous pressure

Beyond the described hemodynamic issues, several non-hemodynamic features, namely the neurohormonal activities and the inflammatory and endothelial effects, are considered to be relevant contributors to, mediators of and communicators in the development of CRS, *type 1*, linking heart and kidneys and impressively demonstrating, how cross-talk and interactions work, and conditions/information are mediated [1, 36, 69, 83, 207].

As such, the renin-angiotensin-system is a typical example of the bidirectional impact, which the heart and the kidneys exert on each other, as well as being a connector of both organs [1, 35, 115]. Increased renal venous pressures [208, 209], diminished renal artery pressure [210], diluted sodium concentration in the distal nephron [211], and enhanced sympathetic discharge [210], all are demonstrated to be associated with, and are conditions of, the pathophysiology of acute and chronic heart failure and kidney afflictions [36, 78, 83, 212]. They have been shown to promote substantial renin release and thus activate the renin-angiotensin cascade [115]. Elevated renin secretion is characteristic of early biventricular heart failure, leading and contributing (via angiotensin II (A II)) to myocardial and renal dysfunction, and promoting edema formation [212]. Activation of the renin-angiotensin system allows to maintain glomerular perfusion pressure and glomerular filtration rate, despite reductions in cardiac output and/or low BPs, through preferential constriction of the efferent glomerular arterioles in patients with HF [213]. The biologically most active representative of the renin-angiotensin-system, angiotensin II, stimulates pro-inflammatory cells, thus induces the generation of reactive oxygen species (via the NADPH/NADH oxidase pathway [214, 215]) and pro-inflammatory mediators [216], and is, as such, coupled to the inflammatory path connecting both organs [1, 176]. A II causes and amplifies renal and systemic vasoconstriction, subsequently enhances LV afterload, diminishes renal perfusion, increases venous pressure and facilitates edema formation [22, 36]. Furthermore, A II (and the RAS) has been shown to be tightly linked to the sympathetic nervous system [217], whereupon signals of the sympathetic nervous system to the kidney are closely related to incipient CRS [218]. Not at least, A II causes aldosterone excretion, and hence promotes tubular water and sodium reabsorption [36]. Both, heart failure and renal failure are substantially influenced by (but also simultaneously facilitate) incitement of the inflammatory and oxidative path, adversely affecting both organs [176, 207]. Meanwhile, oxidative injury is recognized as a "common link between cardiac and renal dysfunction" [207] and the final common pathway in CRSs [36].

As already described, the vascular and cardiac endothelium is another feature, mediator, coordinator and conductor orchestrating inflammatory and vascular reactions and replies. It is not only A II which causes endothelial dysfunction (ED) [216, 220], but rather heart failure and chronic kidney disease are both independently associated with ED [221, 222]. Disrupted NO pathways and reduced NO bioavailability, affiliated with ED, are major issues in heart failure

pathophysiology, substantially influencing renal function [207, 223–225]. ED may considerably affect renal autoregulation [158–161], as ED is also associated with oxidative stress (with effects on renal sodium management, systemic and renal hemodynamics [226–228], and glomerular glycocalyx barrier function [229, 230]) and the inflammatory cascade [1, 36, 176, 231], showing definite cross-links between both organs [72, 232–234]. Indeed, CRS may be considered as a low-grade inflammatory disease, attributed to an imbalance between immune system cell signaling [36, 235–237], and interleukin-6 (IL-6) has been identified as a complex cardiorenal connector [1, 238, 239].

Beyond the activated RAAS, ED, inflammation and ROS, the important role and interconnection of the sympathetic activation in the pathogenesis, pathophysiology and progression of heart (and renal) failure has already been stressed [240]. Enhanced sympathetic drive, by increasing afferent arteriole tone, mitigates RBF and GFR, and thus affects renal function [241, 242]. Other factors discussed as possible contributors include: gut ischemia and (consecutive) endotoxemia [243–245]; superimposed infections [246, 247]; iatrogenic effects (especially drug applied with kidney compromising effects) [248–251]; and a failure of counter-regulatory mechanisms (e.g. natriuretic peptides) dampening the depicted (compensatory) mechanisms and features [36].

To conclude, the pathobiology of the cardiorenal syndromes is complex and multiple mechanisms may be involved [4, 5]. The impact and the importance of each feature contributing may vary from patient to patient [7]. The pathophysiology of CRS, *type 1*, largely includes hemodynamic features such as diminished RBF and deficient renal perfusion pressure, increased intra-renal vascular resistance, as well as enhanced renal venous pressure (with concomitant renal venous congestion) [97], the latter being identified as the "major driver of acute cardiorenal syndrome" *type 1* [36, 76, 169, 174, 252]. Altered renal perfusion in the setting of acute (and chronic) heart failure is attributed to and may be the result of impaired CO, combined with pre-glomerular vasoconstriction and renal venous congestion [253]. However, GFR (and thus renal function) remains stable unless renal autoregulation is attenuated or impaired, as may be (I) in case of severe hypotension and/or markedly reduced CO resulting in hypoperfusion, (II) when renal perfusion pressures are beyond the autoregulatory threshold, (III) and/or in case renal autoregulation is afflicted by features such as renal venous congestion, ED, diminished intrarenal perfusion, and altered (intra)glomerular hemodynamics, all apply in the setting of AHFS [8, 76, 97, 98]. As such, a proper working autoregulation is critical in renal physiology.

All hemodynamic factors are strongly related to volume retention and activated neurohormonal systems (sympathetic and RAAS) [122, 254]. Indeed, features associated with and contributing to CRS *type 1* are sympathetic-mediated fluid redistribution, venous congestion, inflammation, and endothelial dysfunction [174, 255–257]. *Venous congestion, enhanced neurohormonal activity, ED and inflammation* are the main trigger, contributors, and mediators precipitating baseline renal dysfunction by altering intra-renal and intra-glomerular hemodynamics and by

affecting renal auto-regulation [4, 36, 76, 252]. Moreover, *type 1* CRS may, in fact, be also perceived as an inflammatory disorder, as the inflammatory pathway and associated features, namely ED and oxidative stress, markedly contribute to the pathogenesis, and inflammation is fundamental for the occurrence of distant organ damage [7].

7.5 Management

The management of CRS *type 1* predominantly relies upon the approach by which acute heart failure is tackled [5, 32, 36, 43, 175, 207]. Specific renal requirements and issues need to be considered, before taking actions aimed at disrupting cardio-renal connections and dependencies, by applying multi-modal paths addressing the various underlying patho-physiologies [7, 107]. Restauration of physiological renal hemodynamics can be achieved in part by relieving the patient from congestion and symptoms, and further, any measures jeopardizing renal function need to be absolutely avoided [43, 76, 175].

Before it can be beneficial, it is strictly necessary, that any therapeutic measure used to approach AHF does not exert negative effects on kidney performance [258]. Accordingly, particularly nephrotoxic drugs like radiocontrast media, non-steroidal anti-inflammatory agents, and opiates altering renal hemodynamics (and thus impairing autoregulation and thereby negatively affecting kidney function), should be held off [60, 61]. Furthermore, adequate BP (MAP of ≥70–80 mmHg, with 80 mmHg being the target one should definitely aim for in patients with chronic hypertension [259, 260]) guarantees operating renal autoregulation and thus maintains glomerular perfusion [97]. Hypotension and/or intravascular underfilling have to be avoided, eliminated and prevented [147, 261].

7.5.1 Diuretics

The application of diuretics is the cornerstone in the treatment of AHFS [36] and CRS [22, 32, 36], but it is somewhat of a double-edged sword. They are important to resolving congestion and thereby improving patients' symptoms and comfort in general, and with respect to CRS *type 1* in particular, they address renal venous congestion and fluid overload, but unfortunately, they may unfavorably affect kidney function and further activate the neurohormonal systems [262–264]. As such, by reducing elevated central and renal venous pressures, the latter being a major driver of worsening renal function in AHF patients [36, 76, 169, 174], diuretics are an essential and effective feature in the treatment armamentarium [5, 22, 32, 36, 43]. Furthermore, Atherton [265] impressively demonstrated that in decompensated severe heart failure, with considerably elevated LVEDP, diuretics are not only very effective to relieve the patients` symptoms and to improve clinical and hemodynamic conditions, but are generally well tolerated, and do not worsen circulatory issues

(primarily BP). Roughly 50% of all patients admitted to hospital suffer from biventricular failure, and thus the LV is relevantly compromised by pericardial constraint and ventricular interactions (specifically diastolic ventricular interdependence, DVI). Especially unloading of the right heart (thereby attenuating systemic congestion), will optimize LV filling and intraventricular pressure terms, subsequently facilitating LV performance and hence supporting macro-hemodynamics. In any case, no BP drop could be demonstrated, not even in patients without relevant pericardial constraint and DVI, thus no significant hemodynamic setback has to be anticipated if diuretics are applied in those patients.

However, in case of (intermittent) arterial underfilling—due to "overshooting" diuresis, following application of diuretics—renal perfusion may worsen, while the neurohormonal systems will be further activated [115, 262]. As such, the rate of fluid removal should not exceed the rate of fluid mobilization, and tissue fluid reabsorption rate is estimated to range between 12 and 15 mL/min [266, 267].

Early use of diuretics is reported to reduce mortality in severe AHFS, while systemic congestion (indicated by elevated central venous pressure) is related to worsened mortality in AHFS [196]. Effective and substantial decongestion is a decisive prognostic feature, and influences the evolution of the disorder. Incomplete decongestion rather than increasing createnine serum concentrations are associated with disease progression and worsens the chance of survival [268, 269]. On the other hand, a relationship between increased requirement of loop diuretics and increasing mortality has been demonstrated [250, 270, 271]. Thorough monitoring of diuretic use and effect is necessary [36].

Diuretic resistance, a specific issue [75], may complicate CRS [34, 43]. The underlying pathomechanisms are diverse [41, 42] and may include: compromised renal blood flow (e.g. hypotension and/or hypoperfusion) [43, 272], blunted intestinal absorption of the diuretic agent [44, 45], reduced glomerular filtration as loop diuretics act best from the luminal site [46, 47], low albumin concentrations (impair uptake and secretion of active frusemide) [48, 49], and increased levels of urea nitrogen and other organic acids competitively hampering diuretic availability on site [50, 51]. Accordingly, all features leading to reduced availability of the diuretic drug at the site of action (which is the thick ascending limb of the loop of Henle for loop diuretics, and the distal convoluted tubules for thiazide diuretics and metolazone, which is a thiazide-like drug, the latter commonly and preferably applied in CRS), have to be considered and should be addressed if possible [36, 41, 43, 273, 274].

The recommended dosage of diuretic medication at which it becomes effective varies widely [22]. However, *either increasing the dosage of loop diuretics* or *adding a second-site diuretic agent* [275, 276] (e.g. metolazone 10–20 mg bd/tds or hydrochlorthiazide 50–100 mg per day (in severe cases 100–200 mg per day [273])), is generally advised in case of diuretic resistance [22, 32, 82, 273]. As only 50%, or less, of frusemide is absorbed in case of systemic venous congestion and edema [277], i.v. application may overcome intestinal reabsorption difficulties [43].

Furthermore, since no significant differences in renal function have been observed when applying loop diuretics as several bolus injections or via continuous infusion, the kind of intravenous application does not matter [250].

Dosing of loop diuretics recommended in CRS *type 1* [115, 273]:

Frusemide: 40–80 mg i.v., 80–160 mg may be required several times a day, e.g. tds or qds in case of moderate renal insufficiency, if renal impairment is severe, 160–200 mg, e.g. tds or qds. The maximal natriuretic response is reported to be achieved with i.v. bolus injections of 160–200 mg frusemide (or equivalent torasemide/bumtanide dosages) [278, 279].

Torasemide: 20 mg i.v., 20–50 mg tds in case of moderate renal impairment, 50–100 mg tds if severe renal insufficiency.

Bumetanide: 1–2 mg i.v., 4–8 mg in case of moderate renal insufficiency, 8–10 mg if renal dysfunction is severe.

Felker [250] examined the effect of different frusemide dosages, by applying to one group intravenously (either by continuous infusion or i.v. as a bolus every 12 h) the same dose of frusemide which these patients had previously, before admission, taken orally, while he gave the other group of patients, the high dosage group, 2.5 times the amount of oral dose. No significant differences were found between either groups and thus between the dosages, nor between continuous or bolus intravenous application, observed over a period of 72 h. However, although not significantly, the high dose group showed beneficial effects in secondary outcome criteria such as: relief of dyspnea and congestion, amount of weight loss, reduction of elevated cardiac biomarkers (natriuretic peptides), and a trend of a lower rate of hospitalizations, but also developed some mild degree of renal dysfunction which reversed within 1 week.

The addition of *mineralocorticoid diuretics (MRAs)* in an acute setting has not been examined. However, they are recommended in the guidelines for chronic heart failure therapy in low dosages [280, 281]—class I A recommendation [204]. They may be added, even to a combination of loop diuretics and thiazides [282, 283], in acute decompensations at "higher" dosages (50–75 mg daily—12.5 and 25 mg there is no natriuretic effect at all [284]), as smaller observational studies suggest, since MRAs may improve diuresis (in diuretic resistance) and thus the clinical condition of the patient [285, 286].

Note: Dose titration should in general be subject to effectiveness and/or the side-effects experienced [287].

Two randomized controlled studies (UNLOAD and RAPID-CHF) comparing *ultrafiltration* with diuretic medications, revealed a greater fluid removal and significantly fewer re-hospitalizations and unscheduled visits for heart failure in the ultrafiltration groups [288, 289]. However, weight loss within 24 h [289] and dyspnea scores [288] did not differ.

The result of a recently published trial, studying patients with AHFS and cardiorenal syndrome, showed that ultrafiltration was inferior compared to medical treatment, due to worsening renal function and due to more frequent adverse effects in the ultrafiltration group [290].

Consequently, there is currently no evidence favouring ultrafiltration over loop diuretics at all [290, 291]. Ultrafiltration, respectively renal replacement therapy, should be restricted to AHF patients who are: severely volume overloaded, staying oligo-anuric, despite all treatment efforts, are not responding to diuretic treatment, or in cases where acute severe kidney injury ensues [204].

7.5.2 BP/Renal Perfusion Pressure

Maintenance or restauration of a sufficient renal perfusion pressure, MAP (since the MAP best represents perfusion pressure [292]), is essential to preserve or re-establish renal function [118, 293–296].

Studies on mammalians revealed renal autoregulation to be working within a range of 80–180 mmHg [297–299]. Older study results examining the target MAP level in case of renal dysfunction, and even diuretic resistance associated with AHFS and other critical maladies are inconsistent [300–303]. However, more recent studies demonstrate that MAPs between 75 and 85 mmHg do not only enhance renal perfusion pressure as desired and necessary, but are obviously beneficial in addressing altered renal microcirculation [144, 304, 305]. Patients with afflicted renal microhemodynamics will probably benefit from MAPs ≥75 mmHg [305–307]. Furthermore, in patients with coronary artery disease and CS, MAPs between 70(75) and 80 mmHg are suggested in order to stabilize the circulatory conditions [303, 308, 309]. Moreover, once autoregulation has been lost, re-establishment is supposed to require higher MAPs [295, 302]. In the meantime, no concerns and no evidence have been found that *noradrenaline (NA)*, the most advantageous and preferred vasopressor agent [310], may be associated with an increased risk of AKI [145, 302, 311–314], if the indication to apply NA is straightforward, to address arterial hypotension in life-threatening circumstances, shock states and vasodilatory conditions [310, 315–317]. Accordingly, a MAP of around 80 mmHg should be targeted, although in each patient treatment should be individualized [293, 307, 314, 318, 319].

7.5.3 Further Measures

Activation of the renin-angiotensin system allows maintenance of glomerular perfusion pressure and glomerular filtration rate, despite reductions in cardiac output and BP, through preferential constriction of the efferent glomerular arteriole in patients with HF [213]. By addressing the neurohormonal activation and thus affecting heart–kidney cross-talk (attenuating inflammation and endothelial dysfunction), fluid retention and vasoconstriction is blunted, and concurrently cardiac and renal function stabilizes [22, 34, 176, 320]. Further, *ACE-inhibitors* and *angiotensin receptor blockers* are key agents in the therapy of systolic heart failure (HFrEF) [321–325]. They may counteract or mitigate side-effects of the diuretic medication,

potentially further triggering neuroendocrine activity [22]. However, blocking the effects of RAAS may impair autoregulation of GFR [326], as attenuation of angiotensin II effects cause glomerular efferent arteriole dilation with a subsequent drop in glomerular perfusion pressure, resulting in a lower GFR and an increase in serum creatinine [192, 219]. Moreover, there is scarce data about the role of ACE-inhibitors/angiotensin receptor blockers in CRS, and their application in this condition is more or less empirically and based on expert opinion [6, 107, 327]. If ACE-inhibitors/angiotensin receptor blockers are initiated in the presence of

(a) hypotension (MAP <60 mmHg), and/or
(b) LVEDP <15 mmHg, and/or
(c) hyponatremia, and/or
(d) high dosages of loop diuretics are given,

renal function may significantly worsen [328, 329]. Furthermore, timing to initiate ACE-inhibitors/angiotensin receptor blockers is unclear: Some authors recommend that treatment should not be initiated before the patient is stabilized [6, 107]. However, in patients with moderately diminished renal function (and with diuretic resistance), ACE-inhibitors/angiotensin receptor blockers are likely to be beneficial and to offer survival benefit, although renal function may transiently (further) worsen [327]. In case of severely impaired renal function, it is unknown if they are beneficial or deleterious [330]. Dosing should be cautiously carried out *starting with low dosages* and some clinicians tolerate reductions in GFR up to 30% [107, 331]. It may be advisable to reduce the dosages of diuretic drugs before starting up with ACE-inhibitors/angiotensin receptor blockers [331]. Drops in BP should be avoided [6], and in patients who were on ACE-inhibitors/angiotensin receptor blockers prior to cardiac decompensation, a transient dose reduction may be appropriate [332]. Nevertheless, ACE-inhibitors/angiotensin receptor blockers are underused and application even in CRS *type1* needs to be encouraged [333].

For the treatment with *β-blockers*, it may be opportune to withhold them until the patient is hemodynamically stable, unless AMI is the underlying aetiology where low dosages may be beneficial [34, 107]. This is because β-blockers may attenuate necessary and initially beneficial compensatory effects of sympathetic nervous system and thus may contribute to the development of cardiogenic shock (CS) [34, 334].

Notable for practical issues: Mild increases in createnine during diuretic treatment may be interpret as transient intravascular volume depletion or "overdiuresis" (if so, continue less aggressive with lower doses) [207], and may further occur in those patients who are on ACE-inhibitors [328] or where BP is apparently too low [207]. However, study results suggest that some degree of createnine increase, associated with ACE-inhibitor therapy, should be tolerated (increase up to 30% of baseline) [107, 207].

Further, keep in mind, that via fluid retention (and associated elevated CVP and RA-P), a normal MAP could be achieved and preserved (successful compensation), but often at the cost of amplified congestion and oliguria (high renal venous pressure). Diuretics given in such circumstances may worsen the situation by inducing a drop in BP while simultaneously stimulating sodium and water reabsorption. Consecutively a vicious cyle may be established [82].

To summarize, the traditionally close relationship and interconnection between heart and kidney function has recently been termed cardiorenal syndrome, CRS [4]. The pathophysiology is multifactorial and complex, and the features causing renal malfunction in *type 1* CRS may individually vary [4, 5, 7]. However, in *type 1* CRS, diminished RBF and deficient renal perfusion pressure, increased intra-renal vascular resistance and enhanced renal venous pressure (concomitantly causing renal venous congestion), are the fundamental hemodynamic aberrations precipitating intra-renal and intraglomerular alterations, and thus determining the pathophysiology [36, 76, 97, 169, 174, 252]. "Systemic venous congestion" (and thus renal venous congestion) is acknowledged to be "the major driver of acute cardiorenal syndrome" in *type 1* CRS [36, 76, 169, 174, 252]. Nevertheless, GFR remains stable unless renal autoregulation is attenuated or impaired. The latter may arise:

1. in case of severe hypotension and/or markedly reduced CO resulting in hypoperfusion,
2. when renal perfusion pressures are beyond the autoregulatory threshold, and/or
3. in case renal autoregulation is afflicted by features such as: renal venous congestion, ED and associated inflammation, diminished intra-renal perfusion, and altered (intra)glomerular hemodynamics, all applying during AHFS [8, 76, 97, 98].

In fact, venous congestion, enhanced neuroendocrine discharge, ED and inflammation are recognized to be the main trigger and mediators precipitating baseline renal dysfunction, by altering intra-renal and intra-glomerular hemodynamics, consecutively affecting renal auto-regulation [4, 36, 76, 252]. Accordingly, a proper working autoregulation is critical in renal physiology. Sufficient high blood and thus renal perfusion pressures, with MAPs around 75–80 mmHg preserving renal autoregulation, are essential [144, 304–307]. Furthermore, diuretics are the cornerstone in the management of CRS, *type* 1, and sufficiently high dosages of loop diuretics, eventually combined with metolazone, are necessary to overcome diuretic resistance. NA is the vasopressor of choice [310], obviously exerting no adverse effects on kidney function in low to medium dosages [145, 302, 311–314]. ACE-inhibitors may be initiated with caution and low dosages are advisable [107, 331, 333]. Createnine increases of up to 30% of baseline attending diuretic and/or ACE-inhibitor/angiotensin receptor blocker application can be transiently tolerated [107, 207, 330].

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