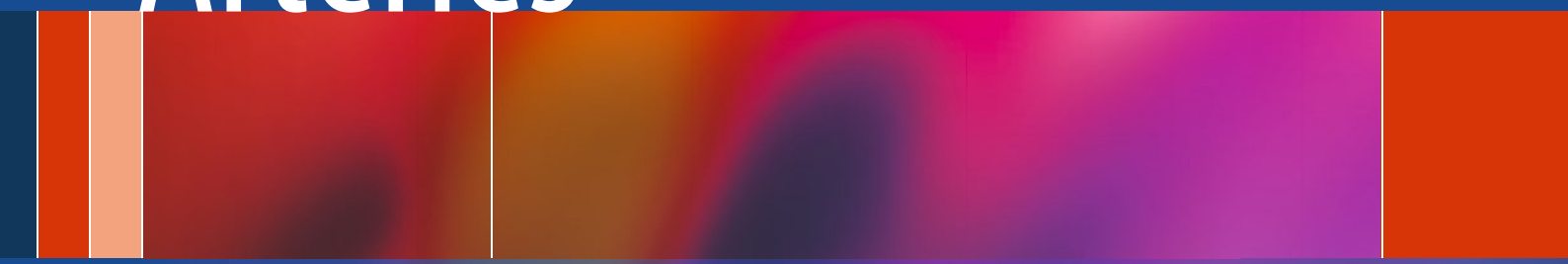
Juan Carlos Kaski
Guy D. Eslick
C. Noel Bairey Merz
Editors

Chest Pain with Normal Coronary Arteries



A Multidisciplinary Approach

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This book is dedicated to all researchers worldwide who over the years have contributed to the understanding of this puzzling condition. In particular, to those who dared thinking beyond the boundaries of established "dogma" and constituted an example for newer generations of physicians and scientists.

Foreword

I am honored and grateful to the authors of this timely volume *Chest Pain with Normal Coronary Arteries* for asking me to write a Foreword for it.

The volume covers, with 32 well integrated chapters, a topic which until now had received insufficient attention because it departs from a deeply established paradigm which I have witnessed over the past 50 years, and still largely conditions cardiac thinking, practice and research.

At medical school, in the 1950s, I was taught that the progression of atherosclerosis reduced coronary flow reserve until the development of coronary insufficiency resulted in effort angina and, when more severe, in acute, myocardial infarction. Thrombosis was by many considered a consequence rather than the cause of acute infarction. The Cardiology textbook by Friedberg stated that "angina might occur also at rest but, if it did not occur also on effort, had a non ischemic origin".

Thus angina could only be caused by an excessive myocardial demand in the presence of obstructive coronary atherosclerosis, and patients with acute infarction were prescribed strict bed rest for 3 weeks as their coronary flow reserve was thought to be exhausted! Accordingly drugs that increased myocardial blood flow in animals, such as dipyridamole, were developed and the beneficial effects of nitrates were attributed to a reduced myocardial demand, rather than to dilatation of constricted vessels.

The first challenge to this dogma came in 1959 from clinical observations by Prinzmetal suggesting that angina at rest with preserved effort tolerance (variant angina) could be caused by an increase in "tonus" at the site of a subcritical stenosis, resulting in transient occlusion.

Fourteen years later, spasm was also described at the site of non-stenosed arteries (the variant of the variant), yet also today, in many institutions spasm is suspected and searched for only in patients with severe symptoms but angiographically normal arteries! The presence of a stenosis by itself is thought a sufficiently plausible cause for angina on effort or at rest!

A second challenge came in the 1970s when the use of Holter recordings allowed the demonstration of ischemic episodes during daily life not preceded by an increased heart rate, the major determination of myocardial demand, suggestive of transient coronary vasoconstriction. Thus the concept of dynamic coronary stenosis became accepted. Subsequently, in 1990, a large variability in residual flow reserve was reported also in selected patients with an isolated single total coronary occlusion, preserved ventricular function and no other stenosis, suggesting that regional coronary flow could be modulated, not only by dynamic stenoses, but also by distal, small coronary vessels constriction.

Thus although overwhelming evidence indicates that coronary vasoconstriction can cause ischemia in the presence of coronary atherosclerosis, the notion that vasoconstriction of large and small coronary branches can cause ischemia and angina also in the absence of coronary stenoses is still not sufficiently prevalent in some catheterization laboratories, as when no stenoses are found the patient's anginal symptoms are often labeled as "non-cardiac"!

This volume is very timely and will most likely serve the important purpose of stimulating clinical investigators with inquisitive minds to dare focusing their research interests on the yet unknown multiple aspects of coronary blood flow regulation and mechanisms of myocardial ischemia, identification of clinical patient subsets, and the varied potential pathogenic

mechanisms responsible for myocardial ischemia in patients with angiographically normal coronary arteries. For this challenge, the 32 chapters that compose the book are all pieces of a clever jigsaw puzzle.

In this innovative task I hope for investigators to be “splitters” rather than “lumpers” and to make an effort to discover relevant associations that link specific pathogenic mechanisms with distinctive clinical symptoms and specific instrumental descriptors rather than searching for single common denominators. In this way, only, the treatment of chest pain can become personalized – patient oriented – rather than standardized and disease oriented.

Prof. Attilio Maseri

Preface

The condition known as "chest pain with normal coronary arteries" or "cardiac syndrome X" has, practically since the advent of coronary arteriography, puzzled physicians and patients alike. Although epicardial coronary artery spasm, as seen in Prinzmetal's variant angina, explains a proportion of cases of typical chest pain despite normal coronary arteriograms, many patients who seek medical attention for exertional and rest angina in the absence of obstructive coronary artery disease are not variant angina cases. The syndrome thus continues to represent a "mystery", rather than a reality, for many in clinical practice. This monographic work, written by many of the most active research groups in the field in different continents, comprehensively tackles the clinical presentation and the pathogenesis of the condition, as well as its management. The syndrome constitutes both a diagnostic and therapeutic challenge.

Women represent a large proportion of the population affected by microvascular dysfunction, believed to be the main pathogenic mechanism of the syndrome, once extracardiac causes of chest pain and variant angina have been excluded. Several chapters in the book deal with aspects directly related to this issue. Contrary to epicardial coronary artery disease, abnormalities of the coronary microcirculation have remained elusive to conventional imaging techniques and only recently researchers appear to be making progress in obtaining much needed information in this field. The present monographic work addresses this aspect of the problem and proposes useful clinical diagnostic algorithms, thus bringing this subject closer to the practicing cardiologist. The functional aspects of the coronary microcirculation, its clinical presentation and prognosis, as well as the diagnostic tests used for the assessment of microvascular dysfunction are important topics highlighted in the book.

The syndrome of chest pain with angiographically normal coronary arteries is not a "rare" syndrome, as over 50 % of patients undergoing diagnostic angiography for the assessment of typical chest pain suggestive of coronary atherosclerosis is found not to have obstructive coronary artery disease. Epidemiological considerations, socio-economic issues, differential diagnoses and gender differences in diagnosis and management are all addressed in specific chapters in the book. Importantly, the condition can – and often does – impair the patient's quality of life and trigger serious psychological disturbances, as discussed in detail in the present monographic work. An adverse prognosis has been reported in certain patient subgroups, and this topic is also tackled in *ad hoc* chapters in the book. Although treatment remains problematic, management strategies are proposed in the book that can improve the patient's symptoms, quality of life and wellbeing. The present work also proposes new research needed to identify the different patient subgroups encompassed by this heterogeneous syndrome, understand its pathogenic mechanisms further and devise newer, more effective therapies. We hope that this book will be a useful practical tool for the clinician, a bank of information for those interested in understanding the causes and mechanisms of the condition and a source of inspiration for both scientists and clinical researchers who work in the field. The ultimate expectation, however, is that the present book helps us in managing our patients better.

Acknowledgments

We are grateful to the authors of the various chapters of this book who generously devoted time to make this monographic work a reality. We are also indebted to the multitude of patients who have, over the past decades, helped researchers carry out investigations to understand the condition better.

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Part I

Introductory Chapters

Cardiac Syndrome X: An Overview

1

Juan Carlos Kaski, C. Noel Bairey Merz,
and Guy D. Eslick

Abstract

Patients with cardiac syndrome X (CSX), defined as typical chest pain associated with electrocardiographic changes suggestive of transient myocardial ischemia despite normal coronary angiograms, continue to constitute a diagnostic and a therapeutic challenge. CSX is not a "rare" syndrome, as up to 50 % of patients undergoing diagnostic angiography for the assessment of typical chest pain are found not to have obstructive coronary artery disease. CSX encompasses a variety of pathogenic subgroups and is most typically seen in peri- and postmenopausal women. The condition can impair the patient's quality of life, is associated with an adverse prognosis in certain patient subgroups, and represents a substantial cost burden to the healthcare system. Not infrequently, a lack of understanding of the pathogenesis of the syndrome by the treating physician results in poor management of the condition. Treatment remains elusive, but management strategies exist that can improve the patient's quality of life and wellbeing. Clinical trials are needed to evaluate the impact of management strategies on major adverse cardiac events. The present book addresses most of the important issues relevant to the understanding of the condition including its epidemiology, pathogenesis, diagnosis and effective management strategies.

Keywords

Cardiac syndrome X • Microvascular angina • Angina with normal coronaries • Pathophysiology

Introduction

Although patients with typical exertional chest pain and positive exercise stress test results usually have obstructive coronary artery disease, particularly when conventional risk factors such as diabetes mellitus, hypertension, smoking and dyslipidemia are present, recent reports indicate that up to 50 % of these patients have no obstructive coronary artery disease [1]. Issues related to the incidence and epidemiology of CSX will be discussed by Tavella and Eslick in Chap. 4. Patients with systemic hypertension, left ventricular hypertrophy, cardiomyopathies and diabetes mellitus are often excluded from CSX series, as it is assumed that the cause for their angina is "known". However little justification exists for these exclusions, as the pathogenic mechanisms operating in these patients do not differ substantially from those in other CSX patients unaffected by those risk factors or co-morbidities. These issues

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are discussed by Lanza and Crea in Chap. 7 in the book. Patients with Prinzmetal's variant angina due to epicardial coronary artery spasm and those with objectively documented extra-cardiac causes for the pain such as the chest wall syndrome, psychological disturbances, and esophageal abnormalities need to be identified and treated accordingly, as suggested by Kaski et al. and Almansa and Achem in Chaps. 1 and 2, respectively.

Despite research efforts by different investigators on both sides of the Atlantic and Pacific in the past four decades, many questions remain regarding the pathogenesis of CSX. The intriguing relationship between CSX and pain perception abnormalities as well as the different mechanisms playing differing roles in subsets of patients encompassed by the syndrome of angina despite angiographicaly normal coronary arteries continue to represent research targets.

Pathogenesis

The pathogenesis of the condition will be discussed in detail in Chap. 7. Briefly, however, microvascular coronary dysfunction (MCD), expressed as either reduced coronary microvascular dilatory responses and/or increased coronary microvascular resistance or microvascular spasm, have been consistently reported in CSX patients. The named "microvascular angina" coined by Cannon in the 1980s [2] refers to this commonly found pathogenic mechanism. MCD has been shown to be responsible for regional myocardial blood flow abnormalities and heterogeneous myocardial perfusion [2–4].

New techniques for the assessment of MCD are discussed by Beltrame in Chap. 24 and the important of assessing abnormal vasomotion in the catheterization laboratory to characterize pathogenic mechanisms is presented by Ong et al. in Chap. 23. Endothelial dysfunction, with reduced bioavailability of endogenous NO and increased plasma levels of endothelin-1 (ET-1), may explain the abnormal behavior of the coronary microvasculature in CSX [4–6]. Transient myocardial perfusion defects have been reported in areas supplied by arteries showing endothelial dysfunction [4] and increased levels of ET-1 correlated, in several studies, with impaired coronary microvascular dilator responses in patients with chest pain and normal coronary arteries [7, 8]. Endothelial dysfunction in microvascular angina appears to be associated with several mechanisms, including the presence of conventional risk factors such as smoking, obesity, hypercholesterolemia, hypertension and inflammation [1]. High plasma C-reactive protein, a marker of inflammation, has been shown to correlate with disease activity [9] and endothelial dysfunction [4–8]. The presence of subangiographic coronary atheroma, not uncommonly present in individuals with microvascular angina, can impair endothelial function, as reported in Chap. 8 by Della Rocca and Pepine. Insulin resistance has also been suggested to have a major pathogenic role in this condition; this issue is exhaustively discussed by Tritto et al. in Chap. 13. The high prevalence (approximately 70 % in most series) of postmenopausal women in the CSX population, has suggested a role for estrogen deficiency as a pathogenic mechanism [10]. As discussed in Chap. 29 by Shufelt and Waldman, estrogen deficiency acting via endothelium-dependent and endothelium-independent mechanisms can lead to microvascular angina [10]. Increased pain sensitivity has been also linked to estrogen deficiency in CSX [10]. Several studies have shown that Impaired endothelial function in postmenopausal CSX patients is improved by the administration of 17β-estradiol [10]. Chapters 30 and 32 by Hermsmeyer et al. and Bairey Merz et al., respectively, address important issues related to hormonal abnormalities other than estrogen deficiency as a potential mechanism for microvascular dysfunction in CSX.

Myocardial Ischemia

The development of transient ECG changes suggestive of myocardial ischemia is a requisite for the diagnosis of CSX. However, objective documentation of myocardial ischemia by means other than ST segment changes during pain has been reported in approximately 40 % of patients with chest pain and normal coronary angiograms. Thus, myocardial ischemia as objectively documented by perfusion scans, stress echocardiography or measurements of lactate in the coronary sinus, for example, has proven elusive in the majority of patients. More recently, however, studies using myocardial-perfusion magnetic resonance imaging (MRI) [11] and 31-Phosphorus nuclear MR [12] have provided evidence for myocardial ischemia in patients with chest pain and normal coronary arteries, as described by Thomson in Chap. 21. The roles of echocardiograpy and positron emission tomography in the diagnosis of CSX and the understanding of its underlying pathogenesis, is also tackled in the book by Lewis and Choi, and Camici and Rimoldi (Chaps. 22 and 20 respectively). Non-ischemic mechanisms have been proposed to explain the occurrence of ischemia-like ST segment changes in CSX, including autonomic nervous system dysfunction [13–15].

Abnormal Pain Perception

Increased pain perception is common in patients with CSX, but the reason for this remains elusive. Potassium and adenosine release, as well as abnormalities in the central modulation of pain perception, have been suggested to play a role [14, 15]. Greater and more extensive cortical activation, particularly of the right insula, suggesting abnormal handling of afferent stimuli by the central nervous system is

seen in CSX patients as compared with controls [15]. CSX patients may thus have an ineffective thalamic gate that would allow inadequate cortical activation by afferent stimuli from the heart, resulting in increased pain perception [15]. Autonomic nervous system imbalance with increased adrenergic activity and impaired parasympathetic tone could explain both increased pain sensitivity and endothelial dysfunction [13–15]. Possible interactions between pain threshold and microvascular dysfunction in CSX have been proposed to explain the relatively common finding of severe chest pain in the absence of documentable myocardial ischemia [8]. Not as yet well defined interactions between chest pain and coronary microvascular dysfunction are likely to be important in the pathogenesis of CSX and may influence the patient's clinical presentation. It is conceivable that a given CSX patient with a markedly increased pain sensitivity (low threshold for pain) could develop chest pain in response to cardiac (and non-cardiac) stimuli able to activate pain receptors in the heart, even in the absence of major coronary microvascular dysfunction or the occurrence of myocardial ischemia [8]. Adenosine and potassium release have been suggested to cause chest pain and ECG changes in CSX patients even when myocardial ischemia is not present. Endothelin-1, estrogen levels and the autonomic nervous system modulate pain threshold. Patients with both a marked MCD leading to myocardial ischemia and a reduced pain threshold will most likely be highly symptomatic [8]. Patients with intermediate degrees of chest pain sensitivity and some MCD may have no detectable myocardial ischemia and symptoms can be of low or moderate intensity. Both pain threshold and MCD have ample gradation spectra regarding severity and are also modulated by factors such as endothelial dysfunction, hormonal influences, inflammation, the autonomic nervous system and psychological mechanism [8].

Thus variable interactions between pain threshold and MCD can explain the heterogeneous clinical presentation of CSX and the variable rates of myocardial ischemia in different research studies. Chapter 32 by Bairey Merz et al. addresses issues related to pain sensitivity and pain management in CSX.

Psychological Morbidity

Patients with chest pain despite normal coronary arteriograms have high rates of psychiatric morbidity [16]; approximately 30 % have a treatable psychiatric disorder and another 30 % have some psychological disorder. However, psychiatric morbidity varies in different series and may, particularly in patients with anxiety disorders, be secondary to inappropriate reassurance regarding the etiology and mechanisms of CSX and the cardiovascular symptoms that lead to an impaired quality of life. Patient uncertainties as to the prognosis of the condition may contribute to psychological morbidity. In Chap. 6, White and Rosenbaum exhaustively deal with these issues.

Cost Economics Issues

L Shaw, in Chap. 5, examines the data on costs of cardiovascular care for women and highlights the importance of chest pain and the burden of persistent angina as driving higher costs of care. A consistent body of evidence reports that women generally utilize more healthcare resources than men. A large component of the costs of care includes those for ongoing symptoms including the burden of angina. In the NIH-NHLBI Women's Ischemia Syndrome Evaluation (WISE) study, costs of care were estimated for symptomatic women with and without obstructive coronary artery disease. Even women with none to mild non-obstructive coronary artery disease had predicted lifetime costs of cardiovascular care of approximately 750,000 dollars. Thus the economic burden of angina, even in the setting of nonobstructive CAD, is costly and can result in high lifetime costs of care. Proper understanding of the condition should result in a reduction of this financial burden.

Prognosis and Quality of Life

Classical forms of CSX, characterized by the triad of chest pain, abnormal stress testing and completely normal coronary arteries, have been reported to have a benign prognosis [3]. More recent data in larger populations with longer follow-up time periods appear to suggest a relatively higher risk for adverse cardiac events [17] such as heart failure and hospitalization in those subjects with myocardial ischemia associated to MCD [18] Patients presenting with left bundle branch block and subjects with MCD secondary to serious systemic diseases (such as amyloidosis or myeloma), have an impaired prognosis regarding left ventricular function and survival, respectively. Specifically, CSX related to MCD has an adverse prognosis and health care cost expenditure comparable to obstructive CAD in both stable angina and unstable acute coronary syndrome patient populations, according to data assessed and discussed by Bairey Merz in Chap. 25. Invasive assessment of coronary reactivity testing, including endothelial and non-endothelial dependent vasomotion provides potent prognostic information in subjects with normal and minimally diseased coronary arteries. Additional assessment by non-invasively determined coronary or myocardial blood flow reserve provides additive prognostic value to routine coronary angiography. MCD predicts a relatively greater proportion of heart failure events compared to myocardial infarction, suggesting potential links between MCD and

heart failure with preserved systolic function, although longer term follow-up of ventricular function has not been performed. Bairey Merz and colleagues argue that the high prevalence of this condition, adverse prognosis in certain patient subgroups and substantial health care costs, particularly in women, coupled with the lack of evidence-base regarding treatment, makes intervention trials in CSX and microvascular angina a research priority area.

In Chap. 26, Rutledge assesses the effects of CSX on quality of life and stresses the fact that although often considered a problem outside of the scope of standard medical care, quality of life is indirectly the most important target of most patient-health care provider relation. Improving physical function, reducing symptom burden, improving endurance, managing pain, helping patients return to work, decreasing depression and anxiety, and increasing independence "are among the many dimensions of quality of life enhanced from care received in cardiology and primary care settings. Poor quality of life is a frequent concern among patients with chest pain and normal coronary arteries or no obstructive coronary artery disease (CAD), with evidence that this population may endure greater quality of life impairment relative even to those with chest pain and obstructive CAD."

Management

The management of CSX is challenging and often frustrating for both patient and physician [19, 20]. In this book, Lanza and Kaski review treatment options available for CSX and propose practical treatment algorithms for the condition (Chap. 27). Successful treatment usually depends on identifying the prevailing pathogenic mechanism and tailoring the intervention to the individual patient. Advice on lifestyle changes and risk factor management–in particular aggressive lipid lowering therapy with statins—should be considered vital components of any therapeutic strategy. A multidisciplinary approach is required in most cases. Briefly, antianginals such as calcium antagonists and β-adrenergic blockers are useful in patients with documented myocardial ischemia or abnormal myocardial perfusion. Sublingual nitrates are effective in approximately 50 % of CSX patients [3]. Little evidence is available in relation to the efficacy of nicorandil, α-adrenergic blockers, trimetazidine, and angiotensin-converting enzyme inhibitors in this setting.

Analgesic intervention with imipramine [21] and with aminophylline [22, 23], has been shown to improve symptoms in patients with chest pain and normal coronary arteriograms. Transcutaneous electrical nerve stimulation and spinal cord stimulation can offer good pain control in some cases. Chapter 32 by Bairey Merz and colleagues is devoted to the management of chest pain and provides useful practical suggestions.

Hormone Therapy

Hormone therapy has been shown to improve chest pain and endothelial function in women with CSX [10]. Estrogen antagonizes the effects of ET-1 and dilates the coronary vasculature. In addition, estrogen modulate pain threshold. Controlled clinical trials have suggested, however, that the risk of developing cardiovascular disease and breast cancer increases in women taking hormone therapy (HT). Thus, although HT has potential cardiovascular benefits, it can also cause harm [24]. The US Preventative Services Task Force has suggested that routine postmenopausal HT should not be advised for the prevention of chronic conditions and women should take an active part in decisions regarding HT. These recommendations apply also to CSX patients. However, HT may be useful in specific cases where a direct relationship exists between estrogen deficiency and CSX symptoms. Several chapters in the book deal with hormones in both pathogenesis and management of CSX. Shufelt and Waldman discuss the management of estrogen deficiency in Chap. 29, whereas Hermsmeyer and Thompson in Chap. 30 develop a new concept regarding the role of progesterone deficiency in CSX. Webb and Collins, in Chap. 28, focus on testosterone.

Psychological Intervention

Psychological intervention may be beneficial for a substantial number of patients, whether or not organic factors are involved [25]. Studies support the role of a structured cognitive behavioral approach to the management of CSX patients with non-ischemic chest pain [25], and this treatment is more likely to be effective if it is begun early after diagnosis.

Physical Training

As a result of physical deconditioning and low pain threshold, CSX patients have an impaired exercise capacity [26]. Physical training improves pain threshold and endothelial function and delays the onset of exertional pain in patients with typical chest pain and normal coronary arteries [26].

Summary

Controversy still exists regarding the pathogenesis and management of CSX. New data have emerged in recent years that provide useful insight regarding pathogenic mechanisms and prognosis of chest pain with normal coronary arteries and the management of these patients. These issues are thoroughly

discussed in the book, with the aim of providing a comprehensive picture that can help physicians to identify the prevailing mechanisms and deliver rational and effective management strategies.

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Non-Cardiac Chest Pain of Non-Esophageal Origin

2

Cristina Almansa and Sami R. Achem

Abstract

Chest pain is a common clinical problem that can be caused by a broad spectrum of diseases other than coronary artery disease or acid reflux. The diagnosis of non cardiac, non esophageal chest pain can be challenging. The chronic occurrence of chest pain interferes with the daily life routine, mood and productivity of those affected by this condition and therefore implies an enormous socio-economic burden in the community. This chapter offers an overview of some of the most relevant conditions that need to be considered in the differential diagnosis of a patient presenting with chest pain, once that a cardiac and/or an esophageal origin of the symptom has been properly excluded.

Keywords

Chest pain • Epigastric pain • Gastric volvulus • Peptic ulcer • Pneumoperitoneum • Cholecystitis • Choledocolitiasis • Cholangitis • Sphincter of Oddi dysfunction • Pancreatitis • Pancreatic pseudocyst • Pleural fistula • Musculoskeletal pain • Chostochondritis • Tietze syndrome • Precordial catch syndrome • Bornholm disease • Muscle injury • Pseudoangina • Thoracic outlet syndrome • Pneumonia • Pleuritis • Pleural effusions • Pulmonary embolism • Pneumothorax • Pneumomediastinum • Pulmonary arterial hypertension • Anxiety • Panic disorder • Fibromyalgia • Acute aortic syndrome • Sickle cell disease • Drug induced chest pain • Herpes zoster

Introduction

Non-cardiac chest pain (NCCP) can be defined as chest pain resembling angina but without objective evidence of coronary artery disease [1]. NCCP is a source of concern for physicians and patients alike. Chest pain is a common clinical problem. A recent meta-analysis estimated a global prevalence of 13 % (95 % CI 9–16), identifying higher rates in studies performed in Australia, where the pooled prevalence was 16 % (95 % CI 0.2–50) [2]. The prevalence of NCCP has not been studied worldwide, for instance there is lack of information from certain regions such as Africa or Centro America. The results of different surveys suggest that NCCP affects equally men and women of all ages [2]. A Chinese study reported that the prevalence of NCCP might be inversely related to the socio-economic status but this data has not been confirmed in other populations [3].

Despite the high prevalence of the problem, an Australian study suggests that only a small proportion of patients consult a physician [4]. Interestingly, this survey identified that males were two-times more likely to consult than females, maybe because they were more aware of the risk of heart diseases than their females counterparts [4].

NCCP is also an important cause of work absenteeism and impaired productivity. In Australia 29 % of subjects attending the emergency department for chest pain reported to have missed at least 1 day of work or school in the prior year with and average of 23 days (range 1–240 days) [5].

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In addition, up to two thirds of those presenting with NCCP referred some interruption on their daily activities (including work) [6]. Furthermore, NCCP induces a significant impairment of the quality of life comparable to that experienced by patients with cardiac chest pain [6, 7].

The socio-economic burden of NCCP is high, especially as one considers the costs derived from work absenteeism, loss of productivity and the costs of health care. In the USA, it has been reported that almost six million patients visited the emergency department for chest pain in 2007 [8]. In addition patients continue using resources and seeking health care evaluations after being dismissed from hospital. A recent follow up study in a cohort of patients attending the emergency department for chest pain reported that up to 49 % of them visited the emergency department again, 42 % had repeated cardiac evaluations, and 15 % consulted a gastroenterologist. Moreover, the number of health care visits was up to 3 times higher in the subset of patients with chest pain of "unknown origin" than in those with a recognized cause of chest pain [9]. Labeling patients with nonspecific terms such as "non-cardiac, non-esophageal chest pain", "atypical chest pain" or "chest pain of unknown origin" seems to increase their anxiety and frustration leading to continuous medical consultations in search for additional reassurance [6].

The purpose of this chapter is to focus on an overview of some of the non-esophageal causes of chest pain confronting the clinician. Esophageal causes of chest pain and coronary artery disease as source of chest pain are discussed in other sections of this book.

Non-Esophageal Causes of Chest Pain

There is a broad spectrum of diseases, others than coronary artery disease that may cause chest pain, including gastrointestinal, musculoskeletal, pleuro-pulmonary and psychological causes among others (Table 2.1). The diagnostic frequency of each of these entities varies depending on the setting where the epidemiologic study is performed; thus, studies performed in the emergency department show a predominance of cardiac and gastrointestinal diagnoses [9–11], while studies done in primary care settings show predominantly complaints due to musculoskeletal conditions [12, 13].

Gastrointestinal Sources of Chest Pain

Gastric Causes

Epigastric pain is the most frequent form of presentation of gastric disorders. However, pain in the upper abdomen may be difficult to localize and tends to overlap between thoracic

Table 2.1 Causes of NCCP

Gastrointestinal	**Esophagus**
	Gastroesophageal reflux disease
	Motility disorders
	Functional chest pain
	Paraesophageal Hernia
	Eosinophilic esophagitis
	Other causes of esophagitis (infectious, pill, caustic, autoimmune)
	Boerhave syndrome
	Stomach
	Peptic Ulcer
	Gastritis
	Gastric volvulus
	Penetrating/perforated peptic ulcer
	Gall bladder and billiary tree
	Cholecystitis
	Choledocolitiasis
	Cholangitis
	Sphincter of Oddi dysfunction
	Pancreas
	Pancreatitis
	Pancreatic Pseudocyst (extending into the thorax)
	Pancreatic pleural fistula
Musculoskeletal	**Thoracic wall joints**
	Chostocondritis
	Tietze syndrome
	Sternum
	Sternoclavicular syndrome
	Myofascial
	Precordial catch syndrome
	Bornholm disease[a]
	Muscle injury
	Cervical and Thoracic spine
	Pseudoangina
	Thoracic Outlet Syndrome
Respiratory	Pneumonia
	Pleuritis and pleural effusions
	Pulmonary embolism
	Pneumothorax and pneumomediastinum
	Pulmonary arterial hypertension
	Bornholm disease[a]
Psychological	Anxiety and panic disorder
	Others: depression, neuroticism, hypocondria etc.
Malignant disease	Gastrointestinal
	Chest wall
	Pulmonary and pleural
	Breast
	Metastatic disease
Miscellaneous	Fibromyalgia
	Acute Aortic Syndrome
	Sickle cell disease
	Drug induced pain
	Herpes zoster

[a]Bornholm disease may cause musculoskeletal and/or respiratory chest pain

and abdominal organs [14], which explains why sometimes it can be difficult to distinguish from chest pain [15] A recent review suggests that up to 81 % of individuals with endoscopically confirmed peptic ulcer disease present with epigastric pain [16], which has a postprandial pattern that varies depending if the ulcer is located in the stomach (increase of pain after meals) or the duodenum (decrease of pain after meals).

Penetrating or perforating ulcers can also cause epigastric pain that, in case of anterior perforations, rapidly spreads throughout the whole abdomen, accompanied of signs of peritoneal irritation (Fig. 2.1). By contrast, the diagnosis of posterior perforation may be difficult to diagnose or delayed because of the insidious symptoms and lack of physical signs. The symptom most often reported in posterior perforations is abdominal pain that can be epigastric or located in the right upper quadrant, sometimes radiating to the back. The duration and severity increases gradually until it becomes constant and severe [17]. Chest pain and dyspnea have been reported as presenting features of a perforated duodenal ulcer [18]. The radiological demonstration of pneumoperitoneum is a sign of visceral perforation that indicates the need for surgery [17]. Acute and chronic gastritis of infectious, inflammatory or chemical origin can also be cause of epigastric pain [19–23].

Gastric volvulus (Fig. 2.2) occurs when the stomach undergoes axial torsion, often as complication of a paraesophageal hernia but also due to other defects of the esophageal junction or the diaphragm [24, 25]. Acute gastric volvulus is a potential life threatening condition that typically presents with sudden severe chest or abdominal pain, retching without vomiting and dysphagia. In later stages it can cause shock, sepsis and multiorgan failure due to strangulation, ischemia, necrosis and or perforation [26].

Chronic gastric volvulus is more often associated with chronic anemia but may cause recurrent episodes of chest pain that can be erroneously interpreted as coronary disease [27]. The treatment of gastric volvulus is surgical reduction, either open or assisted by laparoscopy [25, 26]. Acute, severe cases who may not be a surgical candidate may be considered for endoscopic decompressive treatment, at least temporarily [28].

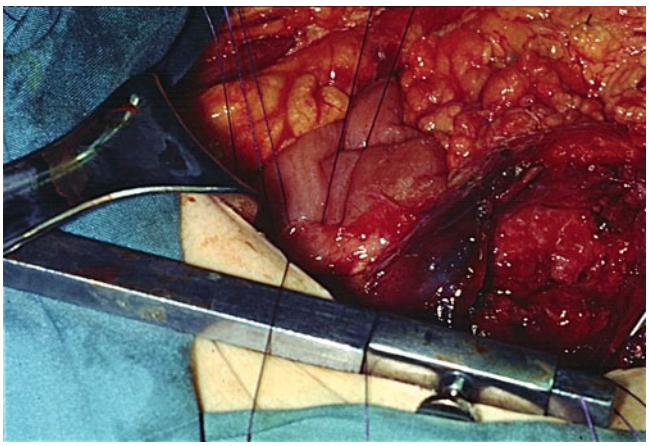

Fig. 2.1 Perforated duodenal ulcer shown at surgery

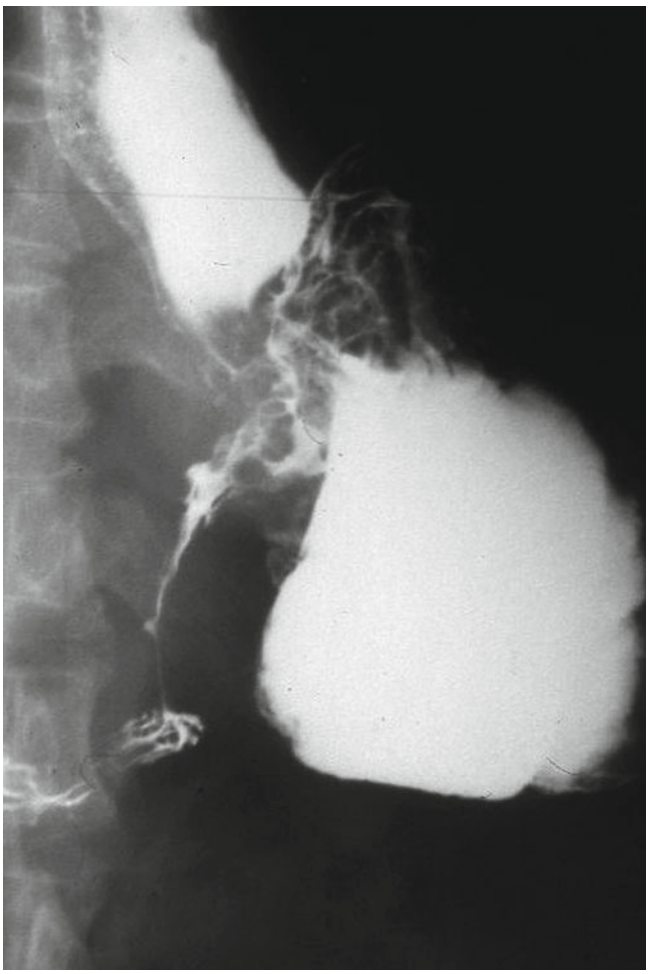

Fig. 2.2 Gastric torsion

Gall Bladder and Biliary Tree

The typical manifestation of symptomatic gallstone disease is biliary pain. Biliary pain is poorly localized in the epigastrium or right upper quadrant and may radiate to the back, right shoulder or the chest. The onset is abrupt, sometimes awakening the patient from sleep. Biliary pain normally occurs as recurrent, not daily, episodes lasting more than 30 min. Though traditionally described as colicky, associated to other unspecific gastrointestinal symptoms and frequently exacerbated after ingestion of fatty meals; recent definitions characterizes it as steady, accompanied by nausea or vomiting but unrelated to other dyspeptic symptoms, and inconsistently triggered by fatty food intake [29–32]. Pseudoangina pain arising from gallbladder disease has been described worldwide by several authors [33–36].

In patients with NCCP (documented by coronary angiography) the prevalence of gallstone disease by abdominal ultrasound (US) has been reported at 6 % [37]. Reinus and Shady studied the value of gallbladder ultrasound in 52 patients with atypical chest pain referred for biliary ultrasonography. Of those, 12 (32 %) had cholelitasis; and 4 underwent cholecystectomy with complete relief of symptoms [38]. This study underscores the importance of screening for gallstone disease in patients with chest pain.

Biliary pain can be associated with fever in cases of acute cholecystitis, jaundice in cases of choledocholithiasis, and both jaundice and fever (Charcot's triad) in cases of cholangitis [29]. Biliary pain can be also present in absence of gallstones in cases of gallbladder dyskinesia or post-cholecystectomy in patients with Sphincter of Oddi dysfunction [30–32]. The initial diagnostic approach of biliary pain includes abdominal US and pancreatic and liver chemistries; in patients with normal US further steps will depend on the clinical suspicion and may involve the performance of endoscopic ultrasound (EUS), computed tomography (CT), magnetic resonance with cholangiopancreatography (MRCP), cholecistokinin – cholescintigraphy (CCK-CS) and endoscopic retrograde colangiopancreatography (ERCP) with or without Sphincter of Oddi manometry [30, 32].

Pancreatic

Pancreatic pain is often described as epigastric with band-like radiation to the back but can also be localized in the right upper quadrant or involve the entire abdomen. Chest pain may occur in some patients with pancreatitis, especially in cases of thoracic complications [39]. Chest pain from pancreatitis or complications of pancreatitis such as pseudocyst (Fig. 2.3) extending into the mediastinum can also resemble myocardial infarction and even lead to electrocardiographic findings suggestive of ischemia despite a normal coronary angiogram [40–44]. Pneumonia and pleural effusions, most often located in the left hemithorax, are common conditions in acute pancreatitis that most of the times resolve with the improvement of the pancreatic disease. Other potential causes of chest pain in pancreatitis, most often associated to chronic pancreatitis of alcoholic origin, are mediastinal pancreatic pseudocysts and chronic massive pleural effusion secondary to pancreatic pleural fistula [39]. These complications normally arise as consequence of a posterior disruption of the main pancreatic duct into the retroperitoneum and the leakage of pancreatic fluid through the diaphragmatic aortic or esophageal hiatus into the posterior mediastinum [45, 46]. Their initial diagnosis is made by chest radiography and analysis of the pleural fluid, that shows a characteristic increase of amylase (>400 U/L), the diagnosis can be confirmed by an imaging test such as CT, MRCP, or ERCP [46].

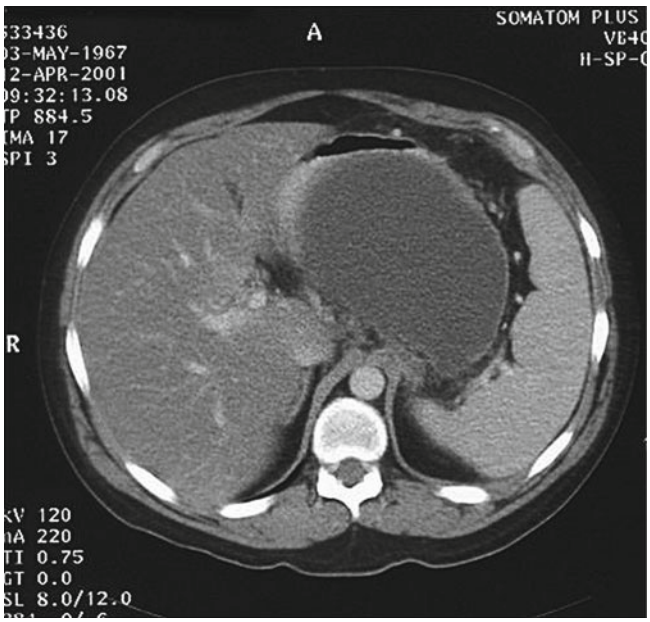

Fig. 2.3 Large pancreatic pseudocyst

Musculoskeletal

Thoracic Wall Joints

Costochondritis

Costochondritis is a common rheumatic condition that represents up to a third of the emergency consultations for acute chest pain [47]. This syndrome can be defined as tenderness of the costochondral and condrosternal joints; and has been termed with different names such as "*costosternal syndrome*", "*parasternal chondrodynia*" and "*anterior chest wall syndrome*" [48]. The etiology of this syndrome remains unclear, most of the patients report a recent history of repetitive physical activity involving the upper body and/or upper extremity that includes excessive coughing in the course of a respiratory infection [49].

The process often involves multiple sites, normally at the same side of the chest and can affect any of the seven costochondral junctions, though it predominates in the third and fourth ribs. Interestingly, the affected areas do not present external signs of inflammation such as swelling or induration [50], a feature that helps to distinguish it from Tietze's syndrome (discussed later).

The pain has been described as sharp or pressure and increases with the movements of the ipsilateral arm or upper body, and certain situations such as energetic coughing and deep breathing. Chest wall pain is characteristically reproduced by palpation of the affected area; however, this finding though suggestive of atypical chest pain, does not exclude cardiac origin [50]; indeed a study assessing the causes of chest

pain in a cohort of 122 patients presenting to the emergency department reported that up to 6 % of those with chostochondritis were also diagnosed with myocardial infarction [47]. The prognosis of chostochondritis is benign and though it can recur, it resolves spontaneously within 1 year [33–36]. The recommended treatment is symptomatic, pain relief with analgesics, anti-inflammatory drugs, rest, physical therapy and reassurance of the benign nature of this process. [50].

Tietze Syndrome

Tietze syndrome is a rare inflammatory disorder that causes non-suppurative swelling of the chostochondral junctions. In contrast with chostochondritis typically affects a single site, most often the second and third ribs, though involvement of the sternoclavicular joint is also possible [49, 50]. Heat and erythema may be present. Tietze syndrome can be secondary to infections, especially in cases of chest wall trauma, rheumatologic disorders and neoplasias [50]. Neoplastic conditions presenting as Tietze syndrome can be primary tumors of the ribs, extensions from a primary process in the vicinity, such as cancers in the pleura, lung or mediastinum or secondary metastatic disease [48, 50–53]. The characteristics of the pain in Tietze syndrome are similar to the described for chostocondritis except for the presence of swelling at the involved site [49]. CT scan can be useful to exclude an infectious or neoplastic process as an underlying cause in suspicious cases [54]. For the most part, the diagnosis is based on history and clinical findings. A recent study suggested that magnetic resonance imaging (MRI) provides a sensitive and reliable tool to confirm the diagnosis [55]. The treatment is similar to that mentioned for chostochondritis.

Ribs

Slipping Rib Syndrome

This syndrome has been referenced in the literature under multiple terms since its first description by Cyriax in 1919 [56]. Synonyms include: "*Cyriax syndrome*" "*rib tip syndrome*", "*clicking rib*", "*slipping rib cartilage syndrome*", "*painful rib syndrome*", "*nerve nipping*", "*twelfth rib syndrome*", "*interchondral subluxation*", "*displaced ribs*" or "*traumatic intercostal neuritis*" [57, 58]. "Slipping rib syndrome", was first used by Davies-Colley in 1922 [59] and is by far the most popular and quoted term. This syndrome is characterized by tenderness and hypermobility of the anterior ends of the false ribs costal cartilages with the affected rib slipping under the upper rib, displacing and irritating the intercostal nerves [50]. It is estimated that it represents about 5 % of musculoskeletal cases of chest pain in primary care [60] The etiology remains unclear, though some patients refer the origin of the symptoms shortly after or some time after a traumatic event; in other cases there is no inciting event such as direct or indirect trauma [61]. The pain starts acutely and remains intermittently for minutes with a sharp and stabbing quality; afterwards, the pain is usually described as a dull ache that in some cases can be confused with angina [62]. The diagnosis is clinical and based on the *hooking maneuver* that consists in curving the fingers of the examiner under the affected costal margin pulling gently the rib cage forward and upward, which will reproduce the pain and cause a characteristic "click" [63]. The treatment requires local anesthetic injections or blockage of the intercostal nerve. In some cases, surgical resections of the affected segment may be required [50, 57, 61]. The prognosis is variable with some cases resolving at 3 months with or without treatment and others remaining chronic for years [61].

Sternum

Sternoclavicular Syndrome

This chronic inflammatory disorder of unknown etiology is characterized by pain, swelling and tenderness of the sternoclavicular area. This syndrome has also been termed under different names such as "*sternoclavicular hyperostosis*", "*chronic recurrent multifocal osteomyelitis*" or "*SAPHO*" acronym for synovitis, acne, pustulosis, hyperostosis and osteitis [64–66]. A review of the literature reported that up to 70 % of the patients present with chest pain and 27 % of them also have limited the motion of the shoulder [67]. The diagnosis of this condition is clinical and supported by complementary tests such as bone scintigraphy, which seems to be the best tool to characterize the disease, CT and MRI may also be helpful [65]. There is not a unique treatment of choice, improvement has been reported with a variety of therapies that include, but are not limited to, non steroidal anti-inflammatory agents, corticosteroids, antibiotics, calcitonin, pamidronate, sulfasalazine, colchicine and infliximab [61, 66, 68]. The prognosis of this syndrome seems to be good at long term [68], but a recent series from the UK reported recurrence of the symptoms in up to 41 % of cases [64].

Myofascial

Precordial Catch Syndrome

Also known as *Texidor twinge*, *costalgia fugax* or *devil's grip* was first described by Miller and Texidor in 1955 [69]. The syndrome typically affects young patients, usually under 35 years that complain of intermittent episodes of stabbing non-radiating precordial pain for seconds to a few minutes. [57, 70, 71]. The pain can appear at rest or during mild to moderate exercise. At rest, the pain seems to have a postural origin and disappear after stretching and correcting the position. It also increases with deep breathing and decreases with

shallow respiration [49]. The etiology is uncertain but a transient pleural pinching has been suggested as potential cause of the symptoms [70, 71]. It does not require treatment, only explanation and reassurance of its benign nature.

Epidemic Myalgia

This disorder is an acute illness caused by the infection by coxackie B viruses transmitted during outbreaks related to contaminated water [72]. It is also known as *Bornholm disease* or *epidemic pleurodinia*. It may cause pulmonary infiltrates, involve the pleura producing pleural effusions or affect the nearby tissues causing myositis of the abdominal and intercostal muscles and even myopericarditis [73]. It causes intermittent chest pain that increases with deep respiration, frequently associated with fever in young adults [49]. The condition is self limiting and only requires symptomatic treatment.

Muscle Injuries

Soreness and/or tears of the intercostal muscles, pectoralis minor and major can be cause of chest pain in subjects not used to exercise or after intensive muscular activity [57, 74–76]; this is frequent after rowing, heavy lifting or even after a respiratory process associated with intense coughing. Characteristically the pain increases with deep inspiration, upper body movement or coughing and there is tenderness to the palpation of the affected area. Most of the times, the patient recalls the traumatic antecedent, which helps to guide the diagnosis [57]. MRI and US of the affected area can be useful to identify muscular lesions as muscular tears, hematomas or interstitial hemorrhages. Treatment implies rest of the affected muscles, avoiding situations that may exacerbate the pain and use of anti-inflammatory medications for injuries of the intercostal muscles [57], while for lesions of the pectoralis the recommended management includes physical therapy, immobilization of the shoulder and potentially, surgery [76].

Cervical and Thoracic Spine

Pseudoangina

Cervical angina is a cause of chest pain that may resemble cardiac origin, but that arises from severe cervical discopathy with compression of C7 nerve root. The diagnosis is based on the clinical history and confirmed with MRI. Treatment includes physical therapy, muscle relaxants and antiinflammatories [77].

Thoracic Outlet Syndrome

Chest pain can also occur in the thoracic outlet syndrome (TOS), due to compression of the brachial plexus, subclavian artery or vein within the thoracic outlet. There are several entities that may cause TOS, including traumatic and congenital abnormalities such as cervical ribs and other anatomical variations [78]. The main clinical manifestation of this syndrome is pain and paresthesias of the upper extremity ipsilateral to the abnormality. Several cases have been reported where the pain radiates anteriorly to the chest mimicking cardiac angina [79, 80]. An occasional case of a patient with TOS in whom elevation of the arms caused irritation of the brachial plexus leading to coronary spasm by activation of sympathetic nerves has been described [81]. The diagnosis of TOS is complex and requires a high index of suspicion; it will require a detailed history and physical examination including careful palpation and neurovascular examination. The therapeutic management of TOS is controversial, though it has been suggested to attempt conservative measures first, leaving surgery for those with lack of response or patients with neurological symptoms [78].

Fibromyalgia

Fibromyalgia (FM) is a common cause of NCCP. The origin of the pain in these patients may be due to both somatic and visceral hypersensitivity [82]. Studies assessing the prevalence of FM in NCCP, have found variable rates ranging from 2.7 to 25 % [82]. These original studies were based on the classic diagnostic criteria of widespread pain (axial, left and right, and upper and lower segment pain) and tenderness on pressure at 11 of the 18 sites tender points [83]. The new FM criteria proposed by the American College of Rheumatology (ACR) in 2010 [84] and its latest modification in 2011 [85], eliminated the tender points and added the widespread pain index (WPI) and the severity score (SS). The SS evaluates the disturbance produced by other complaints commonly associated to FM such as fatigue, waking unrested and cognitive symptoms, the occurrence of headaches, pain or cramps in the lower abdomen and depression in the last 6 months [85]. The presence of chest pain is evaluated in the WPI that assesses the presence of pain over the last week in any of 19 body sites. The current definition of FM requires a WPI $\geq$ 7 and a SS $\geq$ 5 or a WPI 3–6 and a SS $\geq$ 9. In addition, symptoms must be maintained at the same level of severity for a minimum of 3 months and can not be explained by other disorders [85]. The treatment of FM consists in a multidimensional approach addressing the different symptoms of pain, sleep, mood disorders and concomitant somatic complaints that affect these patients [82].

Pulmonary

Pneumonia

Community acquired pneumonia (CAP) is a common condition that can be fatal in elderly people and patients with important co-morbidity [86]. Classical symptoms of pneumonia

may include fever, productive cough, dyspnea and pleuritic chest pain [87]. This later symptom, when present, tends to be localized to the area affected by the pulmonary infection [88]. Atypical symptoms are not infrequent, regardless of the nature of the causal agent, and include arthro-myalgias, headache, and gastrointestinal complaints in up to 30 % of the patients [89]. Pauci-symptomatic presentations are frequent in subjects over 65 years [90]. Diagnostic confirmation of pneumonia requires the identification of pulmonary infiltrate/s at chest radiography; however in some cases, such as in dehydrated patients at early stages of the disease, there maybe few or atypical clinical features [87]. Gram stain and culture of the sputum, when possible, will confirm the microbiological diagnosis and will help guide the antimicrobial treatment. Most patients with CAP can be successfully managed as outpatients; however those at higher risk of complications and mortality must be admitted to the hospital for treatment and close monitoring [91].

Pleuritis and Pleural Effusions

Parietal pleural inflammation is cause of a sharp, unilateral and localized pain that characteristically is aggravated with deep breathing, coughing or any other upper body movements that involve the chest wall. Chest pain can radiate towards the shoulder, neck or the abdomen. Patients with pleuritis, commonly called pleurisy, often present with an exudative pleural effusion, which may be consequence of the increased vascular permeability secondary to the inflammatory process [88]. There are several entities that can lead to parietal pleural inflammation and pleural effusions; the performance of a thoracocentesis to extract and analyze pleural fluid is essential to distinguish between exudates and transudates and guide the differential diagnosis. Characteristically, an exudative pleural fluid contains an increased level of proteins (>0.3 g/dl or ratio pleural fluid protein to serum protein >0.5) and lactate dehydrogenase (LDH) (>200 IU/L or ratio pleural fluid LDH to serum LDH >0.6); a pH <7.2 suggests empyema or pleural malignancies; glucose levels <60 mg/dl is frequent in infections, including tuberculosis but can also denote a rheumathologic origin; amylase levels >200 μg/dl suggest pancreatic disease, rupture of the esophagus or ectopic pregnancy; the presence of blood is indicative of trauma, malignancy or pulmonary embolus; increase levels of tryglicerids (>110 mg/dl) are frequent in tuberculosis or after the rupture of the thoracic duct; overall an increase amount of white blood cells is typical of exudates and specifically the predominance of neutrophils indicates an acute process while the predominance of mononuclear cells suggests chronicity; an increase proportion of lymphocytes is characteristic of tuberculosis or cancer and the rare preponderance of eosinophils is consequence of exposure to asbestos, drugs, parasites or Churg Strauss syndrome [92, 93]. In those cases that remain undiagnosed despite the analysis of the pleural fluid, a pleural biopsy may be indicated. The management of pulmonary effusions will vary depending on the causal entity, though in patients with massive effusions causing dyspnea at rest it will likely include a therapeutic thoracentesis [92].

Pulmonary Embolism

Pulmonary embolism (PE) is consequence of a deep venous thrombosis (DVT) caused by a combination of hypercoagulability, stasis and intimal injury (Virchow's triad) [94]. The most frequent location of DVT is the deep veins of the lower extremities and more rarely in the upper extremities veins (axillary-subclavia veins) [95].

PE classical symptoms are dyspnea of acute onset, chest pain and eventually collapse. Dyspnea is the most common symptom followed by pleuritic chest pain in up to two third of the cases [96]. In the physical exam is relevant the presence of tachypnea and tachycardia, crackles and sometimes an increase in the pulmonary compound of the second sound at cardiac auscultation. A diagnosis of PE is initially suspected in the presence of the classical symptoms and signs in a patient with risk factors for DVT, especially when the arterial oxygen tension (PaO_2) is low. The measurement of circulating D-dimers in plasma can be indicative, but not definitive of PE [97]. An imaging test such as ventilation perfusion scanning, helical CT and pulmonary arteriography will confirm the diagnosis (Fig. 2.4). The treatment of PE requires anticoagulation and if this is not possible, placement of an inferior cava filter.

Pneumothorax and Pneumomediastinum

The diagnosis of pneumothorax implies the presence of air in the pleural space. It may occur spontaneously (primary) or secondary to other underlying conditions such as trauma or pulmonary diseases. Spontaneous pneumothorax usually affects young males that complaint of acute onset of unilateral pleuritic chest pain, cough and dyspnea as a result of spontaneous rupture of apical blebs. Recent reports based on experimental studies suggest that chest pain may be caused by an eosinophilic pleuritis consequence of the air extravasations [88, 98]. The diagnosis is radiographic and involves the demonstration of the visceral pleural line at chest radiography, more evident in expiratory or lateral decubitus radiographic projections (Fig. 2.5) [93].

Pneumomediastinum is characterized by the presence of air in the mediastinum spontaneously or secondary to a trauma. Some causes involve a tear in the esophagus or the rupture of the tracheobronquial tree or alveoli. Clinically, it is characterized by retroesternal chest pain and dyspnea. Severe pneumomediastinum can be accompanied by

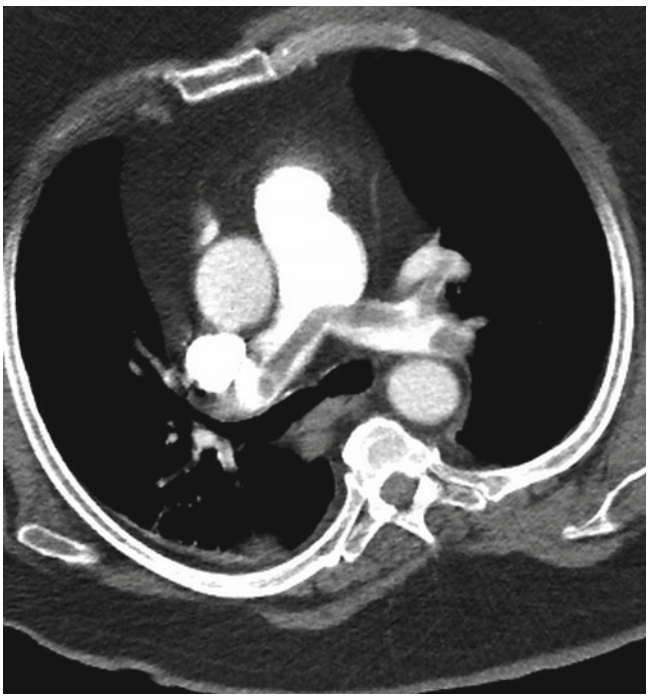

Fig. 2.4 Pulmonary embolism shown using CT

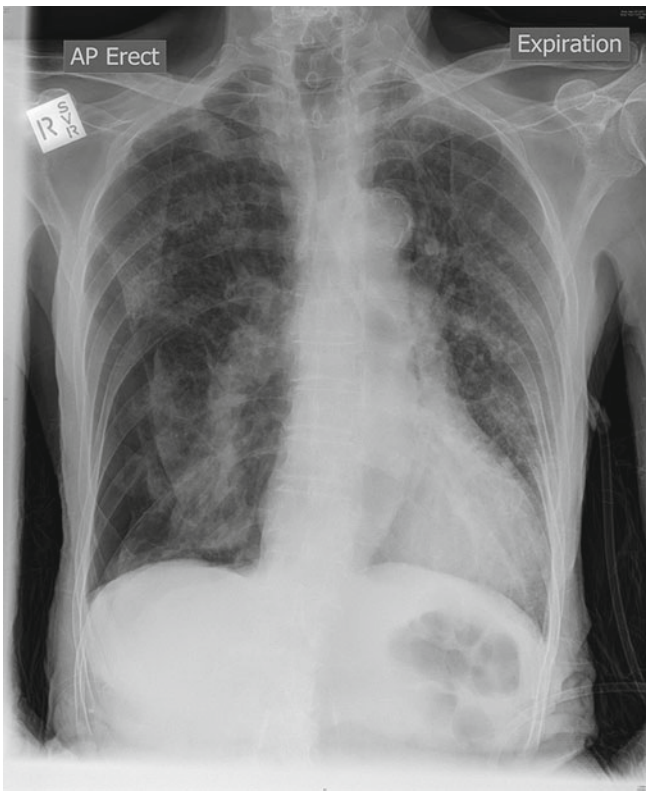

Fig. 2.5 Pneumothorax shown on X-ray

subcutaneous emphysema (air in the subcutaneous tissue), more often located in the chest wall, neck and face. In these cases crepitus can be appreciated on palpation of the affected areas. The diagnosis of pneumomediastinum is based in the clinical suspicion and confirmed with an imaging test such as CT scan [99]. Both pneumomediastium and pneumothorax may reabsorb spontaneously and therefore may be managed conservatively. In cases of large pneumothorax and tension pneumothorax a chest tube drainage will be required; while those cases of pneumomediastinum secondary to visceral rupture may need surgical repair [93].

Pulmonary Arterial Hypertension

Pulmonary arterial hypertension (PAP) is a rare disorder defined as a mean pulmonary arterial pressure of more than 25 mmHg at rest or 30 mmHg during exercise [100]. PAP can be idiopathic, also known as *primary pulmonary hypertension* or associated with other conditions such as collagen vascular diseases, portal hypertension, congenital cardiac shunts, or HIV infection [101]. The earliest and most common symptom of PAH is the gradual onset of dyspnea after physical exertion. Other symptoms include chest pain, fatigue, syncope, peripheral edema and Raynaud syndrome. The origin of chest pain in these patients is not clear, and it has been attributed to right ventricular ischemia [100] and to pulmonary artery dilation and stretching [88]. Indirect signs of PAP can be seen on a chest radiograph and the electrocardiogram; transesophageal echocardiography, especially if used in combined with Doppler and cardiac catheterization, will confirm the diagnosis and help to establish the prognosis [100]. There is not a curative treatment, but patients can benefit by treatment with diverse therapeutic agents such as anticoagulants, anti-platelet agents, vasodilators, anti-inflammatory drugs and vascular-remodeling therapies [101].

Psychological Disorders

Epidemiological studies suggest that psychological factors play an important role in the pathogenesis of chest pain. Moreover, it seems that patients with NCCP suffer from higher rates of psychological disorders than those with cardiac disease, especially panic disorder (PD). The prevalence of PD in patients with NCCP is about 42 % (range 10–63 %) while the reported rate of PD in patients with CAD is 8 % (range 0–22 %) [102–105].

Other psychological disorders also occur with increased prevalence in patients with NCCP including anxiety, depression, neuroticism, hypochondriac behavior, obsessive-compulsive, avoidant and paranoid disorders [106–110].

Different hypothesis have been proposed to explain the association between psychological factors and chest pain, such an increased tension in the thoracic wall muscles as

consequence of anxiety [111], enhanced awareness and monitoring of normal bodily functioning [112], and changes in esophageal motility due to hyperventilation [113, 114].

Longitudinal studies have demonstrated that patients with NCCP and PD present worse psychological outcomes and increased physical impairment that those without PD [115, 116]. A potential association between PD, coronary artery disease and cardiovascular mortality has been suggested [117–119], but this data has not been confirmed in patients with NCCP [116]. Patients with NCCP and PD may have increase rates of suicidal ideation, which could limit their life expectancy [120].

Recognition of potential psychological disorders in patients complaining of chest pain can be essential to improve the outcomes and prognosis of this entity. An algorithm based on gender, age, agoraphobia symptoms and characteristic (quality/location) of pain has demonstrated its usefulness to accurately identify those patients with chest pain presenting a concomitant diagnosis of PD [121].

Malignant Diseases

Chest pain can be precipitated by primary or secondary malignant conditions affecting the pleura and chest wall. Gastrointestinal neoplasias, especially those located in the upper abdomen may also cause epigastric and chest pain.

Chest pain associated with lung cancer is described as isolated, dull and located in the affected side; tumors of the lung apex may cause Pancoast syndrome with pain radiating to the shoulder and chest due to involvement of the braquial plexus; malignant pleural mesothelioma may cause dyspnea and pleuritic pain, that in later stages can be diffuse and of difficult management given the dissemination of the disease through all serous surfaces (pleura and peritoneum) [88].

Chest pain associated with breast cancer is commonly unilateral, persistent and intense; it may radiate to the axilla or arm but otherwise is well localized [122]. Localized mastalgia has been described as an alerting symptom of breast cancer [123], however recent studies suggest that there is not an increased risk of breast cancer in a woman presenting with isolated breast pain [124].

Most common neoplasms of the chest wall are metastatic, especially in the sternum, [74]. Malignant primary chest wall tumors are rare and can arise from any of the structures, bone, cartilage or muscle that constitutes the chest wall. Pain is the most common symptom of both primary and secondary neoplasms of the chest wall. The mechanism of chest pain in chest wall neoplasms is due to periostal or neural invasion. In these cases it is often described as vague, diffuse and confined to a specific area of the thorax. Other frequent symptoms are a palpable mass and in some cases weakness of the upper extremities caused by compression of the braquial plexus [125].

Miscellaneous

Acute Aortic Syndrome

This term coined by Vilacosta el al. in 2001 [126], comprises an heterogeneous group of disorders that share a common clinical presentation and require urgent care [127]. These entities include: penetrating aortic ulcer, intramural hematoma of the aorta, incomplete aortic dissection and complete aortic dissection. The pathogenesis of each of these disorders is different, though a history of severe hypertension seems to be a common risk factor to all of them. The most frequent and characteristic symptom of this syndrome is the presence of severe chest pain that has been described as pulsating, ripping, tearing or migrating, and whose intensity remains constant from its onset [128]. The radiation of the pain can offer a hint about the topography of the lesion. Injuries of the ascending and thoracic arch, also called proximal or type A, usually radiate to the neck, throat and jaw; while type B, distal or lesions of the descending aorta radiate more often to the back or abdomen. The diagnosis of Acute Aortic Syndrome (AAS) is normally suspected by the symptoms and the combination of normal electrocardiogram findings, signs of aortic dilation in the chest radiograph and an increase in the plasma levels of D-dimers. Diagnostic confirmation usually requires a CT chest, MR, transesophageal echocardiogram and/or aortography. The therapeutic management of the AAS depends mainly on the risk of aortic rupture, and it is normally based on the topography of the lesion. Type A or proximal AAS requires early surgery, while type B patients may be managed conservatively or require surgical or endovascular repair in unstable or complicated cases [129].

Sickle Cell Disease

Sickle cell disease is a hemoglobinopathy due to a glutamic acid to valine substitution at the 6th aminoacid of the β-globin chain of human adult hemoglobin (Hb A). This results in formation of sickle hemoglobin, an autosomal recessive disorder characterized by recurrent vaso-occlusive episodes and hemolytic anemia [130]. Chest pain in these patients can be part of the spectrum of symptoms of the *acute chest syndrome*, one of the most important causes of mortality and hospitalization among patients with sickle cell disease. Chest pain is caused by a combination of fat embolism, infections and vaso-occlusive crisis [131]. However chest pain in the context

of sickle cell disease may also be consequence of other cardiopulmonary complications such as pulmonary hypertension and heart disease [130].

Drug-Induced Pain

Cocaine

Chest pain is one of the most common emergency complaints related to the use of smoked, inhaled or injected cocaine. It normally arises within the first hour after cocaine use and remains present an average of 120 min. The pain is more often described as substernal and oppressive and it is frequently associated with shortness of breath and diaforesis [132]. The differential diagnosis of cocaine associated chest pain includes myocardial ischemia, infarction and pulmonary complications such as pneumothorax or pneumomediastinum [133]. Smoked base cocaine, also known as "crack", may cause asthma, interstitial pneumonia or fibrosis and noncardiogenic pulmonary edema. *Crack lung syndrome* is a specific entity associated with the use of smoked base cocaine that often presents with pleuritic chest pain, shortness of breath, cough with carbonaceous sputum and hemoptysis (caused by a combination of pulmonary hemorrhage, pulmonary edema and interstitial disease) [134].

Serotonin Receptor Agonists (Triptans)

The triptans are a group of selective serotonin 5HT 1B/1D receptor agonists that are extensively used for the treatment of moderate-severe migraine. These drugs have all been described to induce chest pain, which is often reported as oppressive and radiated to the throat and/or arms, mimicking myocardial infarction [135, 136]. The pathogenesis of triptans-associated chest pain is not clear. A number of hypothesis have been suggested, including coronary and pulmonary vasoconstriction and changes in esophageal function [137–139]. All triptans may cause chest pain in a dose dependent manner, though this effect seems to be higher with sumatriptan and lower with almotriptan [136, 140].

Other Drugs

Other drugs that may be cause of acute chest pain are aspirin, NSAIDS, ascorbic acid, tetracyclines, ampicilin, clarithromycin, rifampicin, potassium chloride, alendronate and quinidine; The mechanism of production of chest pain in these cases is related to the development pill esophageal injury or pill esophagitis [141].

Herpes Zoster

Thoracic herpes zoster may be a cause of chest pain that occasionally can be misdiagnosed as cardiac angina [10], particularly in those cases when the pain precedes the development of the characteristic skin lesions [142]. Reactivation of varicela zoster has also been recently described as cause of pleuroperdicaditis in an older patient [143]. Despite its rarity this entity needs to be considered in the differential diagnosis of patients with chest pain, especially in those of advanced age or immuno-compromised.

Summary

Chest pain is a common and challenging clinical problem. There is a wide spectrum of clinical conditions that result in chest pain of non-esophageal origin. This chapter offers an overview of some of the common and important causes of non-cardiac, non-esophageal chest pain. A careful clinical history and physical exam frequently provides useful clues to the origin of non-cardiac, non-esophageal chest pain. Recognition of the cause of nonesophageal chest pain may contribute to relieve patients' anxiety and subsequently impact the outcomes.

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Esophageal Chest Pain

3

Anisa Shaker and C. Prakash Gyawali

Abstract

Non-cardiac chest pain (NCCP) consists of recurrent angina-type pain unrelated to ischemic heart disease or other cardiac source after a reasonable workup. The most common esophageal cause of NCCP is gastro-esophageal reflux disease (GERD), followed by esophageal motor disorders and esophageal visceral hypersensitivity. Noxious triggers for NCCP include acidic and non-acidic reflux events, mechanical distension and muscle spasm, particularly longitudinal smooth muscle contraction. Functional chest pain of esophageal origin is diagnosed when endoscopy and esophageal physiologic studies (manometry, ambulatory pH/pH-impedance monitoring) do not reveal a source for NCCP. Once a cardiac etiology has been reliably excluded, an empiric proton pump inhibitor (PPI) trial provides a clinically useful and cost effective mechanism for diagnosis of GERD related NCCP. While endoscopy has a limited diagnostic yield because of the high prevalence of nonerosive disease, histopathology may help evaluate for microscopic evidence of reflux and eosinophilic esophagitis. Ambulatory pH or pH/impedance monitoring off PPI therapy assesses for abnormal esophageal acid exposure and reflux association with NCCP events using simple and statistical symptom association probability tests. Esophageal manometry is typically performed concurrent with ambulatory pH monitoring and can identify esophageal dysmotility, some patterns of which may be associated with esophageal hypersensitivity. Acid suppression with a PPI is the first therapeutic measure initiated even prior to investigation in NCCP. Pain modulators (e.g. low dose tricyclic antidepressants) are often the mainstay of therapy in refractory situations. Smooth muscle relaxants (sublingual nitroglycerine, phosphodiesterase-5 inhibitors, and calcium channel blockers) can be used in hypermotility states, although their efficacy has not been conclusively demonstrated in controlled trials. Hypnotherapy, biofeedback, transcutaneous nerve stimulation, and cognitive and behavioral therapy complement pharmacologic therapy, although additional studies are needed; acupuncture may also be of benefit.

Keywords

Non-cardiac chest pain • Gastroesophageal reflux disease • Esophageal motor disorder • Esophageal visceral hypersensitivity • Ambulatory pH monitoring • Esophageal manometry • Proton pump inhibitor • Neuromodulator

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Introduction

Chest pain is a common entity, accounting for a high proportion of office consultations and emergency room visits [1, 2]. The causes of chest pain are multiple and range in severity

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from merely frustrating to life-threatening. The entity deserving immediate attention and crucial to exclude is cardiac disease, particularly ischemic etiologies, but also non-ischemic disease. Once cardiac etiologies of chest pain have been adequately excluded with cardiology opinion and appropriate diagnostic tests, the focus of further evaluation and management can shift to the entity commonly termed non-cardiac chest pain (NCCP). While routine cardiac testing (stress testing, cardiac catheterization, echocardiography, cardiac MRI) may adequately exclude most active cardiac disease, rare syndromes of intermittent coronary vasospasm or syndrome X may be more difficult to exclude, as is explained in detail elsewhere in the text. Further, cardiac disease can coexist with NCCP, [3]; as many as half of patients with coronary disease may complain of esophageal symptoms [4]. Therefore, patients are recommended to present for urgent evaluation if the character of their symptoms change from those that are designated NCCP after esophageal evaluation.

Non-cardiac chest pain has been defined as recurrent angina-type pain unrelated to ischemic heart disease or other cardiac source after a reasonable workup [5, 6]. A variety of gastroesophageal, other gastrointestinal, pulmonary, musculoskeletal and psychological causes can result in NCCP [7], as described in Chap. 2. The most common origin of NCCP, however, is esophageal. Of the esophageal disorders, gastro-esophageal reflux disease (GERD) dominates the etiology [8, 9]. Less frequent but often cited esophageal causes of chest pain include esophageal dysmotility and esophageal hypersensitivity [10]. This chapter will focus on esophageal pain as a manifestation of NCCP.

Epidemiology

NCCP is a heterogeneous and common disorder with a prevalence ranging from 23.1 % [11] to as high as 33 % in one population based study [1, 12]. The precise epidemiology of esophageal chest pain is difficult to tease out from the bigger category of NCCP, but reports in the literature are likely representative of esophageal pain since this constitutes the bulk of NCCP. Gender prevalence of NCCP is similar although some studies suggest that women tend to seek out medical care for symptoms more frequently than men [1]. Atypical GERD symptoms such as chest pain may also become more prevalent during pregnancy [13]. There is an inverse relationship between the prevalence of NCCP and age [6, 12]. This is likely related to the fact that the esophagus is less sensitive to noxious stimuli with increasing age, and triggers such as reflux events may not invoke as much sensitivity or hypersensitivity as in younger individuals [14–16]. There is a strong link between esophageal pain and affective disorders. Hence, patients with NCCP are also likely to manifest psychological comorbidities such as panic disorder, depression, somatization, and anxiety [6, 17].

Although studies evaluating the cost of NCCP are limited, the economic impact of NCCP cannot be underestimated. Chest pain in general is a cause of multiple outpatient visits, accounting for 2–5 % of emergency room visits, frequent hospitalizations, and often dissatisfaction with provided care [6]. Occupational impairment and work absenteeism rates as high as 29 % have been reported [6, 18]. It is thought that as many as 200,000 new cases of NCCP are diagnosed each year in the US. Most of these patients continue to worry about a sinister cardiac etiology for their pain, sometimes despite documentation of a clear relationship between esophageal events and chest pain. The psychological associations, particularly anxiety and panic disorder, can serve to propagate anxiety and stress, both of which increase physical and psychological comorbidity and health care utilization.

Categories of Esophageal Chest Pain

GERD Related Chest Pain

Gastro-esophageal reflux disease (GERD) is the most common cause of NCCP, accounting for up to 60 % of patients with NCCP [6, 19]. GERD-related NCCP resembles the pain of angina, with squeezing/burning in the substernal location and radiation to the neck, arms or back. This discomfort may persist only a few minutes or last for hours, and may continue intermittently for days [7]. The pain may be worse post-prandially, in the supine position, after exercise, or during emotional stress. Strenuous exercise may initially provoke typical GERD symptoms such as heartburn and regurgitation, which may then in turn lead to NCCP. The presence of esophageal symptoms such as heartburn, dysphagia, and regurgitation can help distinguish NCCP from cardiac angina [17]. There is significant overlap of symptoms, however, and distinguishing the two based on clinical history alone is challenging and not recommended. Patients' description of heartburn and chest pain can overlap, and degree of pain perception can influence symptom intensity and interference with day to day activities. In the setting of GERD, predisposition to abnormal central processing of afferent data may lead to triggering and propagation of chest pain as a symptom, and this can be modified by cognitive and psychological comorbities (Fig. 3.1).

In patients naïve to antisecretory therapy, the likelihood of documenting esophageal erosive changes on upper endoscopy is significantly lower in NCCP (15–20 %) compared to typical reflux presentations (50–60 %) [17]. The incidence of esophagitis goes down even further in patients treated with proton pump inhibitors (PPIs), making endoscopy an unreliable study in diagnosing GERD in NCCP [2, 6, 17]. Endoscopy may have value if visual and histopathologic evidence of Barrett's esophagus is found, indicating a high likelihood of

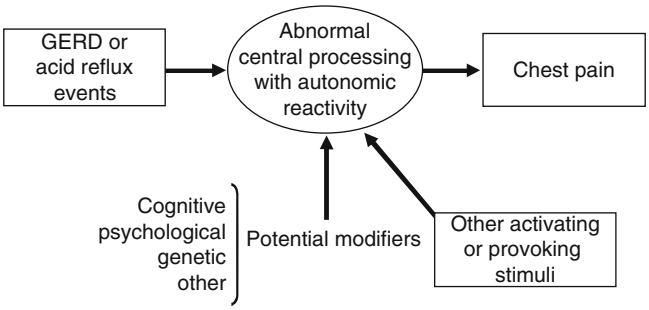

Fig. 3.1 Putative mechanisms by which gastroesophageal reflux disease can trigger chest pain. In patients predisposed to abnormal central processing of peripheral stimuli, reflux events can trigger the perception of chest pain. There may be associated autonomic reactivity, manifesting as dysmotility, inherent to abnormal central processing, and therefore a potential marker of this visceral hypersensitivity pattern. Comorbid cognitive and psychological factors are known modifiers of this process, and genetic predispositions are being identified, but other yet unknown modifiers could exist. In addition to reflux events, other esophageal physiologic or pathologic events could participate in activating or potentiating the process

concurrent GERD and a need for PPI therapy. Histopathology has value in determining nonerosive reflux disease, and in excluding eosinophilic esophagitis, which can also present with chest pain or heartburn. Newer endoscopic modalities such as narrow band imaging may help identify mucosal and vascular changes associated with reflux disease [20, 21]. Although endoscopy is typically the first test performed, the low yield typically leads to further esophageal testing, particularly ambulatory pH or pH/impedance monitoring. When performed off antisecretory therapy, both quantitation of esophageal acid exposure and assessment of correlation between chest pain and reflux events have value in determining the etiology of NCCP. Prolonging the pH recording period beyond the traditional 24 h study using wireless pH monitoring may further improve the diagnostic yield. Prolonged pH monitoring takes into account day-to-day variation in acid exposure while evaluating GERD evidence, and allows more symptoms to develop for symptom reflux correlation [22–24]. The likelihood of documenting abnormal parameters on ambulatory pH studies ranges from 25 to 60 % [7].

Esophageal Dysmotility Related Chest Pain

Up to 30 % of patients with NCCP are reported to have esophageal motor abnormalities including diffuse esophageal spasm, "nutcracker" esophagus, and hypertensive LES [18]. Early balloon distension studies have documented higher sensitivity to lower volumes of balloon distension in NCCP patients compared to healthy normal volunteers in this setting [25]. Graded balloon distension studies have shown lower sensory threshold, and higher degrees of pain to similar balloon distension pressures compared to controls [26]. A positive correlation exists between amplitude of esophageal body contraction and intensity of pain perception, suggesting that hypercontraction is associated with hypersensitivity [27]. Using impedance planimetry, which assesses cross sectional area in the esophagus, muscle reactivity was noted at a lower threshold on balloon distension in NCCP patients compared to controls [26]. This hypersensitivity seen in spastic disorders may further translate into incomplete symptom relief with typical antireflux treatments (including surgery) when these disorders overlap with GERD [28]. Therefore, although a definitive causal relationship between manometric abnormalities and chest pain has not been conclusively established, hypercontraction appears to be associated with hypersensitivity in the esophagus.

Spontaneous and edrophonium induced sustained longitudinal muscle esophageal contractions, evaluated by ultrasonography have been demonstrated to be associated with chest pain [3, 29]. Although sustained esophageal contractions are associated with pain, most patients with NCCP have normal esophageal motility [6]. In those patients with manometric abnormalities, there is no consistent relationship between dysmotility and reports of chest pain. Despite this, the esophagus has been described to be stiff and noncompliant in NCCP patients, especially in the setting of hypercontractile states such as 'nutcracker esophagus' [26, 30]. Blocking reactivity and relaxing the wall with atropine, however, does not remove the hyperalgesia, suggesting that the relationship between hypercontraction and hyperalgesia is more complex [31]. Chest pain is also reported with extreme motor disorders such as achalasia and diffuse esophageal spasm, but these account for only a small proportion of subjects with NCCP [6]. Hypercontractile and spastic disorders represent disorders of esophageal inhibitory nerve function [32, 33] and the possibility remains that hypersensitivity leading to NCCP is an epiphenomenon seen with esophageal inhibitory nerve dysfunction [18]. Psychiatric comorbidities may also participate in symptom perception and reporting in this cohort of patients, as the prevalence of generalized anxiety disorder and major depression are higher in patients with nonspecific spastic disorders of the esophagus (40–42 %) than in NCCP patients in general (14–24 %) [34]. There is enough evidence in the literature to recommend esophageal motility testing in patients with unexplained NCCP, as the finding of a spastic process will prompt consideration of esophageal hypersensitivity as a mechanism for symptoms.

Esophageal Hypersensitivity

Esophageal hypersensitivity overlaps with the above two categories described, and may also overlap with functional chest pain. Esophageal hypersensitivity can be defined as symptoms arising from unexpected reaction to physiological stimuli, and/or exaggerated response to pathological stimuli.

Psychiatric comorbidity may contribute to the exaggerated symptom perception in these patients. There is data to suggest that stressful situations, either simulated or in real life, are associated with heightened esophageal symptom perception [35, 36]. However, benefit in terms of relief of NCCP may not be evident despite change in anxiety or depression ratings, correction of abnormal motility pattern or correction of visceral hypersensitivity. Somatization state and trait also form a subset of subjects with esophageal hypersensitivity and functional chest pain, and can frequently be identified on the basis of symptom check lists and multiple functional diagnoses [37].

Eosinophilic Esophagitis

Eosinophilic esophagitis (EoE) is a distinct clinico-pathologic disorder characterized by PPI refractory esophageal symptoms in combination with dense esophageal eosinophilia. Population based studies suggest an increase in the incidence of EoE over the past 30 years with a prevalence of 55 per 100,000 persons [38]. Affected children and adults are more likely to be male [39, 40]. The clinical presentation of EoE varies with age. In adults, solid food dysphagia and food impaction are the most commonly observed symptoms [41] while in children the range of manifestations are more broad and include feeding difficulties, abdmoninal pain, dysphagia, and vomiting. As recognition of EoE as a disorder has increased, there has a been a corresponding increase in reports of NCCP in association with EoE [41, 42]. A recent retrospective study supports the role for endoscopy with esophageal biopsies especially in males with recurrent unexplained chest pain [42].

Infectious Esophagitis

Infectious esophagitis can result from bacterial, viral, fungal, or parasitic organisms. Although immunocompetent individuals without predisposing factors can develop these infections, infectious esophagitis typically occurs in immunocompromised states, including chemotherapy, transplantation, and HIV infection. Diabetes and recent antibiotic are also predisposing factors. The most commonly described organisms are candida, herpes simplex virus (HSV), and cytomegalovirus (CMV). Less commonly reported agents include cryptosporidium and mycobacterium avium complex (MAC). Although endoscopic and histologic appearances are specific to the infectious agent, clinical manifestations are similar and include dysphagia and/or odynophagia. Odynophagia can be particularly prominent with HSV esophagitis, and may be interpreted as NCCP. It is important to note that HSV esophagitis can also occur in an immunocompetent and otherwise healthy host. Candida esophagitis can also present with retrosternal chest pain [43]. In general, infectious esophagitis has a shorter temporal profile compared to other NCCP etiologies, and may be self limited.

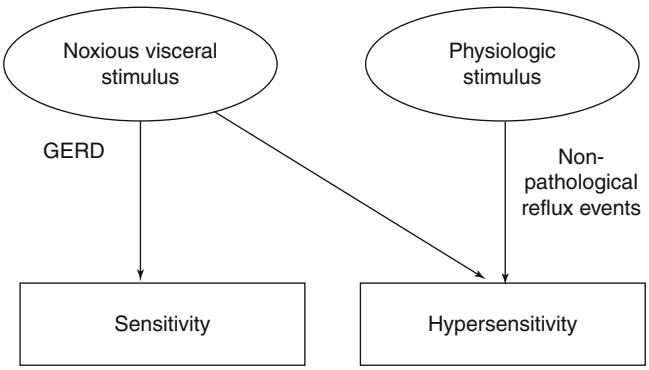

Fig. 3.2 Concepts regarding esophageal sensitivity and hypersensitivity. Noxious peripheral stimuli trigger sensitivity, an expected and physiologic phenomenon. In susceptible individuals, the same noxious stimuli, or in some instances, normal physiologic stimuli can generate an exaggerated perceptive reaction. This exaggerated response is termed hypersensitivity

Functional Chest Pain

Many patients with NCCP have esophageal visceral hypersensitivity concurrent with esophageal dysmotility or GERD [6]. However, there are patients with esophageal chest pain that have normal endoscopy, normal esophageal motility testing and normal ambulatory pH/impedance testing. This pattern is recognized as functional chest pain of presumed esophageal origin (Rome II), defined as "at least 12 weeks, which need not be consecutive, in the preceding 12 months of midline chest pain or discomfort that is not of burning quality; and absence of pathologic gastro-esophageal reflux, achalasia, or other motility disorder with a recognized pathologic basis" [44]. Visceral hypersensitivity, which has been defined as enhanced conscious perception of a visceral stimulus regardless of the stimulus intensity, is thought to play a pathogenic role in functional NCCP [44] (Fig. 3.2). In addition, up to 75 % of patients with NCCP reportedly have some psychological co-morbidity, most commonly panic disorder, anxiety, somatization, or depression [17]. While affective disorders, stress, and luminal events such as mucosal inflammation may act as triggers, these are often not evident, and may not be required for the initiation or propagation of functional chest pain. Core abnormalities are thought to include distorted central processing of peripheral stimuli; autonomic reactivity and dysregulation may contribute, and may be responsible for the epiphenomena seen in the form of motor dysfunction in some patients [45] (Fig. 3.3).

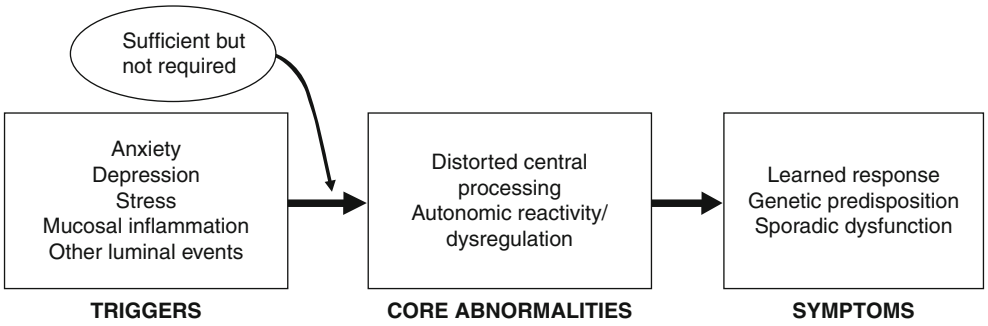

Fig. 3.3 Factors contributing to hypersensitive and functional mechanisms of chest pain. The core abnormalities focus on abnormal central processing of peripheral inputs, which in turn are provoked or triggered by physical luminal events and/or cognitive and psychological events. Once symptoms develop, they may be propagated by the learned response that develops, and therefore can persist long after the triggers resolve. While many cases seem to be sporadic events, genetic predispositions probably exist, and are currently being investigated

Pathophysiology

The mechanisms underlying esophageal chest pain have not yet been definitively elucidated. Animal and human studies have demonstrated that several types of esophageal stimuli can result in chest pain, including acid exposure, mechanical distension, and muscle spasm. How the esophagus responds to these stimuli is an ongoing area of research.

The similarity of esophageal pain to cardiac pain is not altogether surprising given the anatomic proximity of the esophagus and heart and their shared innervation. There is convergence of cardiac and esophageal sensory afferent fibers on the same neurons of the spinal dorsal horn in the cervical and thoracic spinal cord [46, 47]. Areas of pain perception, both primary perception and radiation, are remarkably similar for esophageal and cardiac pain [48]. For instance, radiation to the left shoulder can be seen in 23 % and to the left arm in 18 % of esophageal chest pain [48]. Some characteristics of pain, however, are suggestive of esophageal origin, such as prolonged duration of pain, prompt relief with antacids, pain waking patients' up from sleep, and associated esophageal symptoms such as dysphagia, odynophagia, heartburn and regurgitation. Both esophageal and cardiac pain may be associated with similar high scores when tested for psychosocial factors (stress, anxiety, depression), clinical pain responses, and pain coping strategies, leading some to believe that the abnormal psychological measures may be inherent to the presence of pain rather than caused by pain [49].

The association of chest pain with acid reflux events has been demonstrated in multiple studies [6]. The relationship between NCCP and GERD is further supported by symptom resolution with anti-secretory therapy [6]. The association of GERD with chest pain is likely multi-factorial, however, and several mechanisms underlying this relationship have been proposed. GERD induced NCCP may be a consequence of activation of esophageal wall nociceptors (chemo- and mechano-receptors) in response to chemical and thermal stimulation, and esophageal wall stretch [7]. These signals are transmitted peripherally and centrally. Acid reflux may also manifest as chest pain in these patients by provoking a hypersensitivity response via peripheral sensitization, whereby there is a decrease in the response threshold and a heightened perception to esophageal chemo- and mechano- stimulation [7]. Alternatively, there may be central sensitization at the level of neurons in the spinal cord and brain [1] (Fig. 3.2).

Esophageal acid has also been shown to excite esophageal vagal and spinal sensory afferent fibers via activation of proton-gated ion channels [50]. Candidate receptors for acid sensitivity in the esophagus include the vanilloid receptor 1 (TRPV1) and acid sensing ion channels (ASIC). TRPV1 is expressed by esophageal sensory neurons and is activated by noxious heat, acid pH and ethanol. Upregulation of this acid sensing receptor in esophageal sensory nerve fibers has been proposed as a potential mechanism of esophageal hypersensitivity in NCCP [51]. A reduction in acid related coronary artery flow or a neural cardio-esophageal reflex, has also been proposed as mechanism of acid related NCCP [3, 6, 7, 52]. Acid perfusion has been shown to reduce coronary artery flow in patients with syndrome X; an effect not seen in the denervated heart of heart transplant recipients. Syndrome X, also known as microvascular angina, is characterized by a typical angina symptoms, a positive stress test, and normal coronary angiogram [1].

Although motility abnormalities have been described in patients with non-GERD related chest pain, the significance of these findings in the pathogenesis of chest pain remains unresolved [1]. Esophageal muscle thickness in the absence of esophageal motility abnormalities has been implicated in the pathogenesis of NCCP [6]. There also appears to be a correlation between spontaneous and induced sustained esophageal longitudinal muscle contractions and NCCP [3, 29].

Heightened perception of esophageal acid events, provocation with cholinergic agonists and balloon stimulation under experimental conditions have all been demonstrated in

patients with NCCP [18]. Therefore, peripheral sensitization has been proposed as a mechanism contributing to chest pain in patients with esophageal hypersensitivity. Acid reflux may sensitize esophageal afferent pathways to stimuli, lowering the threshold at which patients perceive otherwise normal esophageal distention [1]. Peripheral sensitization is thought to be the primary contributor of pain hypersensitivity at the injury site, or primary hyperalgesia [53]. Central sensitization with an increase in the excitability of spinal cord neurons and enhanced cerebral processing of esophageal sensory input have also been proposed as mechanisms contributing to chest pain in patients with esophageal hypersensitivity [1, 54]. Secondary hyperalgesia or pain sensitivity that affects not only the site of injury but also the surrounding healthy tissue is thought to result from central sensitization [53].

A unified pathophysiologic model of symptom triggering is depicted in Fig. 3.3. The core abnormality is likely a disturbance in central processing of peripheral stimuli; abnormal autonomic regulation related to this potentially causes the epiphenomenon of hypermotility noted on esophageal manometry in some situations. In addition to physical triggers (chemo- or mechano-receptor stimulation), cognitive and psychological comorbidities may contribute to symptom generation and propagation. A learned response may result in persistent symptoms despite improvement or resolution of the physical or psychological trigger. Candidate gene studies, genome wide association studies and whole genome sequencing are being actively researched in an attempt to identify genetic polymorphisms that would identify a predisposing phenotype [55].

Diagnosis

Given that patient history is not sufficient to distinguish between cardiac and non-cardiac sources of chest pain, initial diagnostic tests should be focused on evaluation of cardiac disease (stress test, angiogram). Once a cardiac etiology has been reliably excluded, esophageal causes of chest pain can then be evaluated (Table 3.1).

Proton Pump Inhibitor Test

The PPI test, a short course of twice a day proton-pump inhibitor, is a sensitive, specific, and cost-effective method of simultaneously diagnosing and treating GERD related NCCP [7]. A meta-analysis showed that the sensitivity and specificity of the PPI test were 80 and 74 % respectively [56]. The original PPI test consisted of omeprazole administered orally in the dose of 40 mg in the morning and 20 mg in the evening before meals for a 7 day period. Since chest pain episodes are less frequent compared to heartburn, there have been suggestions that a PPI trial for NCCP needs to last longer, perhaps a month.

Table 3.1 Typical investigative procedures performed on patients with suspected esophageal chest pain

Clinical	PPI test
	Upper endoscopy with biopsy
	Esophageal manometry (preferably high resolution manometry)
	Ambulatory pH or pH impedance monitoring (off PPI)
	Barium studies (less of a role)
	Psychological assessment when appropriate
Research	Balloon distension studies
	Acid perfusion studies (Bernstein test)
	Impedance planimetry
	High frequency ultrasound
	Multimodal stimulation
	Esophageal evoked potentials
	Functional MRI

PPI proton pump inhibitor, *MRI* magnetic resonance imaging

Response seems to mirror that seen with the original studies on non-selected GERD, ranging from 71 to 95 % in randomized controlled studies [8, 19]. However, response or lack thereof may not be conclusive for establishing or refuting GERD. In one prospective randomized control trial, as many as 39 % of NCCP patients without GERD parameters on ambulatory 24 h pH study had a response to PPI therapy [8]. Further, meta-analysis of a short-term PPI treatment in non-selected GERD demonstrated a specificity of only 54 % for a diagnosis of GERD. This study, however, was hampered by limited information on PPI dose and duration. The observed clinical benefit in patients without objective GERD parameters may represent alternate conditions potentially triggered by reflux events including esophageal hypersensitivity, eosinophilic esophagitis or placebo effect [57].

There is data to suggest that in subjects presenting with chest pain and normal coronary angiography, an approach that starts with empirical antisecretory treatment provides significant cost saving, both in the early follow up period, and after 1 year of follow up, compared to approaches that start with extensive gastrointestinal investigation [58]. Despite the cost savings, the proportion of patients with symptom relief was similar on follow up [59]. Given the ready availability of PPI therapy, including generic formulation, its non-invasive nature, and ultimately a cost-saving approach, a short course of PPI therapy to determine response is reasonable before proceeding with more invasive diagnostic evaluation. Endoscopy for histopathology to evaluate for eosinophilic esophagitis and perhaps Barrett's esophagus is reasonable at this stage, regardless of the outcome of the PPI trial. In most secondary and tertiary referrals, a PPI trial and endoscopy would have been performed before referral. In patients unresponsive to PPI therapy, further diagnostic tests can be considered.

Ambulatory pH Monitoring

Interpretation of esophageal pH monitoring in NCCP continues to evolve. Of the available diagnostic tests, pH monitoring is probably the most helpful in demonstrating a relationship between acid exposure and symptoms in patients with NCCP. Ambulatory pH monitoring can be performed using the traditional catheter based system, or the newer wireless system. Traditional pH catheters typically have two recording sites 15 cm apart, and are placed transnasally with the distal recording site positioned 5 cm proximal to the top of the lower esophageal sphincter (LES) as determined by esophageal manometry. Newer catheters combine pH and impedance, such that impedance electrodes are positioned both proximal and distal to the pH recording sites. The advantage of impedance monitoring is that refluxates can be detected irrespective of pH. With wireless pH monitoring, a pH recording capsule is attached to the esophageal wall 6 cm proximal to the endoscopically identified squamocolumnar junction using a transoral delivery device, to correspond to the typical positioning of the pH catheters 5 cm above the LES. Using a correction factor, the transoral wireless delivery system can be used with manometrically measured LES distance from the nostril.

Typically, objective measurement of pathologic reflux is determined by acid exposure time or AET, defined as the percentage of time esophageal pH is <4 during a 24 h period. To determine abnormal AET, especially in the setting of an incomplete response to PPI therapy, ambulatory pH testing needs to be performed off anti-reflux therapy [9]. Threshold values for AET range from 4.0 to 5.3 %; higher thresholds are recommended for wireless pH monitoring.

Analysis of pH monitoring includes assessment of symptom reflux association to determine if symptoms can be explained by reflux disease. Many reflux events fail to generate symptoms, and all symptoms may not correlate with reflux events. Traditionally, to designate association with a reflux event, the symptom needs to occur within 2 min of the reflux event. Tests and indices have been developed to confer objectivity to symptom reflux association. The simplest of these tests is the symptom index (SI), which describes the proportion of reported symptom events that correlate with esophageal acidification (pH < 4.0), expressed as a percentage. A value ≥50 % indicates positive symptom correlation. The SI can be unreliable with low diagnostic yield when symptoms are infrequent [60], but may have value in designating confidence in symptom reflux associations, particularly when other GERD parameters (such as AET and symptom association probability) are also abnormal. Symptom sensitivity index (SSI) is a rarely used test, depicting the ratio of symptoms associated with reflux episodes to the total number of reflux episodes. Symptom associated probability (SAP) is used more often to assess the likelihood of chance association between symptom and reflux events, using a statistical approach. The entire duration of the pH study is divided into 2 min segments. Each segment is assessed for the presence or absence of reflux events and symptoms. A two by two table is generated with the data, representing sums of four possible combinations, symptom plus reflux, symptom and no reflux, no symptom and reflux, and no symptoms and no reflux. A Fisher's exact test is applied to generate a p value, which suggests less likelihood of chance association if <0.05 [22]. An alternate statistical test, the Ghillebert Probability Estimate (GPE), calculates a similar p value by summing up partial probabilities from data routinely collected during an ambulatory pH study, without need for determining 2 min intervals [22]. In combination with an abnormal AET, a positive symptom association probability has the best value in designating a GERD etiology in NCCP [6, 9]. The SAP has been shown to be independently predictive of symptomatic response to anti-reflux therapy (medical therapy and anti-reflux surgery) in NCCP [9]. Similar symptom association parameters can be applied to pH-impedance monitoring.

If ambulatory pH testing results are normal, other causes of NCCP (esophageal dysmotility, hypersensitivity, psychological co-morbidities) are typically pursued [6, 7].

Endoscopy

Upper endoscopy has limited sensitivity in the evaluation of NCCP, since the majority of individuals with GERD related NCCP have non-erosive disease [60]. Most patients with NCCP undergo endoscopy at some point in their work up. The likelihood of finding erosive esophagitis ranges from 15 to 25 % in symptomatic NCCP patients prior to PPI therapy [8, 17] which decreases further after PPI therapy. However, there may be some value in performing an upper endoscopy. When endoscopic evidence (visual and histopathologic) of Barrett's esophagus is found, the likelihood of GERD is high and PPI therapy is warranted, although this may not fully explain chest pain in all instances. Endoscopy is useful in diagnosing or excluding infectious esophagitis. This may be particularly relevant in acute onset of severe chest pain, which can be seen with herpes esophagitis. Odynophagia and dysphagia can coexist in this setting. Infectious esophagitis is frequently identified in immunocompromised patients, but herpes esophagitis can occur in immunocompetent patients as well [43]. Endoscopy also allows for evaluation and exclusion of eosinophilic esophagitis as a cause for esophageal symptoms. Typical endoscopic findings include linear furrows, circumferential ridging and narrowing, and exudates, although the esophagus can visually appear normal. Biopsies are recommended from both proximal and distal esophagus. Finally, upper endoscopy is also indicated when alarm

symptoms (dysphagia, anemia, bleeding, weight loss) are present; lack of response to PPI therapy can be considered an alarm symptom prompting endoscopy.

Manometry

Esophageal manometry is typically considered when structural and mucosal etiologies for NCCP have been excluded, since esophageal motor disorders may be associated with esophageal hypersensitivity. From a practical standpoint, manometry is performed concurrent with ambulatory pH monitoring, especially when catheter based pH or pH-impedance tests are performed, since placement of the pH catheter requires manometric measurement of the distance to the LES.

Prominent motor disorders such as achalasia and esophageal hypermotility (esophageal spasm, nutcracker esophagus) may have an important chest pain component. However, these disorders represent a small proportion of patients with NCCP [60]. With the advent of high resolution manometry (HRM), manometric characteristics have been identified that may have value in the evaluation of NCCP. For instance, exaggerated smooth muscle contraction may be identified by merging together of smooth muscle contraction segments, and increased vigor of contraction as measured by the distal contractile integral (DCI); this can be associated with chest pain predominant presentations [61]. A lesser version of this, a shift in contraction vigor to the distal smooth muscle contraction segment has been described with acid sensitive NCCP patients, but not with those with GERD [62]. Repetitive contraction of the smooth muscle segments may be seen in 'jackhammer esophagus', another hypercontractile motor disorder [63, 64] However, it is unknown whether these motor abnormalities can be seen in asymptomatic individuals, or if there is significant overlap with other esophageal disorders such as eosinophilic esophagitis and GERD. It is well known that perceptive symptoms such as chest pain may persist even when motor abnormalities are abolished pharmacologically [31]. While manometric abnormalities may play a role in symptom generation, they may not be solely responsible for symptoms, as manometric changes observed during clinical trials have not been influenced by treatment nor by clinical response [65]. Therefore, the true value of manometry, including HRM, in determining the cause of esophageal pain, and correlation of unexplained esophageal symptoms with motor disorders needs further study.

Other Tests

The balloon distention test has been used to demonstrate esophageal hypersensitivity in clinical studies but is infrequently used in practice [17]. Acid perfusion (Bernstein test) may reproduce chest pain symptoms in acid triggered chest pain, when compared to placebo saline infusion, but is another test used in research studies alone [60]. Additional techniques used to evaluate NCCP in research settings include esophageal evoked potentials (EEP) [66] and multimodal stimulation involving chemical, thermal, electrical and mechanical stimuli [67]. Psychological testing has been used to demonstrate symptom association with panic/anxiety disorders. EEPs are stimulus-specific voltage changes that occur after an esophageal stimulus and are used as neural measures of esophageal afferent pathway sensitivity [66]. Relatively non-invasive and inexpensive, EEPs are recorded with silver-silver chloride surface electrodes applied to the scalp and correspond to voltage changes that occur post esophageal stimulation. Profiles of optimal stimulation and recoding parameters such as latency and amplitude, relative to sensory and pain thresholds have been developed that can be used to identify changes in the esophageal afferent pathway or central sensitization [54, 66]. EEPs have thus far been used in the research setting to assess esophageal hypersensitivity and identify distinct phenotypic sub-groups within the NCCP population [66]; i.e. those individuals with NCCP as a consequence of sensitized afferents versus those with abnormal secondary processing of normal stimulation or hypervigilance [54].

Given the frequent psychological co-morbidity in patients with NCCP [60], psychological modeling has been investigated as tool to help discriminate between patients who present with chest pain [68]. In addition, the Hospital Anxiety and Depression scale (HADS) has been used to detect affective disorders in individuals with NCCP [69]. Psychological evaluation of NCCP patients with a positive HADS demonstrates that Type D personality or the tendency to experience emotional distress is associated with anxiety and depression symptoms and with panic disorder [70]. Difficulty identifying or verbalizing emotions (alexithymia) and anxiety sensitivity are also thought to contribute and increase symptom severity in NCCP [71]. Further, health care utilization was associated with an increase in alexithymia and anxiety sensitivity among men and women, respectively [71] Absence of CAD, atypical quality of chest pain, female sex, a younger age, and a high level of self reported anxiety have also been shown to correlate with higher levels of panic disorder among persons with chest pain [72]. Further evaluation by a psychologist or psychiatrist is warranted in those unresponsive to standard medical therapy, especially if there is suspicion of an underlying psychological comorbidity [60].

Management

In many instances, the diagnostic evaluation detailed above will identify a specific cause of NCCP; allowing for therapy tailored to the etiology. Additional therapies that have been

Table 3.2 Management options for esophageal chest pain

Treatment of GERD	Acid suppression (PPI, H2RA)
	Reflux reducing agents (baclofen, baclofen analogues)
	Antireflux surgery in select cases
Treatment of hypermotility	Smooth muscle relaxants (calcium channel blockers, nitroglycerin)
	Botulinum toxin injection into esophageal body or LES
	LES disruption in rare instances (pneumatic dilation, myotomy)
Treatment of hypersensitivity	Sensory neuromodulators (typically low dose antidepressants)
	Analgesics (gabapentin, pregabalin; narcotics not recommended)
	Theophylline
	Topical agents containing antacids, viscous lidocaine
	Acupuncture
	Hypnosis
	Other novel targets (prostaglandin E2 receptor, vanilloid receptor-1, and ASIC receptor modulation)
Treatment of psychiatric comorbidity	Contemporary antidepressants, antianxiety agents
	Cognitive and behavioral therapy
	Psychotherapy
Treatment of other esophageal conditions	Eosinophilic esophagitis (topical steroids, elimination diets)
	Infectious esophagitis (specific antiviral or antifungal agents as appropriate)

GERD gastroesophageal reflux disease, *PPI* proton pump inhibitor, *H2RA* histamine-2 receptor antagonist, *LES* lower esophageal sphincter

evaluated and are being currently investigated are also outlined below and in Table 3.2.

Antireflux Therapy

Acid suppression with a PPI is typically the first therapeutic measure initiated even prior to investigation for patients with NCCP. The benefits of short (1–2 weeks) and long term (6–8 weeks) PPI therapy for NCCP have been demonstrated in numerous clinical trials for individuals with and without pathologic reflux [18]. In randomized controlled trials, response to PPI therapy for NCCP ranges from 71 to 95 % [8, 18]. Acid suppression may also have value in patients with acid sensitivity despite absence of pathologic elevation in esophageal acid exposure. Notably, in one prospective randomized control trial, 39 % of NCCP patients without evidence of GERD by ambulatory 24 h pH study had a response to treatment with omeprazole [8]. Therefore, when there is response to PPI therapy, the medication can be continued, but tapered to the lowest effective dose that offers

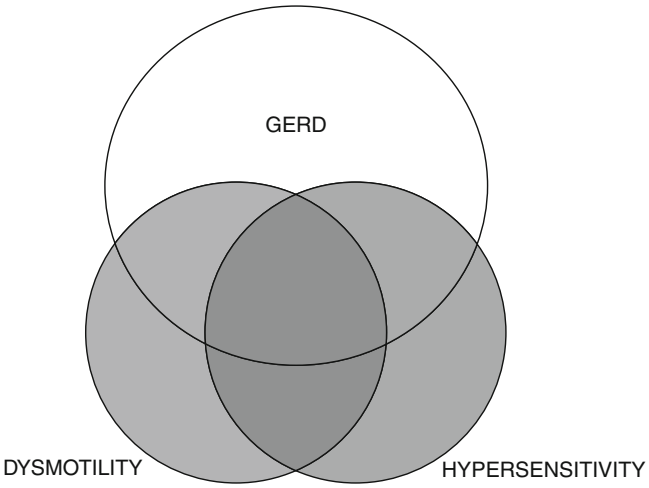

Fig. 3.4 Overlaps between gastroesophageal reflux disease, esophageal dysmotility and esophageal hypersensitivity in noncardiac chest pain. While each of these entities can exist independently, potential overlapping between two or all three can result in incomplete symptom resolution if only one entity is managed. Hypermotility is likely an epiphenomenon associated with hypersensitivity in many instances. Therefore, patients with esophageal hypersensitivity in the setting of gastroesophageal reflux disease, for instance, may have incomplete symptom relief unless both conditions are effectively treated

symptom relief. Other acid suppressive agents (e.g. H2 receptor antagonists, antacids) have not been studied in any detail in NCCP. As with typical GERD symptoms, non-pharmacologic measures (weight loss, avoidance of smoking and alcohol, avoiding lying down within 2–3 h of meals, sleeping with the head end of the bed elevated) may have value in conjunction with pharmacologic therapy.

Antireflux surgery is an option in patients with NCCP with well documented GERD, with abnormal esophageal acid exposure times. Patients with evidence of symptom-reflux correlation (especially positive SAP), and those who respond to PPI have a higher likelihood of symptom improvement after surgery.

Neuromodulators

If GERD is not evident or if it is thought to overlap with esophageal hypersensitivity (Fig. 3.4), the mainstay of therapy involves the use of pain modulators. Low dose antidepressants have been shown to be effective in reducing pain intensity and frequency of NCCP in patients with non GERD related NCCP [1, 73]. The tricyclic antidepressants (amitriptyline, nortriptyline, desipramine, imipramine) have been the most popular neuromodulators; trazodone and doxepin are related agents that share the benefits of tricyclic antidepressants. Tricyclic antidepressants may improve symptoms in as many as three quarters of patients with NCCP [73]. A long term follow-up study of NCCP successfully treated with

low-dose tricyclic antidpressants has demonstrated that 75 % continue to use these medications effectively [73]. Treatment with non mood altering doses of trazodone (100–150 mg/day) resulted in a reduction in ratings of chest pain [65]. Side effects (drowsiness, urinary retention, dryness of the mouth, constipation, arrhythmias, priapism with trazodone) may be limiting, and may trigger decrease in dosage or switch to an alternate less potent agent [18].

Other classes of antidepressants have also been studied in NCCP. Treatment with long term selective serotonin reuptake inhibitors (SSRI) was effective in acid sensitivity, when citalopram 20 mg was administered daily for 6 months [74]. Sertraline started at 50 mg/day and titrated to a maximum of 200 mg/day was also found to be effective in improving NCCP in a randomized control trial [75].

Although data is limited in NCCP, other classes of neuromodulators may also have benefit in NCCP. GABA agonists such as gabapentin and pregabalin have been used in functional and neuropathic pain with benefit [76]. Topical agents including 2 % lidocaine may provide temporary relief of acute painful episodes [76].

Smooth Muscle Relaxants

Studies investigating treatment for nonspecific motility disorders have been mostly uncontrolled and limited by small sample size [18]. Smooth muscle relaxants that reduce esophageal contraction amplitude (sublingual nitroglycerine, phosphodiesterase-5 inhibitors, and calcium channel blockers) are frequently used, although their efficacy has not been conclusively demonstrated in controlled trials [18]. Unfortunately, decreasing contraction amplitude with muscle relaxants has not been demonstrated to reduce hyperalgesia inpatients with spastic motor disorders.

Botulinum Toxin Therapy

Botulinum toxin injected into the LES or the esophageal body has been studied in treatment of achalasia and other disorders with errors of LES relaxation. Botulinum toxin interferes with LES tone by irreversibly binding to cholinergic neurons. Although rarely used as a primary mode of therapy, botulinum injection is beneficial in achalasia patients as a bridge to more definitive therapy or as an alternative in those patients who are unable to undergo pneumatic dilation or Heller myotomy [77–79] There is some evidence to suggest that pain may improve if related to esophageal distension from incomplete bolus clearance. However, systematic improvement of esophageal pain has not been demonstrated [18]. In fact, a pain predominant presentation may be a marker of poor symptom relief with botulinum toxin injection in spastic motor disorders [78]. Response to botulinum toxin injection in individuals with incomplete LES relaxation lasted an average of 12.8 months; however, chest pain predominant symptoms, along with younger age and spastic features, predicted less durable and sub-optimal, short-term response (<6 mo) response [79]. In these individuals, consideration of alternative therapies such as neuromodulators, as discussed above, should be encouraged.

Other Approaches

Theophylline, an adenosine receptor antagonist, provided relief from functional chest pain in an open label trial [18]. After theophylline administration, patients with esophageal hypersensitivity to balloon distension increased their thresholds for discomfort and pain with graded balloon distention. Further, continuation of oral theophylline for 3 months resulted in sustained improvement in symptoms [80]. These findings have been subsequently confirmed in a randomized-placebo controlled trial [81]. However, the use of theophylline is limited by its side effect profile and toxicity. These studies demonstrate that the adenosine receptor could be a future potential target in the therapeutic armamentarium for NCCP [18, 82].

Prostaglandin E2 is a mediator of both central and peripheral sensitization and the prostaglandin E2 receptor (EP-1) has been implicated in esophageal acid-induced visceral hypersensitivity [53]. In a human model of esophageal secondary hyperalgesia, EP-1 antagonism was shown to diminish the pain threshold in the upper esophagus after acid infusion in the lower esophagus [53]. VR1 and ASIC receptor modulation are also potential novel targets for therapy in patients with hypersensitive esophagus [51].

Nonpharmacologic Approaches

Additional interventions including hypnotherapy, biofeedback, and transcutaneous nerve stimulation have been evaluated with some benefit, although additional studies are needed [18]. Finally, acupuncture can also be attempted in refractory situations [83, 84].

Prognosis

Identification of a specific etiology for NCCP improves the likelihood of symptom improvement, especially if NCCP is linked to GERD. Psychologic comorbidities, when prominent, predict continuing patient anxiety, distrust in the diagnosis, and continuing health care utilization.

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Part II

Epidemiology and Pathogenesis

Epidemiology of Cardiac Syndrome X and Microvascular Angina

4

Rosanna Tavella and Guy D. Eslick

Abstract

Chest pain and normal coronary angiography is seen in up 30 % of patients undergoing the investigation. Despite its notable prevalence, the epidemiology of the condition remains poorly documented. Since the turn of the twentieth century, researchers have been baffled by "unmistakable" angina in the absence of coronary artery disease. Curiosity as to the cardiac aetiology of this chest pain became the focus of several key studies investigating the clinical and haemodynamic features of patients with normal coronary angiography. From these early findings, the cardinal features of three specific disorders associated with normal coronary angiography were established – Cardiac Syndrome X, Microvascular Angina and more recently, the Coronary Slow Flow Phenomenon. Although ambiguity in the literature exists, it is likely that an 'ischemic' mechanism for the chest pain in these patients is explained by coronary microvascular dysfunction. It also now understood that despite the absence of significant coronary artery disease, the outcomes of patients are not entirely favourable, with studies suggesting a frequent persistence of chest pain, and increased risk of cardiac events, particularly among women. This chapter will review the available epidemiological data on patients with chest pain and normal coronary angiography, and the clinical features and possible aetiological explanations for the specific coronary microvascular disorders.

Keywords

Normal coronary angiography • Prinzmetal's angina • Coronary heart disease • Myocardial ischemia • Cardiac syndrome X • Microvascular angina • Coronary slow flow pheonemon

Abbreviations

ACS	Acute coronary syndrome
CAD	Coronary artery disease
CHD	Coronary heart disease
CSFP	Coronary slow flow phenomenon
GUSTO	Global utilization of streptokinase and t-PA for occluded coronary arteries
MI	Myocardial infarction
NCA	Normal coronary angiography
TIMI	Thrombosis in myocardial infarction
WISE	Women's ischemia syndrome evaluation

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Definitions

Aetiology
The demonstration of the causes of disease.

Normal coronary angiography
Smooth epicardial coronary arteries or non-obstructive lesions (stenosis <50 %).

Prinzmetal's angina (variant angina)
Angina syndrome consisting of chest pain at rest resulting from myocardial ischemia caused by large vessel coronary vasospasm.

Prevalence
The number of people with the disorder at any give time.

Incidence
The number of new episodes of a disease over a period of time.

Coronary heart disease
A group of diseases involving the coronary vasculature resulting in myocardial ischemia due to impaired coronary blood flow. Coronary heart disease includes coronary atherosclerosis coronary artery spasm and/or coronary microvascular dysfunction.

Myocardial ischemia
A pathological state where myocardial tissues are compromised due to inadequate blood flow.

Cardiac syndrome X
Refers to patients with (i) exertional angina (ii) transistent ST segment depression during exercise stress testing, (iii) angiographically normal epicardial arteries and (iv) absence of other known cardiac causes of chest pain (such as coronary spasm, left ventricular hypertrophy or cardiomyopathy).

Microvascular angina
A group of patients with (i) chest pain (ii) abnormal coronary blood flow response to provocative vasomotor stimuli and (iii) angiographically normal epicardial arteries.

Coronary slow flow pheonemon
An angiographic finding characterised by delayed opacification of the distal vasculature despite the absence of obstructive epicardial coronary artery disease. The criteria that constitutes a diagnosis of the CSFP varies between researches. Some studies employ a Thrombolysis in Myocardial Infarction (TIMI) frame count of greater than 22 frames while others define the observation as three or more beats to opacify the vessel.

Epidemiological Considerations

Epidemiology, plainly translated from Greek, means "*the study of people*". Certainly, the term epidemiology refers to the study of diseases in populations, and specifically involves describing disease patterns, and identifying causes of diseases (aetiology), in order to provide data for disease prevention, evaluation, and management. Patients with chest pain and normal coronary angiography (NCA) are frequently labelled as having "syndrome X", reflecting the obscurity associated with this condition. This chapter will endeavour to provide an overview of descriptions and causations regarding this condition, and specifically, on the recognised coronary microvascular disorders.

Considering the wide spectrum of information that epidemiology covers, this topic has not been comprehensively assessed in the setting of chest pain and NCA. In particular, prevalence and incidence data is not frequently available, in contrast to coronary heart disease (CHD) statistics, which are readily accessible. Although hospital-based cohort studies have investigated the characteristics and cardiac outcomes of patients with chest pain and NCA in general, epidemiological data on specific coronary microvascular disorders is sparse and is mostly limited to small research studies drawn from single centres. Other epidemiological data available are affected by the characterisation of study patients, for example, the extent to which they are investigated. Some studies have investigated the epidemiology of chest pain of "unknown" origin (i.e. populations drawn without information on coronary angiogram findings). Although the constitution of these samples is varied, useful information is still attainable. However, it should be noted that substantial ambiguity exists, and that further research is needed to gain a comprehensive epidemiologic picture of chest pain and NCA.

Defining Normal Coronary Angiography

Normal coronary angiography is defined as no visible disease, or non-obstructive atherosclerotic lesions (stenosis < 50 % judged visually). The coronary angiogram provides a 'snapshot' of the coronary arterial lumen, and so when a coronary angiogram is labelled *normal*, in actual fact, it refers to a normal coronary lumen. A patient with NCA may have diffuse disease or localised lesions within the media of the coronary artery not identified by the coronary angiogram. Nonetheless, generally, the angiogram findings provide adequate information regarding the status of coronary blood flow. Thus, the coronary angiography has acquired predominance in the management of CHD. This has prompted focus on epicardial coronary artery disease (CAD), with little attention on the coronary microvessels. However it should be noted that the epicardial vessels usually contribute to less than 10 % of coronary vascular resistance, in contrast to the coronary microvessels, which are responsible for more than 70 % of the coronary resistance[1] . During the later half the twentieth century, as chest pain with NCA become recognised and investigated, important insights regarding the coronary microcirculation evolved.

Historical Evolution of 'Syndrome X'

Since the introduction of coronary angiography, it became clear that some patients with classic angina symptoms showed no evidence of significant coronary artery disease. This syndrome was first described in 1910 by William

Table 4.1 Landmark research findings in the study of 'syndrome X'

Study	*N*	Female	Patient features in addition to NCA
Likoff et al. 1967 [3]	15	15	Exertional chest pain, abnormal ECG at rest
Key findings: Normal hemodynamic response to exertion			
Arbogast and Bourassa 1973 [4]	10	6 F	Exertional chest oain
Key findings: ECG and transmyocardial lactate evidence of myocardial ischemia during atrial pacing			
Kemp 1973 [5]			
Introduced the term '***syndrome X***' to define patients with exertional chest pain and NCA			
Opherk et al. 1981 [6]	21	6	Exertional chest pain, few ST segment changes
Key findings: All exhibited abnormal coronary blood flow response to vasomotor stimuli Some exhibited metabolic evidence of myocardial ischemia			
Cannon and Epstein 1988 [7]			
Introduced the term '***microvascular angina***' *to describe patients with evidence of dynamic microvascular dysfunction*			
Tambe et al. 1972 [8]	6		Rest pain in one third, abnormal resting ECG
Key findings: Strikingly slow passage of contrast medium through the coronary arterial tree			
Beltrame et al. 2002 [9]			
Introduced the term '***coronary slow flow phenomenon***' *to describe delayed opacification of distal vasculature despite NCA*			

Osler [2], who described this form of chest pain as "the chief difficultly" when diagnosing "true" angina pectoris. Coinciding with the more widespread use of coronary angiography, over the last 40 years research groups have investigated the mechanisms behind the "angina-like" chest pain. Several key studies have evolved the understanding of chest pain and NCA by examining the clinical and hemodynamic features of small groups of patients with chest pain and NCA. These studies generally indicated a reduced coronary flow reserve in patients however, not all patients demonstrated definitive evidence for myocardial ischemia. The clinical presentation of patients also differed, and although this may have just reflected the heterogeneous nature of the syndrome, it became clear that certain condition-specific characteristics had been recognised. Consequently, these conditions were labelled as *Syndrome X*, *Microvascular Angina*, and more recently, the *Coronary Slow Flow Phenomenon*. Detailed below are these key landmark findings in the studies of chest pain and NCA (Table 4.1)

Prevalence and Incidence Data

Chest Pain and Normal Coronary Angiography

Population based studies on the epidemiology and thus prevalence of chest pain and NCA are infrequent, and most studies are hospital-based. Furthermore, data on the incidence of the condition is rarely, if not ever, reported. Most likely, epidemiological statistics are not frequently available since there is lack of routine documentation of NCA in hospital administrative registries and thus a global lack of routine surveillance. Without true incidence data available to establish background population rates, it is difficult to assess the actual burden that this condition imposes. Prevalence data is typically generated by tertiary referral centres, and with this, the resulting problems of referral bias, uncertainty of denominator population and the inclusion of only small samples should be noted.

Hospital-based studies have typically drawn populations from consecutive patients undergoing cardiac catheterization. These studies have generally revealed on average that around 20 % (range 6–31 %) of patients undergoing angiography for the investigation of angina-like chest pain show normal epicardial coronary arteries [10–13]. In regards to the specific coronary microvascular disorders, under-diagnosis and thus under-reporting make it difficult to evaluate the actual prevalence of these conditions. Furthermore, many studies in the medical literature consist of case reports and case series data by clinicians, with an emphasis on the clinical rather the epidemiological descriptions. These conditions will be further discussed later in the chapter.

Chest Pain of Unknown Origin

Other population-based studies that have investigated chest pain of "unknown" origin have not classified patients on the basis of coronary angiogram findings. These studies reflect the heterogeneous nature of the disorder since different criteria have been used to describe the condition. Thus, there is a considerable variation in prevalence of this chest pain. Geographically, there also seems to be variation in the epidemiology of the condition. As detailed in Fig. 4.1, low prevalence rates have been reported in Hong Kong [14] (14 %), whereas, a high prevalence has been reported in Australia (33 %) [15].

Although population based epidemiological studies have differed substantially in terms of methodology, it should be

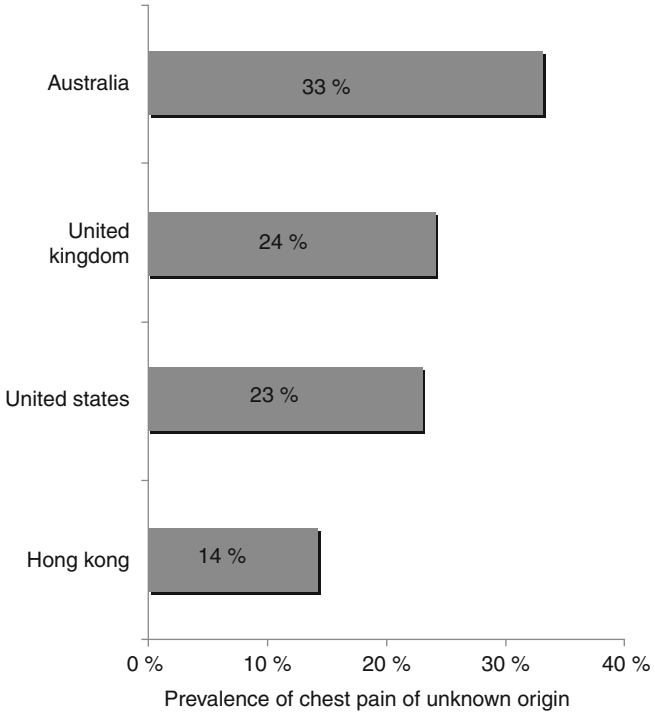

Fig. 4.1 Geographical variation in the prevalence of chest pain of unknown origin. Note: Study definitions for chest pain of unknown origin. Australia [15]: (1) Chest pain that was not angina according to the rose angina questionnaire criteria, and (2) absence of ischemic heart disease as diagnosed by a doctor. Population, n = 1,000, randomly selected from the community; United Kingdom [16]: (1) Non-exertional chest pain, (2) history of other prolonged chest severe pain and (3) absence of angina or myocardial infarction. Population, n = 7,735, randomly selected from general practice, 100 % male; United States [17]: (1) Presence of chest pain but no self-reported history of cardiac disease. Population, n = 1,511, selected randomly from the community; Hong Kong [14]: (1) Non exertional chest pain according to the Rose Angina Questionnaire and (2) absence of ischemic heart disease as diagnosed by a doctor. Population, n = 2,209, selected randomly from the community

noted that most studies reveal several consistent findings: (a) a fairly significant prevalence of the condition (identified by coronary angiograms or other means); (b) decreasing prevalence with increasing age; and (c) an increased prevalence among females (Fig. 4.2 and Table 4.2).

Natural History of Chest Pain and Normal Coronary Angiography

Up to one third of patients undergoing coronary angiography for the evaluation of chest pain have NCA. However, the natural history of patients with significant CAD is well reported, the course of patients with NCA requires further exploration. In 1990, Chambers and Bass [23] presented a thorough review of the natural history of patients with chest pain and NCA, however, since then little prospective work

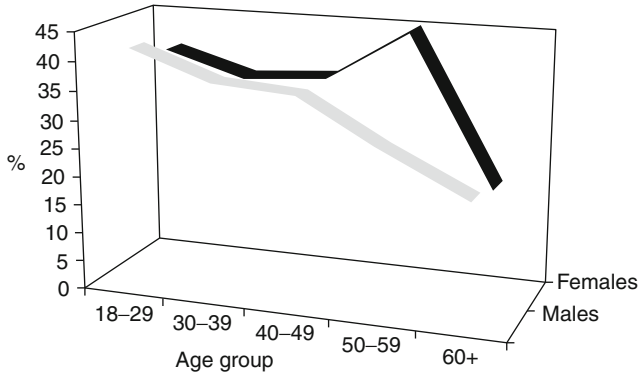

Fig. 4.2 Population prevalence of chest pain of unknown origin by age and gender (Reprinted from Eslick [18]. With permission from Elsevier)

has been undertaken. Although long-term cohort studies have assessed mortality, the clinical characteristics and the results of non-invasive investigations also have not adequately described. This section will review current understanding of the clinical features and cardiac events associated with chest pain and NCA.

Clinical Features

Hospital based populations drawn from patients undergoing catheterisation typically show that the average age is in the late forties, similar to those with significant CAD. However, the proportion of males is smaller, with over 50 % commonly female. Of note, this female predominance is consistent irrespective of the definition used for sample inclusion. In contrast, the prevalence of cardiovascular risk factors has been shown to be similar to patients with CAD. One half of patients with NCA display ST or T wave changes and 25 % have ST segment depression on exercise. Interestingly, the episodes of ST segment depression are often indistinguishable from those observed in patients with CAD, particularly among Cardiac Syndrome X patients.

Chest Pain Characteristics

The description of chest pain is often simplified, particularly in research settings, as “typical” or “atypical” of cardiac origin. Due to the wide variation in interpretation and the subjective nature of descriptions, there is few objective data regarding chest pain characteristics in patients with NCA. Reports on the prevalence of pain that is typical of cardiac origin have ranged from 9 % [24] to over 50 % [25]. The uncertainty in the definitions, (i.e. how to define chest pain reproducible to exertion), contribute to the dissimilarities

Table 4.2 Prevalence of normal coronary angiography in females compared to males

	n/(%)		
	Females	Males	p
GUSTO [19]	343/1,768 (19 %)	394/4,638 (8 %)	<0.001
TIMI 18 [20]	95/555 (17 %)	99/1,091 (9 %)	<0.001
Unstable angina [19]	252/826 (31 %)	220/1,580 (14 %)	<0.001
TIMI IIIa [21]	30/113 (27 %)	27/278 (8 %)	<0.001
MI without ST-segment elevation [19]	41/450 (9 %)	55/1,299 (4 %)	0.001
MI with ST segment elevation [19]	50/492 (10 %)	119/1,759 (7 %)	0.02

Reprinted from Bugiardini, and Bairey Merz [22] with permission from American Medical Association
Abbreviations: GUSTO global utilization of streptokinase and t-PA for occluded coronary arteries, *TIMI* thrombosis in myocardial infarction, *MI* myocardial infarction

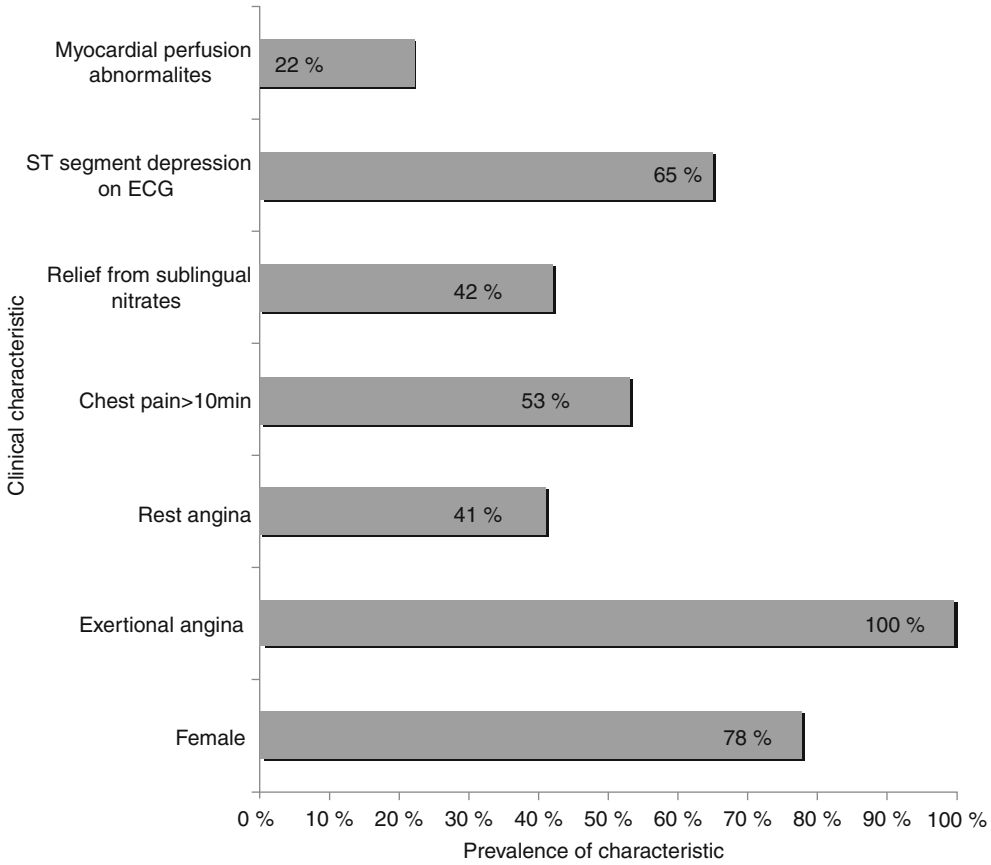

Fig. 4.3 Clinical characteristics of patients with normal coronary angiography. n = 99, 78 females, all patients underwent cardiac catheterisation, exercise stress testing, ambulatory electrocardiography monitoring and echocardiography assessment. *ECG* electrocardiogram (Based on data from Kaski [26])

observed in these studies. Nonetheless, generally around 25 % of patients report pain typical of cardiac origin. It is thus well recognised that chest pain in patients with NCA includes many atypical features [10]. This is well described by Kaski [26], who discusses patients with NCA referred to a specialist pain clinic. The majority of patients reported pain that was typical for angina, but several atypical features were noted, including (1) chest pain at rest; (2) prolonged duration of pain; and (3) a poor response to sublingual nitrates (Fig. 4.3).

Cardiac Events

Long-term hospital-based cohort studies have demonstrated favourable prognosis in patients with chest pain and NCA, with the incidence of myocardial infarction or death almost 0 %. These studies show that myocardial infarction occurs in at most 1 % of patients, and death in 0.6 %, for follow-up periods for as long as 10 years [23]. Although these studies provide reassurance with regards to life expectancy, whether, a subgroup with poorer prognosis may have been

Table 4.3 Functional disability in patients with chest pain and NCA

Study	n	Hospital readmission (%)	Debilitated (%)	Physician consult (%)	Repeat coronary angiogram (%)	Ongoing cardiac medications (%)
Kemp, 1973 [10]	200	10				40
Bermiller, 1973 [31]	37				19	75
Day, 1976 [25]	45	5				25
Lavey, 1979 [32]	45	27	77	82	9	56
Ockene, 1980 [33]	57	15	51	71		25
Isner, 1981 [28]	121	18			3	64
Faxon, 1982 [34]	52	20	32			61
Bass, 1983 [35]	46		54			48
Papanicolaou, 1986 [13]	1,491	13	50			27
Lantinga, 1988 [36]	24		42	63		79

Reprinted from Chambers and Bass [23] with permission from Elsevier

concealed in these large cohorts remained largely unknown for several years.

In 2005, a systematic review revealed that the prognosis of patients with NCA may not be as benign as previously documented, in particular among those with unstable symptoms. This data indicate that patients with evidence of myocardial ischemia and NCA show a 2 % risk of death or myocardial infarction at 30-days follow-up [22]. Females, in particular, have a relatively poor prognosis compared to females with NCA and no evidence of myocardial ischemia. Data from the Women's Ischemic Syndrome Evaluation (WISE) [27] study indicate that this includes an increased risk for cardiovascular disease including sudden death, myocardial infarction and stroke.

Functional Outcomes

Morbidity poses a significant problem for patients with NCA, as many remain symptomatic. Around 75 % of patients continue to report persistent chest pain causing limitations in daily life activities. Episodes of persistent chest pain have been found to persist for as long as 4 years in many patients with NCA [28]. In addition, a significant proportion of individuals are unemployed due to the significant disability that persistent chest pain can cause. Thus, it is not surprising that patients continue to seek clinical advice, and this is despite some reports of anti-anginal treatment with multiple drug combinations [26, 29] (Table 4.3). Re-hospitalization for chest pain is also not infrequent, occurring in an estimated 20–50 % of patients. In addition, to the impact on individual functioning, the persistence of chest pain also increases the risk for adverse events. Among patients with NCA and coronary microvascular dysfunction, persistent chest pain is associated with increased risk of cardiovascular events, including myocardial infarction, heart failure and even sudden cardiac death [30].

Possible Causes of Chest Pain with Normal Coronary Angiography

Pain is a sensory and emotional experience, and since almost any structure in the chest may cause chest pain, there are many causes of chest pain to be considered in the setting of NCA. Accordingly, although patients with chest pain and NCA are often referred to as a distinct clinical entity, they undoubtedly represent a heterogeneous group of patients. When evaluating these patients, the first consideration is whether the pain is due to a cardiac but non-coronary aetiology, or secondly a non-cardiac cause (Table 4.4). In a small proportion of patients undergoing coronary angiography, *Printzmetal's* angina, identified by provocative spasm testing, may also explain chest pain in the absence of obstructive CAD.

Delineating between cardiac and non-cardiac causes of chest pain is difficult, as is differentiating between the various non-cardiac causes. Non-coronary conditions, such as cardiomyopathy or pericarditis, are usually obvious from patient history, clinical examination and routine cardiac investigations. It has been suggested that in up to 50 % of patients presenting with chest pain prompting medical attention, non-cardiac causes are implicated [38] and the chest pain may be attributed to a variety of disorders, including oesophageal abnormalities [39], musculoskeletal pain [40] and psychiatric disorders [41]. Several studies have attempted to determine the cause of chest pain, and a variety of approaches have been adopted to ascertain a diagnosis.

In Denmark, among patients who were admitted to hospital with acute chest pain but without myocardial infarction, a non-invasive screening programme revealed that 42 % of patients had gastroesophageal disease, 31 % showed ischemic heart disease, and 28 % has chest wall syndromes [42]. In a study by Husser et al. [43], 40 consecutive patients with NCA and no evidence of coronary spasm or syndrome X, underwent screening assessment for gastrointestinal, musculoskeletal and psychiatric causes of their chest pain. Although

Table 4.4 Differential diagnosis of chest pain and normal coronary angiography

Cardiac aetiologies	
Coronary causes	Variant angina (Prinzmetal angina)
	Syndrome X
	Microvascular angina
	Coronary slow flow phenomenon
Non-coronary causes	Pericarditis, myocarditis
	Cardiomyopathy
	Mitral valveprolapse
Non-cardiac aetiologies	
Respiratory system	Pneumothorax
	Pneumonia
	Pulmonary embolism
	Acute asthma
Gastrointestinal system	Oesophagitis, oesophageal spasm
	Gastroesophageal reflux
	Hiatus hernia
	Biliary colic, pancreatitis
Other causes	Chest wall syndromes, costochondritis (Tietze's syndrome)
	Psychogenic, panic attacks
	Munchausen syndrome

Based on data from Beltrame [37]

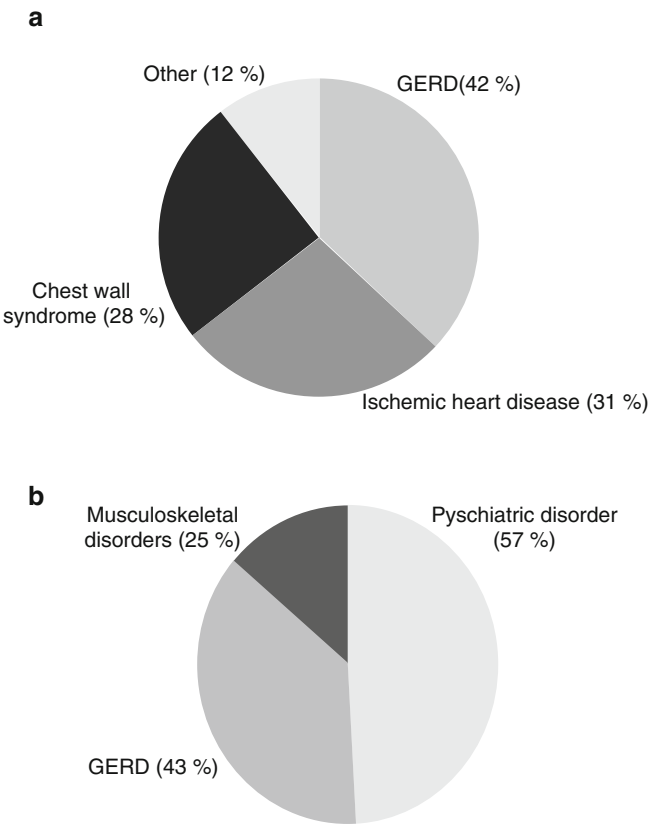

Fig. 4.4 (**a**) Differential diagnoses of patients admitted to hospital with acute chest pain n = 204. Other includes perciarditis, pneuomina, pulmonary embolism, lung cancer, aortic aneurysm, aortic stenosis, and herpes zoster infection. *GERD* gastro-esophageal reflux disease (Adpated from Fruergaard et al. [42] with permission from Oxford University Press) (**b**) Differential diagnoses of patients with normal coronary angiography n = 40. *GERD* gastroesophageal reflux disease (Based on data from Husser [43])

the sample size was small, 57 % had DSM-IV-R criteria for psychiatric disorders, 43 % had evidence of gastroesophageal reflux disease (i.e. responded to high dose proton pump inhibitor), and 16 % had evidence of a musculoskeletal cause on clinical examination (Fig. 4.4). It is important to note that regardless of the methodology employed to assess conditions, substantial overlap between the various causes is commonly reported.

Cardiac Causes

Although there are several potential causes of chest pain in patients with NCA who show no evidence of the above non-coronary causes of chest pain, the clinical suspicion has remained that these patients experience 'true' angina – the symptomatic manifestation of myocardial ischemia – in the absence of large vessel CAD. This is the group of patients frequently referred to as 'syndrome X'. A number of aetiological mechanisms for ischemia in the presence of normal coronary angiography have been proposed, including coronary small vessel disease [44].

Historically, these 'syndrome X' patients have been characterised by various approaches, as described in Section "Epidemiological Considerations". Specifically, these patients may be identified by the presence of 'ischemic' ST segment changes, abnormal coronary blood flow responses, or the delayed passage of contrast observed during coronary angiography (Table 4.1). Due to the limitations of coronary angiography, coronary microvascular disease is not readily recognised and diagnosed. Thus, the proportion of patients with chest pain patients and NCA that is explained by microvascular disease is undetermined.

In general, the prevalence of patients with typical exertional chest pain, positive exercise stress test and NCA is approximately 20 % of populations undergoing coronary angiography.

Adding to this, some studies suggest that coronary microvascular dysfunction is present in approximately 50 % of women with chest pain and NCA [45]. These patients tend to be younger, with the average age in the fifth decade of her life. It is suggested that the slow flow of dye in large coronary vessels is not an infrequent finding in patients during routine coronary angiography. In Europe, Mangieri et al. reports that this observation is prevalent in 7 % of patients with presenting with chest pain but normal coronary arteries [46]. Data from Australia report that the coronary slow flow phenomenon (CSFP) is seen in 1 % of the total diagnostic angiograms, based upon reports from the cardiologist performing the procedure [9]. More recent data from Australia

suggest the CSFP is prevalent in 3 % of patients with NCA [47]. Australian findings are based upon the definition of three or more beats to opacity the left anterior descending artery.

Specific Coronary Microvascular Disorders

Abnormal vasomotor tone in the coronary microvessels has been implicated in patients with angina-like chest pain and NCA. Pathophysiologically, this may be explained by attenuated augmentation of coronary blood flow in response to increased myocardial oxygen demand [6, 48]. This may arise from excessive vasoconstriction or impaired compensatory vasodilatory mechanisms. In particular, endothelial dysfunction, with reduced bioavailability of endogenous nitric oxide and increased plasma levels of endothelin-1 (ET-1), may explain the abnormal behaviour of the coronary microvessels.

As outlined above, generally researchers have identified these patients on the basis of several approaches. However, coronary microvascular disorders are not readily identifiable and typically require specialised investigations that are usually performed in a research context. This section will discuss the clinical and pathophysiologic aspects of these coronary microvascular disorders.

Cardiac Syndrome X (Syndrome X)

Cardiac Syndrome X was first described in 1973 in relation to a landmark study by Arbogast and Bourassa [4]. This study evaluated transmyocardial lactate production in patients with exertional angina, a positive exercise test and either obstructive CAD (Group C) or no CAD (Group X) on angiography. Metabolic evidence of myocardial ischemia was demonstrated in both the Group C and X patients despite normal angiography in the later group. In the accompanying editorial by Kemp [10], he referred to the puzzling 'Group X' patients as 'Syndrome X'. This disorder should however, be distinguished from metabolic syndrome X, a condition characterised by insulin resistance, hyperglycaemia, hypertension, low high density lipoprotein cholesterol and raised triglycerides [49].

Syndrome X may be a generic term to describe patients with chest pain and NCA [50], and thus may be confused with large vessel coronary spasm. However, in its purest definition, Syndrome X patients are defined by certain characteristics (Table 4.5). In keeping with these specific criteria, the features of this disorder are summarised below. In regards to pathophysiology, numerous mechanisms have been proposed. Given the high prevalence of postmenopausal women in the Syndrome X population (approximately 70 %), estrogen deficiency has been suggested as a pathogenic agent acting via endothelium-dependent and endothelium-independent mechanisms. Despite the lack of metabolic evidence of myocardial ischemia in patients, support for an 'ischemic hypothesis' includes the presence of surrogate markers of ischemia, such as sub-endocardial perfusion defects on magnetic resonance imaging [51] and reduction of high-energy phosphates on nuclear magnetic spectroscopy [52]. However, there is also evidence for a 'non-ischemic' hypothesis, including the demonstration of altered pain perception in these patients. It is likely that several pathways are important in the pathogenesis of Syndrome X.

Table 4.5 Cardiac syndrome X: definition and clinical features

Defining criteria for syndrome X
1. Exertional angina
2. ST segment depression on exercise testing
3. Absence of obstructive CAD on angiography
4. Absence of other cardiac disorders (coronary spasm, left ventricular hypertrophy, systemic hypertension, and valvular heart disease).
Clinical characteristics
Most often female
Typically present with prolonged episodes of exertional angina
Report significant disability due to on-going chest pain symptoms
Seldom experience myocardial infarction or cardiac death
Reported pathophysiological abnormalities
Myocardial ischemia
Abnormal coronary blood flow
Coronary microvascular abnormalities
Abnormal cardiac autonomic regulation
Endothelial dysfunction
Abnormal platelet aggregation
Abnormal pain perception
Metabolic and hormonal abnormalities
Systemic vascular abnormalities
Management
Beta-blockers effective in relieving chest pain
Nitrates are of limited benefit
Preliminary evidence showing a benefit with other therapies including:
Enalapril, pravastatin, simvastatin, nicroandil
Estradiol patches in women
Impramine, transcutaneous nerve stimulators and spinal cord stimulation

Based on data from Beltrame [37]

Microvascular Angina

Initial studies characterising microvascular angina described patients with chest pain who showed reduced coronary blood flow response to atrial pacing despite the absence of large vessel disease [53]. A sub-group of patients also showed metabolic evidence of myocardial ischemia. Later studies documented similar results showing reduced vasodilator response to dipyridamole, and this supported an impaired dynamic response by the coronary resistance vessels to vasomotor stimuli [54]. Cannon and Epstein suggested that this

Table 4.6 Microvascular angina: clinical features

Clinical characteristics
Unlike syndrome X
Infrequent display of ST changes on exercise stress testing
Exertional angina is less commonly observed
Similar to syndrome X
Females most often affected
Resting left ventricular ejection fraction is usually normal
Among patients with left bundle branch block, a fall in ejection fraction with exercise is not uncommon
Pathophysiology
Few data in this condition, investigations have focused on:
Generalised smooth muscle dysfunction
Abnormal esophageal motility
Bronchial hyper-responsiveness to methcholine
Impaired forearm microvascular vasodilatory responses
Increased sensitivity to cardiac and cutaneous nociceptive stimuli
Association with anxiety states
Management
Calcium channel blockers may be of benefit
Few therapeutic studies undertaken

Table 4.7 Coronary slow flow phenomenon: clinical features

Clinical characteristics
Unlike Syndrome X and microvascular angina
More often male
Present with rest pain
Coronary angiography typically performed following ACS admission
Risk of subsequent MI is low
Re-admission for severe chest pain in one third of patients
Recurrent chest pain in 80 %
Pathophysiology
Involves abnormalities of the coronary microvasculature
Elevated coronary vascular resistance
Variable response to vasomotor stimuli
Ventricular biopsy suggest presence of structural abnormalities
Management
Dipyrdiamole may be beneficial
Mibrefradil shown to be effective
Few therapeutic studies undertaken

Abbreviations: ACS acute coronary sydnrome, *MI* myocardial infarction

could be explained by abnormal prearterioal vasodilation in the coronary microcirculation, and referred to these patients as having 'microvascular angina'. This term is generally reserved for patients where coronary microvascular dysfunction is evidenced by abnormal coronary flow response to vasomotor stimuli. The clinical features of the disorder are summarised below (Table 4.6).

Coronary Slow Flow Phenomenon

The slow progression of dye down the coronary arteries in the absence of obstructive CAD was described by Tambe and colleagues in 1972 [8]. Recently, the Coronary Slow Flow Phenomenon (CSFP) has been defined as the angiographic observation of delayed opacification of epicardial vessels in patients with normal angiography [9]. Serial angiographic studies have demonstrated that the CSFP is persistent observation, although the severity of flow impairment may vary. Although in the literature there is disagreement on the diagnostic criteria to identify the presence of 'slow flow', the clinical features of the condition are well described (Table 4.7).

Conclusion

The understanding of patients with chest pain and normal coronary has undergone a prominent evolution since the condition was first noted at the turn of the twentieth century. Patients have historically been reassured the absence of heart disease and a benign prognosis. Contemporary data now call for a re-assessment of the outcomes associated with NCA. Many patients have persistence of symptoms, are re-hospitalised for chest pain and undergo a notable risk of cardiac events.

The specific disorders associated with NCA (Syndrome X, Microvascular Angina and CSFP) are well-characterised in terms of distinguishing clinical features. However, uncertainty still exists with regards to the diagnostic criteria and pathophysiological abnormalities. Since specialised investigations are typically required, there is a lack of large-scale epidemiological data leaving many questions unanswered. For example, the number of NCA patients with evidence of coronary microvascular disease and how this varies by country or region is not known, nor the number of new cases being diagnosed. Finally, uncertainty about the mechanisms of the symptoms makes management difficult. Due to a lack of epidemiological descriptions, the true impact of the NCA is likely underestimated.

Considering the functional impact that we are aware of, it is clear that additional large-scale clinical therapeutic studies are needed to determine effectiveness of treatment on chest pain symptoms. Future studies should also determine the value of less invasive methods of diagnosis. This may aid the feasibility of the fulfilling the need for urgent prospective epidemiological data.

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Healthcare Costs of Angina in Women

5

Leslee J. Shaw

Abstract

This chapter examines the data on costs of cardiovascular care for women and highlights the importance of chest pain and the burden of persistent angina as driving higher costs of care. For women, a consistent body of evidence reports that women (generally) utilize more healthcare resources than men. A large component of the costs of care includes those for ongoing symptoms including the burden of angina. Within the NIH-NHLBI Women's Ischemia Syndrome Evaluation (WISE) study, costs of care were estimated for symptomatic women with and without obstructive coronary artery disease. Even women with none to mild non-obstructive coronary artery disease had predicted lifetime costs of cardiovascular care of approximately 750,000 US dollars and this amount increased for women with coronary artery disease. The economic burden of angina, even in the setting of nonobstructive CAD, is costly and can result in high lifetime costs of care. Physicians should consider the intensity of resources required to adequately care for women with angina including the financial burden of family household resources.

Keywords

Economics • Women • Drug treatment • Angina

Trends in Healthcare Costs

Of the most expensive healthcare conditions, ischemic heart disease (IHD) ranks as number one [1]. In a recent evaluation of US Medicare data, IHD encompassed 14 % of all expenditures [2]. There has been a rapid escalation in healthcare costs, in particular those related to cardiovascular disease (CVD). For example, over the last 15 years, CVD surgical procedures increased 33 % to more than 7.2 million procedures annually. In 2007, the total expenditures related to CVD approached 450 billion US dollars (USD).

For IHD, the total expenditures may be broken down into estimated costs for medical therapy, procedures, and outpatient visits as well as home health and other related services, such as rehabilitation or for a skilled nursing facility. For all of the common procedures, utilization patterns have increased dramatically over the past decade including nearly 11 % annual increase in the use of stress tests and 12 % per annum increase in the use of cardiac catheterization [3].

Resource Consumption Patterns

Factors that generally contribute to high cost healthcare include an in-hospital death or for a stroke, end-stage care for heart failure; all of which can encumber a substantial proportion of lifetime costs of care. Figure 5.1 detail common clinical and other factors contributing to healthcare resource consumption. The vast majority of lifetime expenditures, estimates of one-third to one-half, are encumbered in adult middle-aged to elderly patients [4, 5]. Women generally have higher lifetime costs and are considered "high end" resource users within the healthcare system. For example, for diabetic

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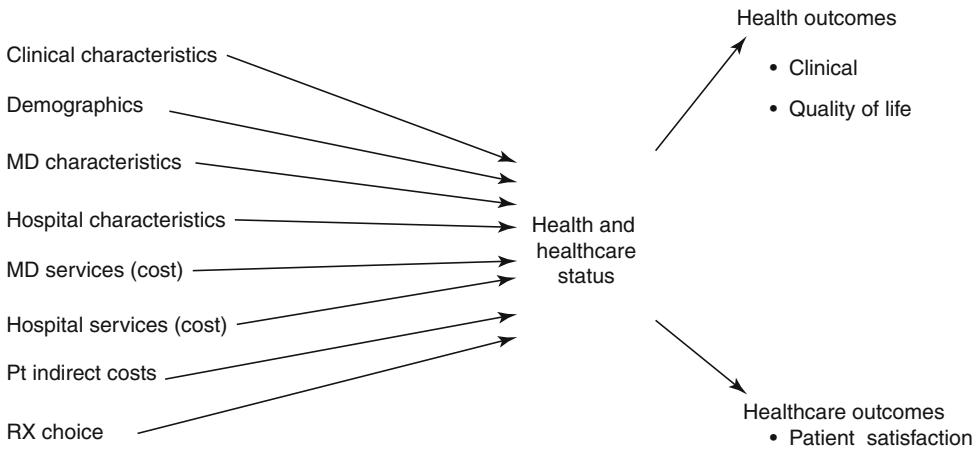

Fig. 5.1 Factors affecting healthcare utilization

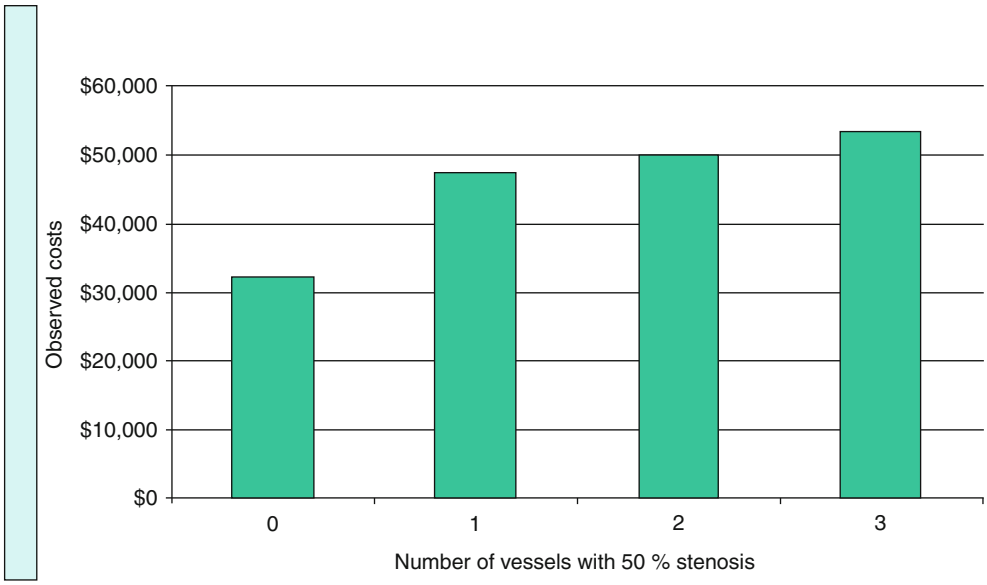

Fig. 5.2 Observed 5-year and Estimated Lifetime Costs for CVD in the NIH-NHLBI-Sponsored WISE study (Adapted from Shaw et al. [8]. With permission from Wolter Kluwers Health)

females, lifetime costs for hospitalizations were reported to be in excess of 230,000 USD and increased to more than 420,000 USD for those with CVD [5]. Of course, the higher rate of resource consumption patterns is largely driven the by presence of comorbodity and concurrent diagnoses and, as such, the greater risk factor burden and comorbid illness would expectedly result in higher costs of care; when compared to men. The World Health Organization estimates that women with multiple cardiac risk factors are costly with lifetime costs of care more than 38,000 USD [6, 7]. Another expected observation is that the presence of ongoing symptoms also drives higher utilization of healthcare resources including more office visits and higher use of drug therapy [8]. To that end, symptom-driven care is costly.

Another vulnerable subset of patients includes those with a lower household income [9]. This is largely due to their greater degrees of comorbidity and risk factors, and greater prevalence of obstructive CAD when compared to higher income individuals. As well, lower income women have less resources to pay for regular office visits and co-pays for drug therapies. Of course, a lack of available resources impact on medication adherence as well as prescription refilling rates [10]. Due to their limited financial resources, lower income patients have frequent unmet needs which contribute to their frequently reported higher rates of CVD events [11–19]. Within the WISE registry, healthcare costs encumbered nearly 20 % of low income households. This result is similar to national averages where nearly 1 in 5 families spend ~10 % of their income on healthcare [11]. The lower rates of compliance with prescribed care impact on downstream care that is more complex and intensive (i.e., more costly).

Gender-Specific Patterns of Healthcare Resource Consumption

For women with angina, the burden of symptoms and ongoing treatment for risk factors results in a heavy economic burden. In the WISE registry, we reported 5-year costs for CVD ranging from 32 to 53,000 USD for women with nonobstructive

to multi-vessel CAD [8]. Surprisingly, from these results, even women with mild or nonobstructive CAD were projected to consume nearly 750,000 USD during their lifetime. Figure 5.2 details 5-year observed and estimated lifetime costs of care from the WISE registry for women with nonobstructive CAD and 1–3 vessel CAD. An interesting observation was that the reason for the high costs of care was due to the presence and persistence of ongoing angina symptoms. In fact, the costs of anti-anginal drug therapy was higher for women with nonobstructive CAD as compared to those with obstructive CAD ($p=0.004$). These results support the concept of ongoing symptoms and, in this case, angina symptoms are prominently influencing the costs of care. In a related report, persistent chest pain was frequent in women despite a heavy burden of anti-anginal treatment [20]. It is estimated that nearly half of women presenting for a de novo chest pain evaluation will still have angina symptoms at 5 years of follow-up [8]. Thus, one can easily envision how high costs of care can be heavily influenced by chest pain symptoms.

Conclusions

The costs of IHD are high and rank among the costliest conditions in healthcare. For women, a consistent body of evidence reports that women (generally) utilize more healthcare resources than men. A large component of the costs of care includes those for ongoing symptoms including the burden of angina. The economic burden of angina, even in the setting of nonobstructive CAD, is costly and can result in high lifetime costs of care. Physicians should consider the intensity of resources required to adequately care for women with angina including the financial burden of family household resources. Research is needed to determine whether anti-anginal therapy can reduce healthcare expenditure in this population.

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Psychological Aspects: Diagnosis and Management

6

Kamila S. White and Diane L. Rosenbaum

Abstract

Chest pain is a common presenting complaint that raises the possibility of serious medical pathology and often precipitates comprehensive medical evaluations and referrals. Since it is associated with coronary artery disease and myocardial infarction, it is perhaps understandable that chest pain is one of the most anxiety-provoking medical complaints for patients and their families. Approximately one-half of patients who undergo cardiac evaluations do not show evidence of cardiac dysfunction underlying their pain [1]. The syndrome of non-CAD chest pain is characterized by recurrent chest pain in the absence of identifiable cardiac etiology and is often accompanied by emotional distress (i.e., anxiety, depression), functional impairment, and is associated with reduced quality of life. In this chapter, we describe non-CAD chest pain from a psychological perspective and highlight the complex biopsychosocial nature of this condition. The prevalence of psychopathology within this population is high, and this chapter reviews psychological factors that may accompany and exacerbate the experience of chest pain for some patients. Following this is a description of the clinical aspects of psychological diagnosis with this population, including differential diagnosis. We conclude with a review and analysis of the evidence-based intervention efforts conducted with these patients, particularly cognitive-behavioral approaches.

Keywords

Chest pain • Non-cardiac chest pain • Non-CAD • Chest pain • Psychological factors Treatment • Cognitive behavior therapy

Chest pain is a common pain complaint that can be worrisome to patients because it raises the possibility of serious medical pathology. It often leads to comprehensive medical evaluations and referrals because of its association with coronary artery disease (CAD) and myocardial infarction. As such, it may be understandable that chest pain is one of the most anxiety-provoking medical complaints for patients and their families. Among US adults, chest pain prompts 8.9 million visits to physician offices [2] and 6 million visits to emergency departments each year [3], making it the second most common presenting complaint. However, many patients experience chest pain but are free of obstructive cardiac disease. In fact, more than 50 % of patients referred for cardiovascular evaluation for chest pain are determined to have non-CAD chest pain; that is, their chest pain is not caused by

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myocardial ischemia or obstructive CAD [1, 4–6]. The presence of angina-like pain in the absence of detectible ischemic heart disease is known specifically as non-CAD chest pain or sometimes more generally as noncardiac chest pain (NCCP) [7, 8]. Many patients who experience non-CAD chest pain are not reassured by this diagnosis [9, 10]; and some patients seek recurrent medical evaluation for their chest pain and related symptoms [9, 11]. A physical basis for non-CAD chest pain such as gastroesophageal reflux disease [12] is found in some cases, yet, these conditions are often not sufficient to fully explain the persistent healthcare seeking in many patients [13, 14]. This condition is a global health problem linked to high rates of healthcare seeking and interruption of daily activity [15].

Although non-CAD chest pain is thought to be benign in the short-term, emerging research shows a higher than expected long-term risk of cardiac events [16–18], particularly among older women [19]. Traditional cardiovascular risk factors are present among this group of chest pain patients, and this risk is associated with increased anxiety and chest pain [20]. Emotional disorders are prevalent in patients with this chest pain syndrome [21, 22], and emotional distress appears to exacerbate chest pain over time [23]. It may be that treatment of psychological factors may reduce chest pain and related distress and healthcare utilization. Unfortunately, non-CAD chest pain patients are generally offered medical reassurance but no additional assessment or treatments beyond standard care [24]. In this chapter, we describe non-CAD chest pain from a psychological perspective and highlight the complex biopsychosocial nature of this condition. The prevalence of psychopathology within this population is high, and this chapter reviews psychological factors that may accompany and exacerbate the experience of chest pain for some patients. Following this is a description of the clinical aspects of psychological diagnosis with this population, including differential diagnosis. We conclude with a critical review and analysis of the intervention efforts conducted with these patients.

Definitions and Terminology

The biopsychosocial study of chest pain in the absence of causal organic pathology is complex, and sustained advancement in the psychological study of this chest pain syndrome may benefit from clarification of terminology. The majority of published literature on the psychological study of this chest pain syndrome is drawn from heterogeneous samples of patients described as noncardiac chest pain (NCCP). Although NCCP nomenclature and classification remains a debated issue [25] and varies across disciplines, it is characterized as no more than one typical angina symptom [26].[1] Unlike NCCP, non-CAD chest pain studies require the additional screening of a coronary catheterization. Study inclusion based upon a normal or near normal coronary catheterization procedure to demonstrate the absence of obstructive CAD and other cardiac etiologies [27] indicates a higher level of confidence in the non-obstructive CAD chest pain in the sample. Most empirical studies to date of psychosocial factors have examined patients with NCCP – and studies of psychosocial factors in patient samples of non-CAD chest pain are less studied. Further, we are not aware of published comparative studies on the psychosocial similarities or differences between these two methods of sampling patients with this chest pain syndrome. In this chapter, we generally use the broad classification of NCCP to describe this syndrome, and in which the research examined patients after coronary angiography we use the term non-CAD chest pain.

Theory

Non-CAD chest pain is a multidisciplinary problem, and biopsychosocial approaches are useful to conceptualize this syndrome. Biopsychosocial approaches indicate that biological, psychological, and sociological factors interact to produce health and disease. As part of a larger biopsychosocial conceptualization, psychological concerns are one essential component of a diathesis-stress model of non-CAD chest pain. Diathesis-stress models posit that vulnerability factors (including psychological vulnerability, learning history, biological vulnerability) come together with situational factors (e.g., stressful situation, physical illness) to bring about problematic physical, cognitive, and behavioral responses resulting in chest pain accompanied by anxious arousal [10]. These vulnerability factors may influence chest pain onset and clinical course independently and in combination. Moreover, theory suggests that non-CAD chest pain and the emotion of anxiety may be associated through similar development and maintenance factors [10, 28, 29]. Similar to panic disorder theory [30], non-CAD chest pain theories suggest patients with this syndrome

[1] Guidelines of the American Heart Association define NCCP as chest pain with one or zero symptoms of typical chest pain [26]. Typical chest pain is experienced under the chest bone and is often described as heavy or squeezing sensation with radiation to the arm or jaw, it is exacerbated by physical or emotional stress, and is relieved by rest or nitroglycerin [26]. Atypical chest pain meets two of the characteristics of typical chest pain. In NCCP, the likelihood of CAD ranges from 19 to 69 %; in patients with low cardiac risk factor indices (i.e., diabetes, hyperlipidemia, smoking), the CAD likelihood among those presenting with NCCP lowers to 3–49 % [26].

may be vulnerable to misinterpretation of states of heightened arousal as threats to health and safety (e.g., cardiac danger) [10, 28, 29]. Some symptoms of non-CAD chest pain and panic disorder are similar [31], however, non-CAD chest pain is not identical in its presentation to panic [32]. As such, several biopsychological mechanisms have been postulated as contributors to non-CAD chest pain, including gastroesophageal dysfunction [33]. Examples of characteristics shared across non-CAD chest pain and panic attacks are presented in Fig. 6.1.

Patients with NCCP chest pain, particularly those with comorbid anxiety disorders, are hypervigilant to physical sensations [34], particularly cardiac-related sensations [35], which may exacerbate and extend the persistence of symptoms. NCCP patients with comorbid anxiety disorders may be most at-risk for heightened vigilance. NCCP patients may also be particularly interoceptively sensitive toward changes in their physical and mental state and engage in frequent monitoring behaviors [34]. Research has shown that patients with NCCP chest pain are more likely to adopt catastrophic cognitive interpretations of cardiac cues and experience related emotional distress [14]. Subsequently, this creates greater opportunity to perceive changes in arousal as cardiac danger in the absence of true risk. This increased attention toward fearful sensations may help to explain why many individuals with non-CAD are not reassured by negative test results [36] and continue to seek medical evaluation [15]. Cognitive-behavioral models of anxiety suggest that thoughts, behaviors, and physiological sensations are interrelated (see Fig. 6.2a). This model may be applied to non-CAD chest pain (see Fig. 6.2b). In this model, the influence of thoughts, behaviors, and physiological sensations creates self-perpetuating reinforcement of anxiety. The experience can be described as cyclical in that a situation (e.g., exercise) may trigger worried thoughts (e.g., "What if this exertion is too much for my heart?"), negative emotions (e.g., nervousness), and avoidance behaviors (e.g., discontinuation of physical activity) which in turn perpetuate future maladaptive responses to similar situations. This process has been theorized to produce a cycle of distress wherein desires and actions toward immediate reduction of anxiety (e.g., avoidance of physical activity) leads to decreased aerobic conditioning as well as continued cardiac-related worry and medical reassurance seeking. In this model, non-CAD chest pain is maintained as a result of limited opportunities to experience cardiac arousal without accompanying anxiety [28, 38].

Relevant Psychological Factors

Psychological factors that may contribute to the development or maintenance of NCCP can often occur in the context of a psychiatric diagnosis, however, this is not always the case. Approximately two thirds of patients with NCCP fail to meet research criteria for a clinically significant disorder, however, their pain may be impacted by psychological factors nonetheless [38]. In addition to affecting pain, some research has suggested that broad psychological factors impact the severity of comorbid psychological

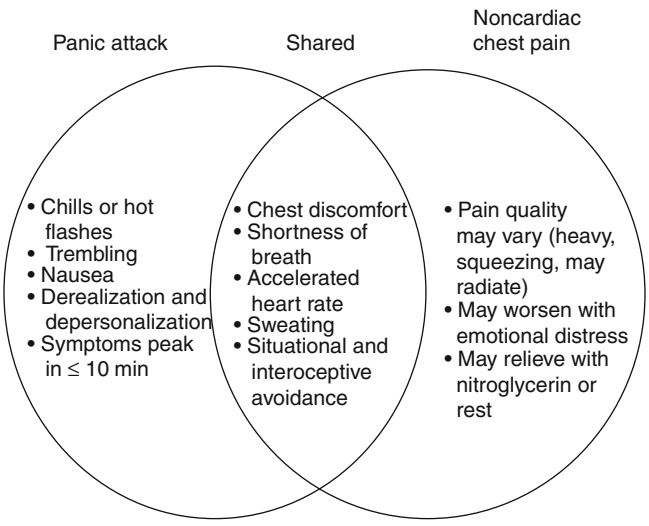


Fig. 6.1 Figure of selected physical symptoms of panic attack from DSM-IV-TR [86], noncardiac chest pain from the American Heart Association [26], and some of their shared characteristics

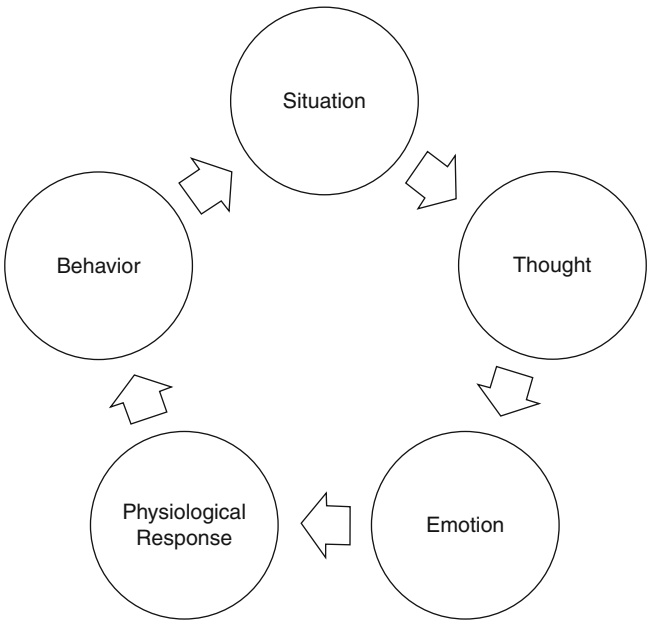
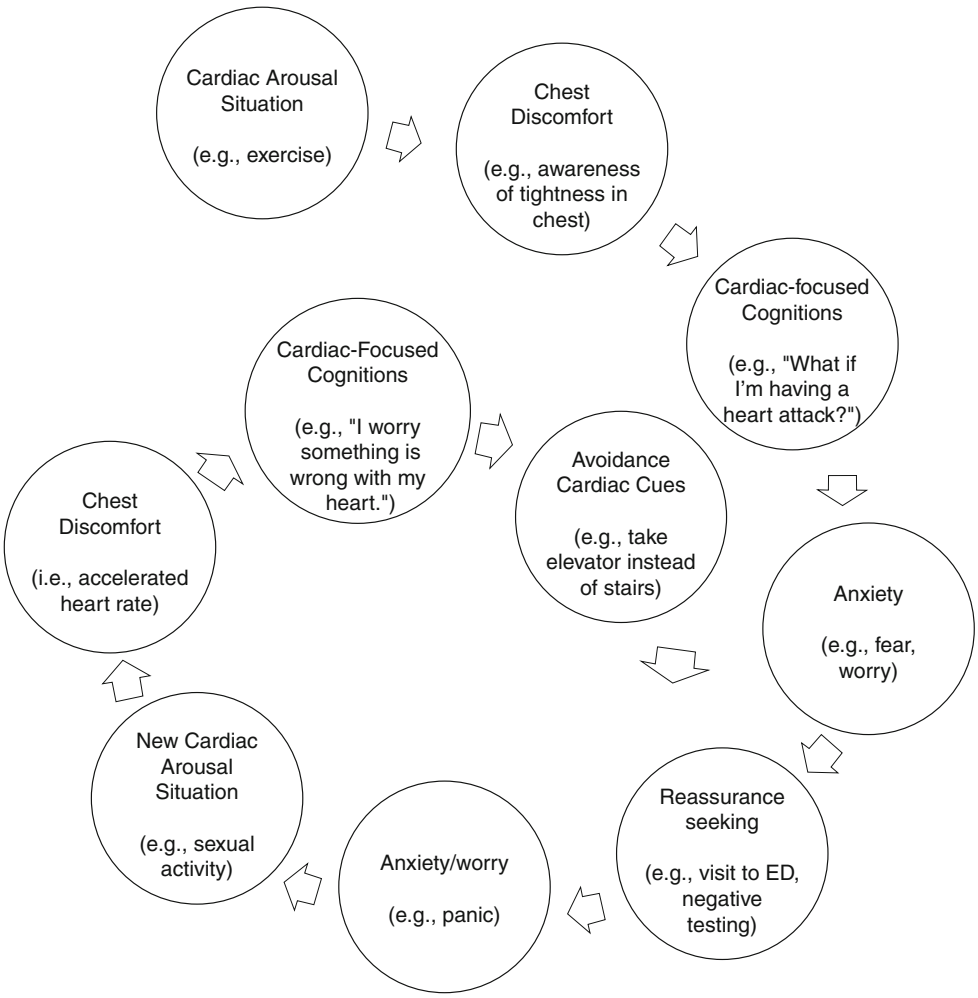


Fig. 6.2 (**a**) A cognitive behavioral model. (**b**) An example of situations, thoughts, behaviors, and physiological responses in a patient with non-CAD chest pain

Fig. 6.2 (continued)



disorders in NCCP. These relations may be complex and varied. For instance, while perceived control is related to both mood and anxiety disorder severity, it appears to function differently across these disorders [39]. Table 6.1 provides some examples of broad psychological factors that are prevalent among patients NCCP [14, 28, 34, 35, 40–44].

In addition to serving as correlates of this syndrome, psychosocial factors have been suggested to impact pathogenesis of non-CAD chest pain [45]. While some psychological characteristics of non-CAD chest pain patients overlap with those found among CAD patients, a distinct psychological profile including features such as alexithymia and medical reassurance seeking has been established for non-CAD chest pain patients [46]. It has also been suggested that poor coping strategies, such as passive wishful thinking can distinguish between those patients with non-CAD chest pain who have psychiatric disorders and those who do not [47]. In addition to passive coping strategies, reinforcement of pain behaviors by social supports (e.g., spouse) is unique to patients with chronic non-CAD chest pain as opposed to other types of patients with chronic pain [48].

Table 6.1 General psychological factors and anxiety-related psychological factors associated with non-CAD chest pain

Psychological factor	
General:	*Anxiety-related*:
Stress[a]	Body vigilance[g]
Limited social support[b]	Arousal avoidance[h]
Limited coping skills[c]	Heart-focused worry[e]
Limited psychological flexibility[b]	Reassurance-seeking[e]
Alexithymia[d]	Fear of cardiopulmonary sensations[i]
Anger[e]	Anxiety sensitivity[j]
Type D personality[f]	

[a][89], [b][42], [c][88], [d][40], [e][28], [f][41], [g][35], [h][89], [i][34], [j][40]

Psychological Disorders

Psychological disorders are prevalent among patients with non-CAD chest pain. Anxiety and mood disorders are the most frequent psychological diagnoses with estimated prevalence rates of 40–46 % and 12–34 %, respectively [21, 49, 50].

In fact, non-CAD chest pain patients are two to three times more likely to suffer from anxiety and depression than CAD patients [51, 52]. Subclinical anxiety and depression symptoms (i.e., those which are distressing and impairing but do not reach the full diagnostic threshold) are also prevalent [21].

Some published research studies have focused on the high rates of panic disorder [53, 54] in this population, and other research has confirmed a high rate of anxiety disorders and mood disorders that is common among patients with NCCP, including generalized anxiety disorder, social anxiety disorder, and major depressive disorder [21]. In sum, these findings suggest that patients with NCCP and the emotional disorders of anxiety and depression may share broader similarities, such as maladaptive cognitive style and avoidance behaviors. Moreover, the rather high prevalence of DSM-IV-TR anxiety disorders (particularly the high rate of panic attacks) in these chest pain samples suggest that chest pain patients may be experiencing significant interoceptive sensitivity and fears associated with autonomic arousal.

Psychological and Physical Functioning

The overrepresentation of psychopathology suggests psychological factors may be of importance to understanding non-CAD chest pain and associated impairments in functioning. Notably, impaired functioning (e.g., disability, low quality of life) is one way in which clinically significant psychological disorders are distinguished from subclinical profiles. As such, research regarding quality of life among patients with non-CAD chest pain may clarify the functional implications of diagnostic labels [55].

Non-CAD chest pain patients that have psychological diagnoses, such as anxiety and depression, report greater pain severity, frequency and distress related to pain [21, 49]. Similarly, history of a psychiatric disorder is associated greater risk for continued pain and higher mortality risk among chest pain patients, regardless of whether the cause is attributable to cardiac origins [56]. Patients with non-CAD chest pain with psychiatric disorders also report reduced quality of life and less treatment satisfaction than those without psychiatric disorders [49]. Psychological factors have also been shown to impact the perception of chest pain, independent of cardiac origin [57].

A formal comparison of non-CAD chest pain patients' clinical and subclinical psychological disorders is not available in the published literature, however psychological symptom severity and fear of pain have both been linked to impairments in quality of life among non-CAD chest pain patients [58]. This suggests the relation between psychological impairment and functional impairment may be linear. These findings support previously mentioned theories and suggest the identification of psychological symptoms among non-CAD chest pain patients may prove imperative for effective treatment of chest pain and increased quality of life.

Psychological factors of non-CAD chest pain may contribute to the severity of patients' reported functionality. Specifically, heightened interoceptive fear for cardiac-related sensations and related avoidance of cardiac-arousing activities, such as exercise, may increase the salience of cardiac cues when they are unavoidable or unpredictable [35]. Research indicates greater persistence of chest pain and impairments to physical stamina have been reported for NCCP patients with comorbid anxiety disorders [59]. Cardiac re-evaluation and estimated health prognosis may be complicated by anxiety-related behavioral avoidance as severe limitations in physical activity may increase risk for authentic cardiac difficulties. Indeed, the current literature reflects varied reports regarding the long-term health consequences of non-CAD chest pain [16, 61, 62]. More research is needed to determine if morbidity and mortality risks of non-CAD chest pain differ according to psychological and behavioral factors, including avoidance.

Psychological Assessment and Diagnosis

Before referral for psychological assessment and diagnosis, the symptom of chest pain requires a thorough medical evaluation. The broad differential diagnosis for chest pain includes the possibility for fatal or serious causes, and medical evaluation and rule out is essential. Moreover, psychological treatment cannot commence in the absence of medical release and any medical limitations for care need clarification. For some patients with non-CAD chest pain, assessment of psychological dysfunction may be useful as part of a comprehensive treatment plan. Reactions to anxiety, worry, and general life stress may remit according to a natural course before reaching a diagnostic threshold of distress or impairment. Alternatively, symptoms that follow a pattern typical a psychiatric diagnosis suggest the use of a psychotherapeutic intervention and/or the use of psychopharmacological interventions.

Interdisciplinary and Differential Diagnosis

Psychological assessment and treatment of non-CAD chest pain and its comorbidities likely benefits from collaboration across an interdisciplinary team (see Fig. 6.3). Communication across referring clinicians safeguards and minimizes any risks to patient safety [62]. Also, close collaboration helps guide diagnostic clarity and prevent unnecessary expenditures of resources. Similarly, collaborative evaluation and care is often in the patient's best interest as it allows for information sharing when symptoms fluctuate or change. Medical release and access to a sufficient level of diagnostic

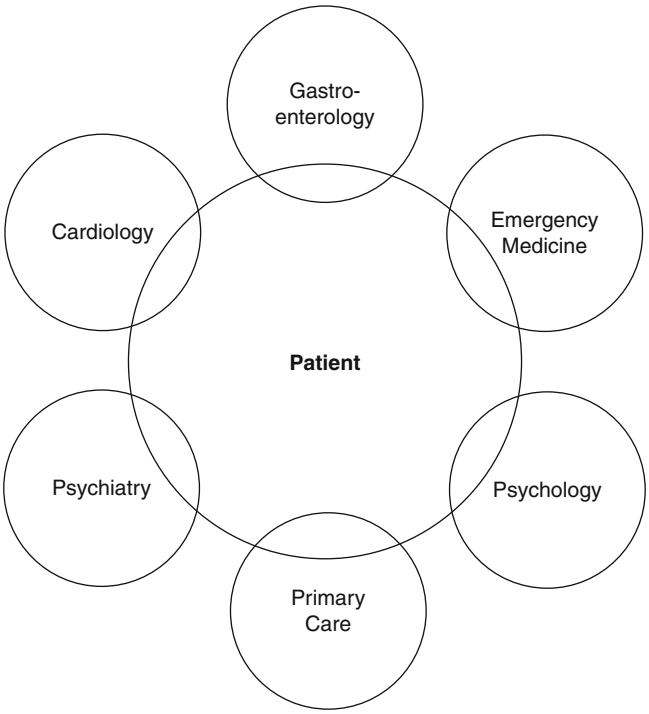


Fig. 6.3 The psychologist may be one of many providers in a collaborative care environment for a patient with non-CAD chest pain, and effective psychological diagnosis and treatment will may require careful collaboration across several areas of practice including nursing providers who can often be expert medical liaisons across healthcare areas

assessment is a likely requisite before a psychological diagnosis can be assigned. Moreover, some psychological symptoms, including cardiac-related worry or beliefs that a serious cardiac disease or illness is present (i.e., "disease conviction"), may not become apparent until after a patient has received the report that their heart is functioning within normal limits [28].

Clinical Methods of Assessment

Several well-validated diagnostic instruments are available to facilitate the assessment of psychological dysfunction. Clinician-administered interviews, such as the Anxiety Disorders Interview Schedule for the Diagnostic and Statistical Manual-Text Revision DSM-IV-TR (ADIS-IV-TR) [63] or Structured Clinical Interview for DSM-IV (SCID) [64] yield the greatest depth and breadth of information. These types of instruments are useful in an outpatient multidisciplinary setting; however, there are barriers that may limit their use in other medical settings. A reasonably high-level of psychological training (i.e., Master's Degree or higher) is required in order to administer these measures. Similarly, the lengthy administration time (i.e., minimum approximately 1 h) may be difficult to fit into busy hospital schedules. Despite these potential obstacles to widespread use, psychometrically sound interviews are preferable when the objective is diagnosis of psychological disorders [62]. Although lengthy, semi-structured interviews offer some of the best safeguards against misdiagnosis as they allow for inquiry regarding patients' responses to differentiate symptoms that may overlap across medical and psychological domains (e.g., appetite change, sleep disturbance). Similarly, symptom ratings are assigned based on clinical judgment to mitigate the risk of bias that may be present in patients' self-reports.

Clinicians who desire brief overviews of psychological functioning may administer screening questionnaires. Measures that assess the most common domains of dysfunction, such as the Hospital Anxiety and Depression Scale (HADS) [65] are well accepted. While screening measures provide a general profile of symptoms, caution should be used in diagnosing psychological conditions from these self-report questionnaire data. Patients may not be accurate reporters of their symptoms for a variety of reasons including failure to understand elements of the question or distorted perceptions of their level of impairment [66]. Screening questionnaires have their greatest utility in determining which patients may benefit from a more comprehensive psychological assessment. Independent of assessment modality, dimensional approaches to assessing psychological symptoms may yield the greatest utility as they capture a spectrum of symptoms including both subclinical and clinically significant difficulties.

In addition to collecting information via self-report or interview, behavioral data collection and collateral source reports may also enhance accuracy of diagnosis. Behavioral data collection is particularly appealing in its objectivity. For instance, actigraphy may be one behavioral measure of physical activity to consider to aid in assessment of avoidance of cardiopulmonary arousal. Similarly, heart rate monitors and skin conductance levels can be objective measures of arousal associated with anxiety. Multitrait, multimethod approaches to assessment also serve to estimate the validity of patients' self-reported data, facilitating accurate diagnosis. Similarly, these measures may be used to estimate outcomes and treatment progress.

Treatment

Effective interventions for non-CAD chest pain and its psychiatric morbidities are vital for a number of reasons. First, this untreated chest pain syndrome is associated with poor quality of life and costly health care seeking in some patients [7]. Second, untreated co-occurring psychiatric disorders exacerbate chest pain perception [35] and reduce quality of life [67]. Third, treatable psychiatric disorders are prevalent in patients with this chest pain syndrome. For these reasons, evidence has accumulated for interventions aimed at both the

reduction of chest pain and its psychiatric morbidities in patients with non-CAD chest pain. Because the co-occurrence of psychiatric factors with non-CAD chest pain is evident in empirical studies, many successful treatments have aimed to both reduce chest pain and the co-occurring psychological factors.

The Role of Reassurance

The conventional approach to management of the non-CAD chest pain has been a medical evaluation joined with a reassurance that the patient does not have an obstructive or other cardiac diagnosis. Research has shown that this approach is ineffective at managing this syndrome, as many patients who receive this method are not reassured, remain concerned, and report continued disabling chest pain and impairment [5, 68, 69]. Some researchers have placed emphasis on the role of reassurance in the treatment of NCCP [70], and reassurance seeking is often more complex. It is uncommon for patients' symptoms to be relieved by reassurance alone, and more often than not, an additional therapeutic plan is needed [71]. Although reassurance seeking can temporarily reduce concerns about chest pain in the short-term (as it temporarily reduces anxiety), it may increase it in the long-term when the chest pain recurs. Patients with non-CAD chest pain can perplex medical providers with their frequent health care seeking despite negative testing.

Some non-CAD chest pain patients may be preoccupied with the concern that the provider failed to detect a medical etiology, and they may be hypervigilant to checking their own body for any signs of chest discomfort. In a longitudinal study, patients with NCCP continued to seek medical evaluation and treatment related to their initial presentation with chest pain at the five year follow-up point [23]. And, many patients with NCCP continue to experience symptoms for years after their initial presentation [68] and continue to believe they have a cardiac condition after being informed of negative diagnostic test results [9]. In fact, data indicate patients with NCCP visit the emergency department for chest pain at a similar rate to those with organic cardiac complaints [23]. In the next section, we highlight the psychological, psychopharmacological, and combined treatment approaches that have some shown promising treatment outcomes for the NCCP patient.

Psychological Treatments

A limited number of empirical studies show promising support for psychological treatments for patients with NCCP. A recent review showed modest to moderate effects for 10 psychological interventions for NCCP, see [72] for a Cochrane review. Perhaps the most empirically-supported treatment approach for NCCP is cognitive-behavior therapy (CBT), a time-limited form of psychotherapy based cognitive behavioral theory. As the Cochrane review group points out, too few practitioners have the requisite skill-set or time necessary to administer CBT to their patients. In a recent randomized controlled trial, Spinhoven and colleagues (2010) found that CBT was superior to paroxetine and placebo [73]. Further, these investigators found that heart-focused anxiety (i.e., the fear of cardiac-related bodily sensations including palpitations based on their presumed negative consequences) mediated pain reduction in the CBT condition. These findings support the need to target cognitive responses to chest sensations (e.g., fear of pain) in CBT treatments for NCCP.

The premise of cognitive behavioral treatments (some of which are modeled on treatments for panic disorder) and medically unexplained physical conditions is that patients misinterpret benign bodily sensations as indication of heart disease. These physical sensations trigger fear and anxiety. Anxiety in general and heart-focused fear in particular then leads to more vigilance and attention focused on bodily sensations (e.g., heart-rate monitoring). Patients with NCCP are known to engage in avoidance situations (e.g., exercise) or avoidance of interoceptive cues (e.g., expression of strong emotions, caffeine) that elicit symptoms. The objective of CBT of NCCP is to assist patients to patients to reduce pain and emotional distress. Other studies based on CBT models have applied coping skills approaches [74] and social problem solving approaches [75] with success. CBT is effective compared to usual care [76].

Some components are more common among the evidence-based CBT treatments. More common components among the evidence-based interventions include: Psychoeducation, breathing retraining, relaxation techniques, and cognitive therapy including identifying catastrophic misinterpretations, cognitive restructuring, and conducting behavioral experiments (see Table 6.2). Other components may be effective but may require dismantling trials for explicit evaluation (e.g., interoceptive exposure, relaxation). Other effective psychological interventions have included hypnotherapy [77] and biofeedback [78]. One study by Jones and colleagues (2006) showed that hypnotherapy was superior to control condition of supportive listening plus placebo medication in reducing chest pain and improving overall wellbeing but not anxiety or depression. Biofeedback has also shown some efficacy compared to a primary care treatment; however, high treatment dropout (52 %) hindered the biofeedback intervention [78].

Finally, based on cognitive behavioral theory, transdiagnostic treatments may have applicability to patients with NCCP with psychiatric comorbidities. Effective treatments

Table 6.2 Common cognitive-behavior therapy components in treatments for non-CAD chest pain

Psychoeducation
Relaxation techniques
Breathing retraining
Progressive muscle relaxation training
Imagery
Interoceptive exposure
Cognitive therapy
Identifying maladaptive cognitions
Cognitive restructuring
Situational exposure
Management of reassurance seeking

Clinical techniques have combined and variable empirical support and are tailored to individual patient's needs

for the emotional disorders exist, and recent scientific advances support parsimonious psychological treatments that target underlying cognitive, behavioral, and emotion regulation processes. Transdiagnostic, emotion-focused cognitive-behavioral treatments [79, 80] may be effective methods for the treatment of emotional disorders in NCCP patient. To date, there have been very few treatment trials for NCCP, and no randomized trials examining whether CBT can improve outcomes for NCCP patients with emotional disorders.

Psychopharmacological Treatments

Empirical research has also supported the use of tricyclic antidepressants and selective serotonin reuptake inhibitors (SSRIs). Patients who received imipramine showed decreased chest pain [81]; however, because imipramine has been linked with cardiac arrhythmias – it has had limited clinical use with NCCP patients. Others have found some support for SSRIs in reducing chest pain (sertraline) [74, 82], with some exceptions (paroxetine) [83]. Moreover, sertraline has been shown to reduce associated emotional distress including anxiety [74], but not depression [82].

Combined Treatments

The relative benefits of pharmacological and psychological treatments for NCCP are not well-understood. In one recent randomized controlled study, Keefe and colleagues (2011) concluded that the combination treatment of coping skills training (CST) and sertraline was superior to either condition alone or CST + placebo in reducing NCCP patients pain intensity and unpleasantness as well as pain catastrophizing across 34-weeks of study [74]. Moreover, in this study the combination treatment resulted in promising decrements in patient anxiety (but not depression) compared to the placebo alone condition. Empirical study of the comparative and additive benefits of combined psychological and pharmacological treatment for NCCP and co-occurring emotional distress are needed. Also, designs that investigate how treatment acceptability and patient preferences may influence retention and dropout are needed.

Mechanisms of Action

Few studies have investigated the mechanisms of action underlying treatments for NCCP. Spinhoven and colleagues (2010) showed that heart-focused anxiety is reduced by effective CBT and pharmacological treatment compared to placebo control [73]. Future work is needed on the mechanisms of action of effective treatments.

Treatment Acceptability

The data on treatment acceptability are mixed. On one hand, in one trial NCCP patient participation was hindered by pharmacological interventions: 79 % of patients refused clinical trial participation due to unwillingness to be randomized to medication [73]. However, in another trial, a brief psychological intervention delivered by trained cardiac nurses did not prove to be acceptable to patients following cardiac catheterization [84]. That said, data on study refusal rates are often not reported, and some recent comparative studies (i.e., pharmacological and psychological interventions) have reported subject attrition within expected limits (e.g., 30 %) [74].

Conclusion and Future Directions

Treatment of NCCP is difficult due in part to the heterogeneous nature of this syndrome. Published research has demonstrated high rates of comorbid emotional disorders, particularly anxiety disorders, in NCCP. Anxiety disorders show a poor cardiac outcome but the directionality and the mechanism of this association needs more exploration. One pathway through which anxiety exerts its negative impact on cardiac health is through increased health compromising behaviors; in some cases, patients are "too scared to move" to engage in cardioprotective behaviors. It may be that the biological correlates of anxiety disorders exert negative health consequences through their impact on heart rate variability. Perhaps anxiety disorders are associated with increased health compromising behaviors (i.e., interoceptive

avoidance behaviors) this is another possible reasons that anxiety is associated with increased cardiovascular risk factors [35, 85]. Whichever the case, mechanistic research is needed to examine the psychological factors that may contribute to and maintain the syndrome of NCCP.

In order to appropriately and efficiently identify NCCP patients for psychological intervention, empirical study of the short-term and long-term effects of the syndrome needs more study. Clinical investigations of NCCP and non-CAD chest pain are emerging and important questions remain unexamined. Epidemiological and clinical studies suggest a bimodal distribution of patients who present for evaluation with non-CAD chest pain – some patients who are relieved by their noncardiac pain status and some patients who are distressed and impaired by their NCCP diagnosis. Longitudinal research is needed to examine the biological precursors, familial and developmental factors, clinical course, functional impairment, and healthcare utilization in both groups. Research on the heritability of non-CAD chest pain is needed to explore the extent that genes might play a role in development of this syndrome and its correlates. And finally, although no published guidelines exist to ease the pain and distress in patients with non-CAD chest pain, this paper described a theoretical conceptualization of non-CAD chest pain, and summarized and critiqued the empirical evidence supporting treatment studies on medically unexplained chest pain. Effective treatments for NCCP exist, but few patients receive referral for psychological care in routine care settings. Future research will likely point to whether singular or sequencing of combined treatment is needed and the optimal sequencing of those interventions has yet to be examined.

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Cardiac Syndrome X and Myocardial Ischemia: Pathogenesis

7

Gaetano Antonio Lanza and Filippo Crea

Abstract

Cardiac syndrome X (CSX) is characterized by: (1) angina chest pain triggered by effort; (2) ST-segment depression on exercise stress electrocardiogram or other findings compatible with myocardial ischemia; (3) normal coronary arteries at angiography, in absence of any specific cardiac or systemic disease. Myocardial ischemia related to abnormalities in coronary microcirculation is in most cases responsible for the angina symptoms (microvascular angina, MVA). Metabolic evidence of myocardial ischemia has been found in a sizeable, although variable proportion of patients, whereas left ventricular contractile abnormalities during stress tests have been detected in only a minority of patients. A plausible explanation for the typical lack of left ventricular dysfunction and metabolic abnormalities can reside in the fact that the coronary microvascular dysfunction is patchily distributed across the myocardial wall, rather than being confluent in large areas.

The mechanisms responsible for coronary microvascular dysfunction (CMVD) include both reduced coronary microvascular dilation and enhanced coronary microvascular constriction. Moreover, the impaired microvascular dilator function may involve both endothelium-independent and endothelium-dependent mechanisms.

The causes responsible for CMVD in CSX are also heterogeneous. Traditional cardiovascular risk factors, including hypertension, dyslipidaemia, blood glucose disorders and smoking might play some role. Some conditions frequently found associated with CSX, however, include abnormal adrenergic nerve function, insulin resistance, inflammation and (in women) estrogen deficiency.

CMVD can be responsible for angina in other groups of patients presenting with a different clinical picture than CSX. In particular, in some patients MVA can present as an acute/unstable form of angina, simulating non ST elevation acute coronary syndrome. The mechanisms responsible for CMVD in these patients have not been adequately investigated; however, intense vasoconstriction of prearteriolar and/or arteriolar coronary vessels is expected to represent the major mechanism of ischemia.

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Introduction

Cardiac syndrome X (CSX) is classically characterized by the concurrence of the following findings: (1) angina-like chest pain exclusively or predominantly triggered by effort, and typical enough to suggest obstructive coronary artery disease; (2) ST-segment depression on the electrocardiogram during exercise stress test or other abnormal findings compatible with myocardial ischemia (e.g., reversible perfusion defects on radionuclide stress tests); (3) normal or near normal (i.e., irregularities or very mild stenosis [<20 %]) coronary arteries at angiography. Furthermore, the presence of any specific cardiac or systemic disease should be excluded [1].

The causes of CSX have been debated since its first descriptions [2–4]. A large body of evidence, however, strongly supports the hypothesis that myocardial ischemia related to abnormalities in coronary microcirculation is in most cases responsible for the syndrome [5]. Accordingly, the term "microvascular angina" (MVA) is now preferred to describe this condition [6].

In some patients, however, a pathogenesis different from coronary microvascular dysfunction (CMVD) might be responsible for chest pain, including gastro-oesophageal, musculo-skeletal disorders or psychosomatic disturbances, which should therefore be carefully excluded. Moreover, in a number of patients, a nociceptive abnormality, resulting in an enhanced painful perception of usually innocuous cardiac stimuli, can be present, and may give a substantial contribution to the characteristics of frequency and severity of chest pain episodes [7, 8].

Accordingly, we have recently suggested that the definitive diagnosis of MVA should be achieved by a direct documentation of CMVD rather than being only based on the exclusion of other conditions (mainly obstructive coronary artery disease) known to cause chest pain [6].

Evidence of Myocardial Ischemia

In agreement with the definition, the fundamental clue to the occurrence of myocardial ischemia in patients with the clinical picture of CSX is the presence of transient ST-segment depression at the ECG, associated with angina-like chest pain, on non invasive stress tests, including exercise stress test, atrial pacing or pharmacological (adenosine, dipyridamole, dobutamine) stress tests, or also during normal daily activities, as detected by Holter monitoring. However, ST-segment depression is not believed a highly specific sign of myocardial ischemia and, in the absence of demonstrable structural and/or functional epicardial coronary abnormalities, it is usually considered a false positive result.

A similar issue concerns the evidence of stress (exercise or pharmacological)-induced reversible perfusion defects at myocardial scintigraphy, which can be detected in at least 50–60 % of typical CSX patients [9, 10]. Indeed, in the absence of flow-limiting stenosis, the suboptimal specificity of these tests in the diagnosis of obstructive CAD may also raise the issue of a false positive result [11].

Thus, several authors have questioned the cardiac ischaemic origin of the syndrome and reclaimed for more unequivocal evidence of myocardial ischaemia, including, in particular, the demonstration of typical ischaemic metabolic abnormalities of cardiomyocytes and/or of reversible left ventricular (LV) contractile alterations.

Metabolic Evidence of Myocardial Ischaemia

Several studies have investigated the occurrence of ischemic metabolic abnormalities in the heart of patients with CSX. Importantly, while a clear evidence of myocardial ischemia was often not obtained, a careful assessment of the published data shows that metabolic evidence of stress-induced myocardial ischemia has frequently been observed in a sizeable proportion of enrolled patients.

Myocardial lactate production, comparable to that found in patients with obstructive CAD, had already been demonstrated in the original study by Arbogast and Bourassa in their group X patients [3], which gave the name to the syndrome [4]. Subsequently, several studies have assessed myocardial lactate metabolism in patients with CSX or, more generally, in patients with angina and normal coronary arteries, reporting abnormal findings in a proportion of patients ranging from 0 to 100 % (Table 7.1) [12–25]. The reasons for these discordant results are unclear, but they may, at least in part, be accounted for differences in patients' selection and applied methods.

Other metabolic markers of myocardial ischemia have included the detection during atrial pacing of oxygen desaturation [26] and pH reduction [27] in 20–30 % of patients.

Moreover, in a recent study, Buchtal et al., using magnetic resonance spectroscopy during handgrip stress test, have shown typical metabolic ischemic changes of myocardial 31-phosphorus metabolism in about 20 % of CSX women; of note, the result was comparable to that found in a group of

Table 7.1 Results of studies which assessed myocardial lactate metabolism in patients with angina and normal coronary arteries or typical cardiac syndrome X

	Population	No. patients	Abnormal findings (%)	Stress test
Kemp et al. [12]	Angina, NCAs	100	20	Isoproterenol, atrial pacing
Bemiller et al. [13]	Angina, NCAs	14	71	Atrial pacing
Richardson et al. [14]	Angina, NCAs	7	100	Atrial pacing
Boudoulas et al. [15]	Angina, NCAs	29	31	Atrial pacing
Mammohansingh and Parker [16]	CSX	15	27	Atrial pacing [4]
Jackson et al. [17]	Angina, NCAs	35	54	Atrial pacing
Opherk et al. [18]	Angina, NCAs	8	100	Atrial pacing
Cannon et al. [19]	Angina, <50 % CAD	22	63	Atrial pacing and CPT
Greenberg et al. [20]	Angina, NCAs	27	37	Atrial pacing
Lagerqvist et al. [21]	Angina, NCAs	20	55	CPT, atrial pacing, dipyrdamole
Camici et al. [22]	CSX	12	0	Atrial pacing
Waldenström et al. [23]	Angina, NCAs	7	100	Lactate concentration in myocardial biopsy
Nagayama et al. [24]	MVA	7	100	Exercise stress test
Bøtker et al. [25]	CSX	18	0	Atrial pacing

CAD coronary artery disease, *CPT* cold pressor test, *CSX* cardiac syndrome X, *MVA* microvascular angina, *NCAs* normal coronary arteries

CAD patients (Fig. 7.1) [28]. As the stressor used in this study was mild, it can be supposed that the proportion of patients with evidence of myocardial ischemia might have been higher if a more stressful stimulus had been used.

Finally, Buffon et al., in a group of CSX patients, found a high myocardial release of lipoperoxide products in the coronary circulation following atrial pacing; also in this case the results were similar to those detectable in a group of CAD patients during myocardial ischemia induced by coronary balloon occlusion during a percutaneous coronary intervention [29].

Mechanical Evidence of Myocardial Ischaemia

Left ventricular contractile abnormalities in CSX patients have usually been undetectable by 2D-echocardiographic exercise or pharmacological stress tests [30, 31], and this has been taken as the most valid reason to question the occurrence of myocardial ischemia [32].

Interestingly, however, stress-induced systolic left ventricular dysfunction has occasionally been detected on imaging stress tests in CSX patients [33, 34], and some echocardiographic studies have shown reversible stress-related diastolic left ventricular dysfunction [35].

Myocardial Ischaemia: How to Interpret Current Evidence

The notion that left ventricular contractile abnormalities, as well as typical myocardial metabolic changes, should be demonstrated to prove myocardial ischemia, mainly stems on the observation that they appear earlier in the typical ischemic cascade, whereas electrical changes and (in patients)

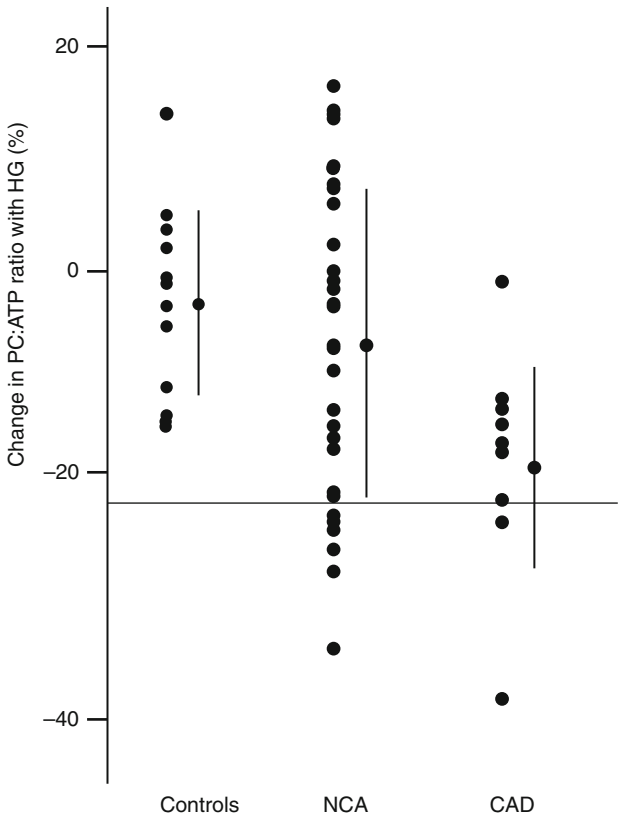

Fig. 7.1 Myocardial dephosphorylation during handgrip (*HG*) as assessed by spectroscopic cardiac magnetic resonance in female patients with stable obstructive coronary artery disease (*CAD*), angina with normal coronary arteries (*NCA*) and healthy controls. A similar proportion of CAD and NCA patients shows abnormal findings (data points *below* the *horizontal line*) (Based on data from Buchthal et al. [28])

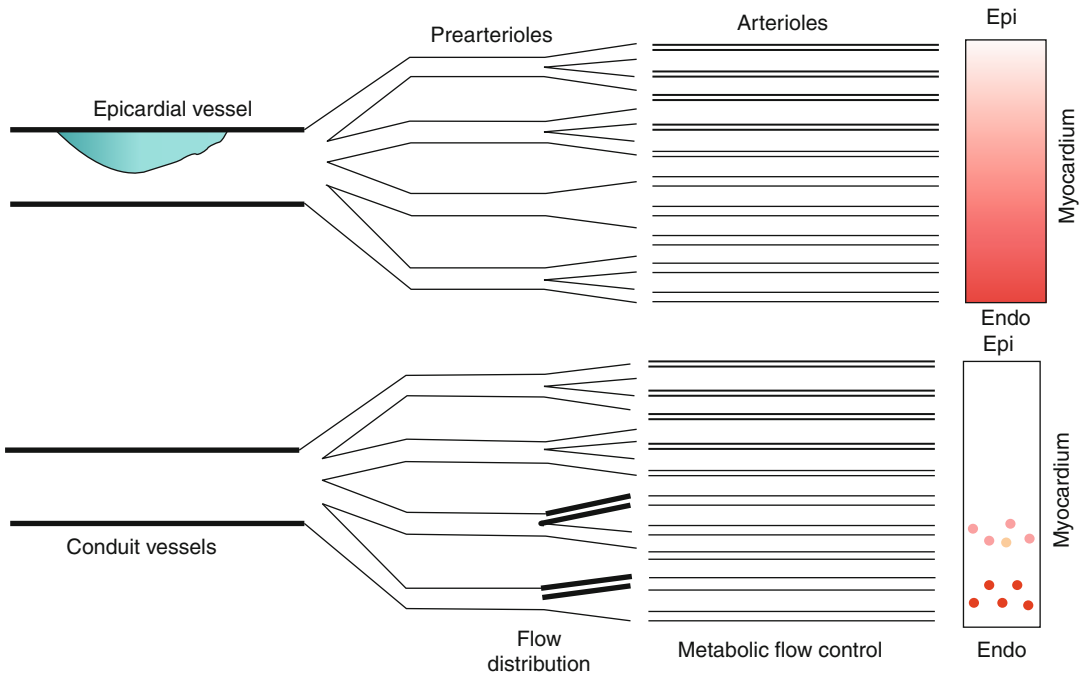

Fig. 7.2 Differences in myocardial ischemia caused by a coronary artery stenosis (*upper drawing*) or coronary microvascular abnormalities (*bottom drawing*). In case of an epicardial stenosis, ischaemia diffusely involves the myocardial (usually subendocardial) territory supplied by the vessel (*red area*), which results in impairment of regional contractile function. In case of microvascular dysfunction ischaemia is likely localized only in small myocardial areas, patchily diffused in the myocardial wall (*small circles*); this does not usually result in detectable impairment of contractile function due to the presence of normal contractile myocardial cells in the same territory (Modified from Lanza and Crea [6])

symptoms appear later [36]. This view, however, presents several shortcomings.

First, while the typical sequence of the ischemic cascade has convincingly been demonstrated in experimental models, in which myocardial ischaemia is caused by acute coronary occlusion, its consistency in the clinical setting has never adequately been assessed, and, in fact, is unlikely to occur. For example, it is not uncommon to observe angina in absence of significant ECG changes during exercise stress test in patients with obstructive CAD. Moreover, ST-segment depression may occur in the absence of reversible left ventricular wall motion abnormalities at standard echocardiographic imaging in case of mild myocardial ischemia [37].

A plausible explanation for the typical lack of LV dysfunction during chest pain and ECG changes in CSX patients can reside in the fact that the coronary microvascular dysfunction is patchily distributed across the myocardial wall, rather than being confluent in large areas [5]. Thus, the possible reduction of cardiomyocyte contractility in the small myocardial regions with CMVD might be obscured by the normal, or even increased, function of adjacent and interposed myocardial areas (Fig. 7.2). Of note, the local release of significant amounts of vasodilators might limit the impairment of CBF and the degree of the mechanical, as well as metabolic, impairment. Adenosine has, in this context, been suggested to play a significant role, as it might prevent significant myocardial ischemia but cause, at the same time, chest pain and ST-segment changes [5].

Similar considerations apply to ischemic metabolites. Their stress-induced release from the small ischemic areas might indeed not be detected in the coronary sinus as they are diluted in the coronary blood draining from normal myocardial areas.

This situation contrasts with that of patients with flow-limiting epicardial stenosis, in whom stress tests induce ischemia in large subendocardial areas, thus more easily resulting in abnormal LV function and metabolic evidence of ischemia (Fig. 7.2) [6].

Coronary Microvascular Dysfunction

In contrast with epicardial vessels, which can be assessed directly by angiography and other imaging techniques, the structure and function of small coronary artery vessels cannot be investigated directly in man.

Structural abnormalities might be identified only at microscopic analysis of bioptic samples, but these may fail to show a significant number of valid small coronary arteries or to detect myocardial regions with CMVD; furthermore, performing endomyocardial biopsy in clinical practice may not be considered ethical due to the potential risks and the

Table 7.2 Main results of studies which assessed histological abnormalities on endomyocardial biopsy specimens in patients with angina and normal coronary arteries or typical cardiac syndrome X

	No. patients	No. patients with abnormal findings	Hystologic abnormalities
Richardson et al. [14]	15	15	No relevant histological abnormalities
Opherk et al. [18]	18	17	Normal small coronary artery vessels Alterations of myocardial mitochondria
Mosseri et al. [38]	6	6	Medial hyperplasia and hypertrophy Myointimal proliferation Endothelial degeneration Swollen capillaries Myocardial hypertrophy Lipofuscin deposition and patchy fibrosis
Schwartzkopff et al. [39]			Medial arteriolar hypertrophy Periarteriolar fibrosis
Satake et al. [40]	24	24	Medial and basal membrane thickening Thickening and proliferation of endothelial cells Arterialization of capillary vessels Capillary vessels rarefaction with collagen replacement
Zorc-Pleskovic et al. [41]	31	13	Inflammation in small blood vessels (76 %) TUNEL-positive endothelial cells (17 %) Inflammation and apoptosis of endothelial cells in patients with increased CRP levels
Chimenti et al. [42]	13	13	Viral genomes in intramural vessels (nine patients) and in cardiomyocytes (eight patients) Cardiomyocyte hypertrophy and degeneration Interstitial fibrosis Focal lymphocytic myocarditis (three patients)

negligible clinical impact that histological results may have on patient management. Finally, the few studies that assessed the presence of structural abnormalities in biopsy samples of CSX patients, or more generally with angina and normal coronary arteries, have shown discordant results, showing no alterations or heterogeneous findings (Table 7.2) [38–42], thus putting into question the interpretation and reliability of the results. Accordingly, the role of structural microvascular alterations in the pathogenesis of CSX remains at present to be better elucidated.

Of note, some studies have suggested that also capillary rarefaction might be involved as a structural abnormality in the CMVD of CSX patients [39, 43], but the role of this finding and its relation with the dysfunction of small coronary arteries needs further investigation.

Regardless the presence of structural changes, abnormalities in coronary microvascular function have consistently been shown, with few exceptions, in a large number of studies.

The presence of CMVD has usually been obtained by the demonstration of abnormal CBF variations in response to vasoactive stimuli which act on resistance coronary arteries, using various, invasive and non invasive, methods, including thermodilution, gas wash-out, intracoronary Doppler recording, positron emission tomography [PET], cardiovascular magnetic resonance [CMR] and myocardial contrast echocardiography.

Furthermore, both reduced coronary microvascular dilation and enhanced coronary microvascular constriction have been shown to possibly contribute to the CMVD. Moreover, the impaired microvascular dilator function may involve both endothelium-independent and endothelium-dependent mechanisms.

Endothelium-Independent Vasodilation

Opherk et al. [18] first reported, using the argon washout method, a lower increase in CBF in response to the intravenous administration of dipyridamole in CSX patients compared to a control group of healthy subjects. Dipyridamole is an arteriolar vasodilator which acts by inhibiting the cell uptake (and consequent breakdown) of adenosine, a major metabolic vasodilator substance released by cardiomyocytes during myocardial ischaemia which acts through stimulation of A_2 receptors on vascular smooth muscle cells (SMCs).

This finding was subsequently confirmed by several other studies, thus supporting the presence of abnormalities of SMC relaxation of small coronary artery vessels.

Thus, using intracoronary Doppler wire recording, Chauhan et al. showed that papaverine caused a lower increase of CBF in CSX patients, compared to a control group [44].

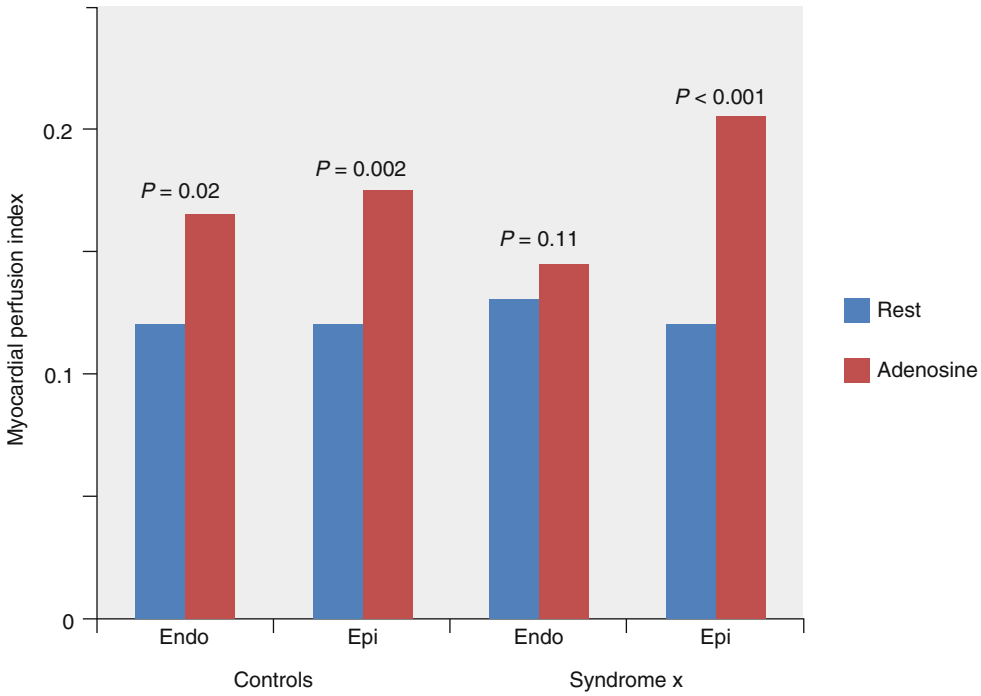

Fig. 7.3 Change in myocardial perfusion index in subendocardial and subepicardial layers in response to adenosine (140 μg/kg/min), as assessed by gadolinium cardiac magnetic resonance, in a group of 20 patients with cardiac syndrome X and in a group of 10 control subjects. A blunted vasodilator response in the subendocardium is observed in syndrome X patients (Based on data from Panting et al. [48])

Several PET studies have also documented the lower increase of myocardial blood flow with direct vasodilator stimuli. Bøttcher et al., for example, showed a lower CBF increase in response to dipyridamole in CSX women than in matched controls [45]. Of note, two PET studies have shown a significant heterogeneity in the regional response of MBF to dipyridamole in CSX patients, thus supporting the hypothesis of a non homogeneous, patchy distribution of the coronary microvascular abnormality in most patients [46, 47].

Evidence of an impaired coronary microvascular dilation has recently also been obtained by CMR. Panting et al. have shown a selective impairment of subendocardial perfusion in response to adenosine in a group of CSX patients compared to a control group, whereas no impairment of the microvascular dilator function was observed in subepicardial layers [48] (Fig. 7.3). In this study, the reduced CBF response to adenosine in subendocardial layers was not diffuse, but was limited to 47 % of the regions of interest in which the subendocardium was divided, further supporting the notion of a non homogeneous distribution of CMV abnormality in the myocardium.

In a recent study we have found reversible subendocardial perfusion defects at CMR during dobutamine stress test in 56 % of CSX patients [49]. Importantly, the presence of dobutamine-related perfusion defects correlated with a lower CBF response to adenosine in the left anterior descending coronary artery, as assessed by transthoracic Doppler echocardiography (TTDE) [49]. CBF reserve was also lower, compared to controls, in CSX patients without evidence of reversible regional perfusion defects at stress-CMR, suggesting a wider impairment of coronary microvascular function in this subgroup (Fig. 7.4) [49].

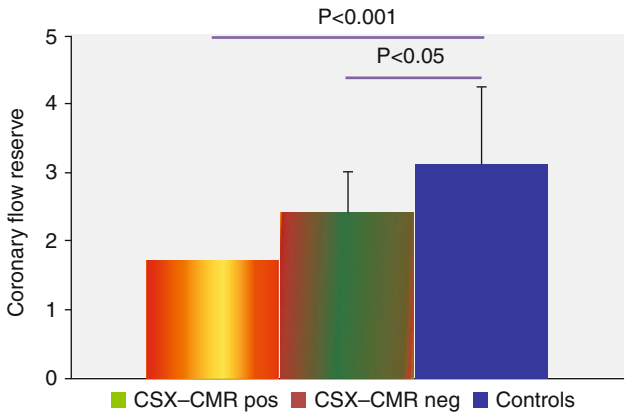

Fig. 7.4 Coronary velocity blood flow reserve following adenosine administration in the left anterior descending (*LAD*) coronary artery, as assessed by transthoracic echo-Doppler measure of coronary blood flow velocity, in 18 patients with cardiac syndrome X (CSX) and in ten healthy controls. Patients were divided in two subgroups, those with (CSX/CMR pos, n = 10) and those without (CSX/CMR neg, n = 8) reversible regional perfusion defects in the LAD territory on cardiovascular magnetic resonance during dobutamine stress test (Based on data from Lanza et al. [49])

In a further study, we have also found an impairment of coronary microvascular dilation in response to adenosine in 17 CSX patients by myocardial contrast echocardiography, with the results showing a good correlation with those obtained in the same patients by TTDE [50].

Of note, the induction of symptoms and ECG signs of myocardial ischemia in response to dipyridamole suggests that, in at least a group of patients, a constriction of prearteriolar coronary vessels, not resolved or poorly influenced

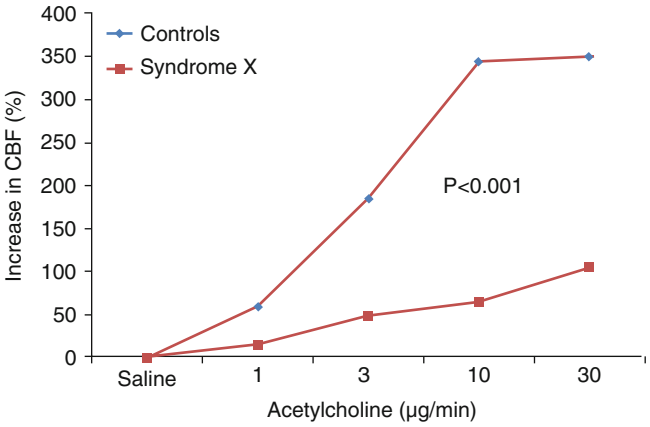

Fig. 7.5 Reduced vasodilator response to multiple doses of intracoronary acetylcholine in patients with cardiac syndrome X, as compared to control subjects with atypical chest pain (Based on data from Egashira et al. [52])

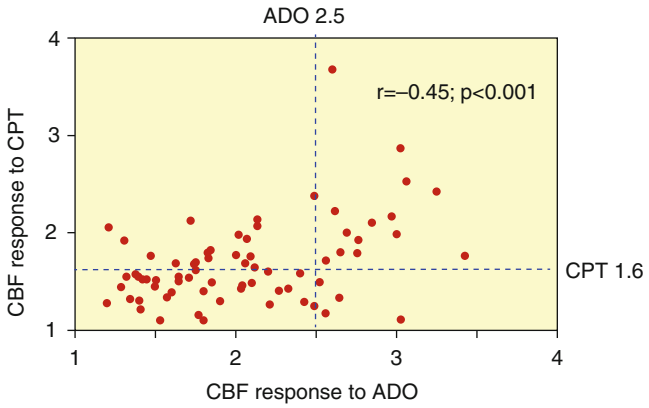

Fig. 7.6 Coronary blood flow response to adenosine (*ADO*) and to cold pressor test (*CPT*) in 71 patients with cardiac syndrome X. Cut-off for reduced values for the two tests are shown. Response to adenosine was more frequently impaired, but a few patients showed impairment of the response to CPT only (Modified from Sestito et al. [54])

by the vasodilator effect of the drug and favouring "blood steal" by normal microcirculation during maximal vasodilation, may constitute the primary microvascular abnormality [5].

Endothelium-Dependent Vasodilation

An impairment in CSX patients of the endothelium-dependent coronary microvascular dilation has also been suggested by several studies, which have shown a reduced increase in CBF response to stimuli known to cause vasodilation through the release of dilator substance, mainly nitric oxide, by endothelial cells.

Motz et al. first reported an impairment of coronary microvascular dilation in response to the intracoronary administration of acetylcholine in 14 out of 23 CSX patients [51]. Interestingly, in this study an impaired vasodilator response to the endothelium-dependent stimulus or to an endothelium-independent stimulus (dipyridamole), or to both, was observed in different patients.

An impairment of endothelium-dependent and endothelium-independent coronary microvascular dilation (as assessed by acetylcholine and papaverine, respectively) was also reported in CSX patients by Chauhan et al. (Fig. 7.4) [44]. The impairment of the acetylcholine-mediated coronary microvascular dilation in CSX patients was documented in more detail in subsequent studies which showed a reduced increase in CBF, compared to controls, at each of multiple increasing doses of acetylcholine (Fig. 7.5) [52, 53].

A limitation in the interpretation of these data, however, is that acetylcholine is not simply a substance with endothelium-mediated vasodilator effects; indeed, it may also exert direct vasoconstrictor effects on smooth muscle cells of susceptible vessels through stimulation of muscarinic receptors. Thus, the relative contribution of these two vascular effects of acetylcholine in CSX remains under scrutiny.

Cold pressor test (CPT) has also been used in a few studies to assess endothelium-mediated coronary microvascular dilation in CSX patients. CPT causes a mild increase in blood pressure and heart rate, and therefore in myocardial oxygen consumption; this is usually associated with metabolic arteriolar dilation and pre-arteriolar flow-mediated dilation; an impairment of CBF response is probably related to impaired pre-arteriolar endothelium-dependent dilation.

An impairment of CBF in response to CPT was first reported by Cannon et al. using the thermodilution method [19] and subsequently confirmed in a PET study [45]. We have recently shown that CMV dilation in response to CPT was impaired in 36 out of 71 (51 %) patients with CSX as assessed by tans-thoracic Doppler echocardiography [54]. Of note, in this study 53 patients (75 %) showed a CFR in response to adenosine <2.5, with 32 (45 %) showing an impaired response to both stimuli (Fig. 7.6). The interpretation of an impaired response to CPT, however, is, again, difficult as the reflex activation of the adrenergic system might also trigger abnormal vasoconstriction in susceptible vessels.

The assessment of CBF response to pure endothelium-dependent vasodilator substances has, in fact, questioned the presence of a significant impairment of endothelium-mediated coronary microvascular dilation in CSX [55]. The evidence that L-arginine (the substrate for NO synthesis) [56] and tetrahydrobiopterin (an NO synthase cofactor) [57] may normalize the coronary microvascular dilator response to acetylcholine in CSX patients, however, suggests that a lower release of NO by endothelial cells is involved in the microvascular abnormalities in at least a group of these patients.

Interestingly, an impairment of endothelium-dependent vasodilation has also been shown in peripheral resistance

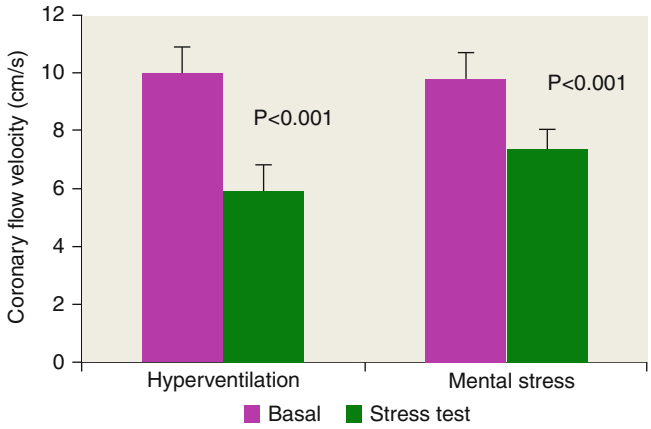

Fig. 7.7 Reduction of resting coronary blood flow in patients with cardiac syndrome X in response to hyperventilation and mental stress test (Based on data from Chauhan et al. [60])

arteries and/or in epicardial coronary arteries [58, 59], suggesting that, at least in a subset of patients, CMVD in CSX patients is part of a more generalized abnormality with subclinical involvement of the entire coronary circulation, or even of the whole arterial circulation.

Increased Vasoconstrictor Response

An enhanced response to vasoconstrictor stimuli of small coronary arteries has also been shown in CSX patients. Intravenous ergonovine (0.15 mg) was indeed found to further reduce the already blunted increase in CBF, and also facilitate the appearance of chest pain, during atrial pacing in patients with MVA [19].

Furthermore, a reduction of CBF, suggesting increased microvascular constriction, has been reported following administration of low-dose acetylcholine [51], hyperventilation, mental stress (Fig. 7.7) and acid oesophageal stimulation [60, 61].

The potential role of vasoconstriction is also supported by the detection of increased plasma levels of endothelin-1, which might be released by an activated dysfunctional endothelium [62]. In particular, an increased ET-1 release has been shown in the coronary sinus of CSX patients during atrial pacing, suggesting that an endothelium-mediated increase in vasoconstriction might have a role in the impairment of CBF at least in some patients [63].

Finally, the role of an enhanced coronary microvascular response to constrictor stimuli in the CSX is supported by the evidence of an increased constrictor response of epicardial coronary arteries to ergonovine [64], as well as by the presence of a concomitant occurrence of epicardial coronary artery spasm in some patients [65]. Again, these findings suggest that, occasionally, the abnormalities of coronary circulation are localized both in the microcirculation and in epicardial coronary arteries.

Summary

In summary, the pathogenic mechanisms responsible for CMVD in patients with the typical syndrome of stable MVA are likely to be multiple and heterogeneous among patients (Fig. 7.8). Their characterization in individual patients might be very helpful, however, for appropriate management.

Causes of Microvascular Dysfunction

The causes responsible for CMVD in CSX are also likely to be heterogeneous. In some patients traditional cardiovascular risk factors (CVRFs), including hypertension, dyslipidaemia, blood glucose disorders and smoking, might play a significant pathogenic role. All traditional CVRFs, indeed, have been demonstrated to cause CMVD, mainly through impairment of endothelium-dependent vasodilation, but also possibly involving impaired endothelium-independent vasodilation, or enhanced coronary microvascular constriction [66–69].

As in patients with obstructive CAD, the presence of CMVD will be revealed by the occurrence of angina symptoms, which might be favoured, at least in some patients, by the presence of enhanced pain perception [7, 8]. This notion is supported by our recent observation that patients with ischaemic ST-segment depression but angiographically normal coronary arteries do have CMVD similar to that found in matched patients with MVA, differing, however, for some features in cortical processing of pain stimuli [70].

It can be speculated that angina patients with obstructive CAD and those with MVA might have common CVRFs but the latter might have some protective factors against the development of the macrovascular disease and of acute complications [6] (Fig. 7.9). This is suggested by the lower platelet activation in response to both physical and mental stress tests that MVA angina patients display, as compared with both CAD patients and healthy controls [71].

The significant prevalence of women in peri-menopausal state reported among CSX patients suggests that oestrogen deficiency may play a significant role in the pathogenesis of CSX in female patients [72]. Of note, menopause also increases the risk of obstructive CAD; thus, the development of CMVD, rather than coronary macrovascular atherosclerotic disease, might still depend on the different individual response to CVRFs.

Other abnormalities that have frequently been reported and have been suggested to play a pathogenetic role in CSX patients include insulin resistance and low-grade inflammation. Dean et al. first showed that glucose load

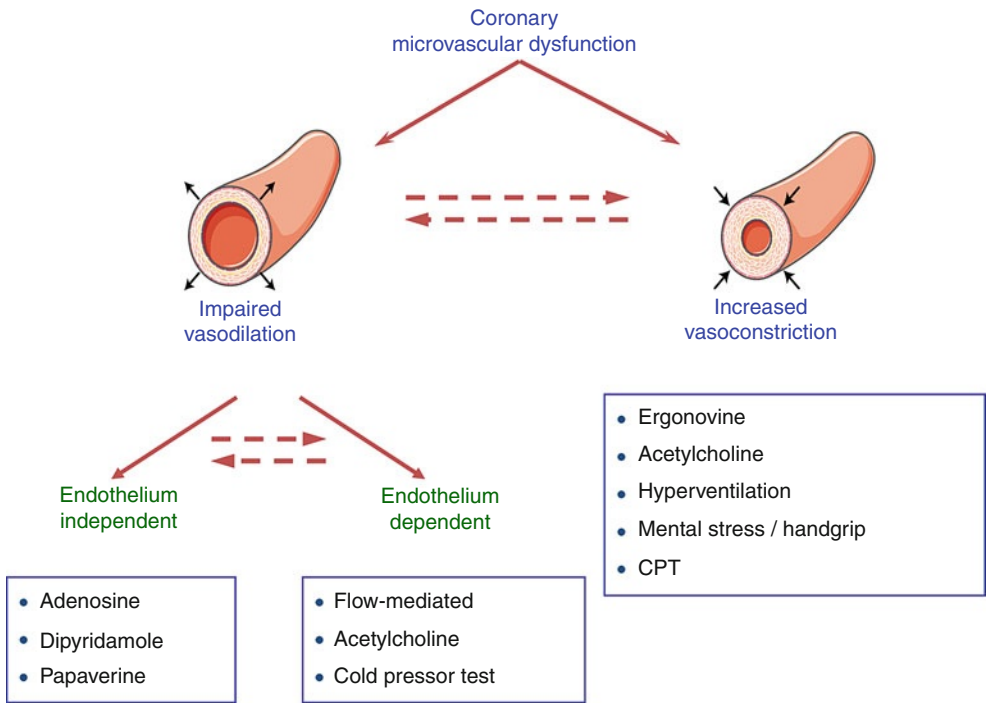

Fig. 7.8 Summary of the potential pathophysiologic abnormalities involved in coronary microvascular dysfunction in patients with microvascular angina and tests used for their identification

resulted in a hyperinsulinemic response in 11 patients with MVA, compared to matched controls, suggesting a role for increased concentrations of insulin in CMVD [73]. This finding was confirmed in subsequent studies using the clamp method [74]. Interestingly, we found lower levels of insulin-like growth factor-1 in MVA patients, which correlated with a hyperinsulinemic response to glucose administration and might mediate the negative effects of hyperinsulinemia on coronary microcirculation [75].

A role for inflammation in CSX has been suggested by the increased serum levels of C-reactive protein (CRP) showed in CSX patients in several studies. A correlation between CRP levels and severity of angina symptoms has been reported in a study [76]. We have also shown increased levels of C-reactive protein [CRP] and interleukin-1 receptor antagonist [IL-1Ra] in CSX patients, compared to matched healthy subjects, with IL-1Ra showing levels similar to those of stable CAD patients [77] (Fig. 7.10). CRP levels have also been shown to be associated with an impaired vasodilator response to both acetylcholine and to adenosine [54, 78], suggesting possible mixed impairment of endothelium-dependent and endothelium-independent coronary microvascular dilator function.

The association between known CVRFs and CMVD in patients with MVA, however, is limited [54, 79], suggesting that other factors are involved as pathogenetic factors in CSX.

In particular, *increased adrenergic* activity has been suggested to play a major pathogenetic role in CSX. A faster increase in heart rate during exercise and evidence of sympatho-vagal imbalance at heart rate variability analysis have been described in these patients [80, 81]. Moreover, we have consistently shown a dramatic impairment of global and/or regional cardiac uptake of meta-iodo-benzylguanidine (MIBG), an analogue of noradrenaline, which suggests an abnormal handling of norepinephrine at cardiac sympathetic nerve endings, in most CSX patients (Fig. 7.11) [82]. The exact mechanisms and consequences of these abnormal findings are not clear, but they suggest that structural or functional alterations of sympathetic cardiac nerves are in some way involved in the CMVD of these patients, although we failed to find a strict correlation between cardiac MIBG uptake and impairment of CMV dilation [83].

Interestingly, some potential cellular mediators of an increased vasoconstrictor response of SMCs have been described. An increased membrane Na^+-H^+ exchanger activity, the major regulator of intracellular pH, which is also able to influence cellular Ca^{2+} handling, and therefore favour vasoconstriction, has also been found in red blood cells and platelets of CSX patients [84, 85], suggesting it can be also increased in SMCs.

Furthermore, a possible role for Rho-kinase, an intracellular enzyme which favours SMC sensitivity to calcium has been suggested to play a role in coronary microvascular spasm [86], and it cannot be excluded that it might also be involved in CMV constriction in MVA patients.

Enhanced Pain Perception

Some patients with obstructive CAD do not usually develop symptoms during myocardial ischemia, even if severe [87]. Why these patients have a predominant or exclusive form

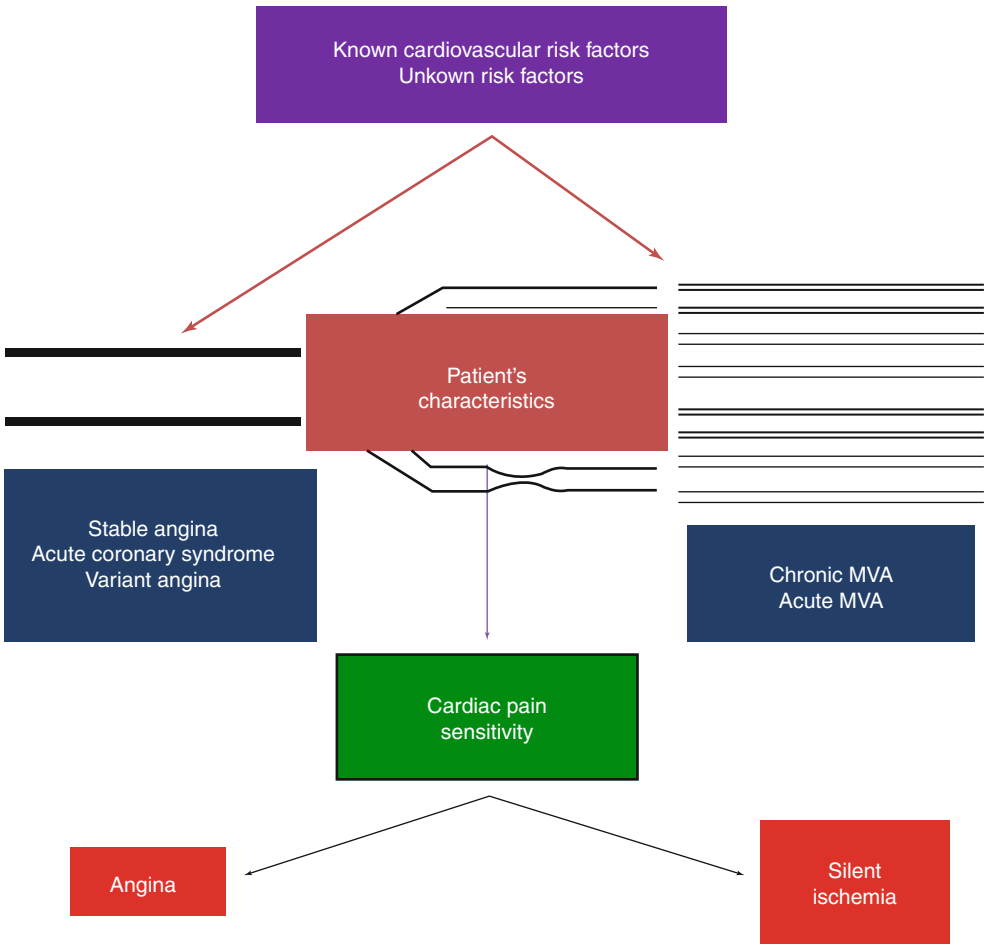

Fig. 7.9 Hypothesis regarding the pathogenesis of microvascular and macrovascular ischemia. Pathogenetic factors of coronary artery injury might be similar, but individual factors may determine the development of only macrovascular or microvascular coronary artery disease (or also both or none). In particular, protective factors against the development of atherosclerosis and its complications might favour the manifestation of the microvascular disease. Factors influencing pain perception influence the development of symptoms or of a silent form of ischaemia only. *MVA* microvascular angina

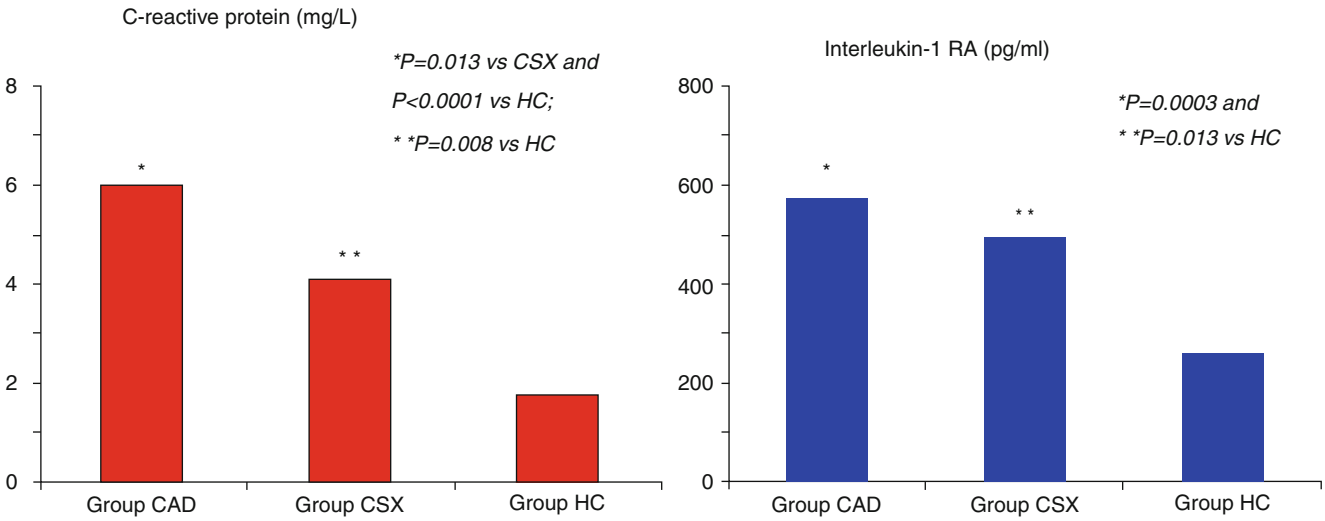

Fig. 7.10 Plasma levels of C-reactive protein and of interleukin-1 receptor antagonist in 55 patients with cardiac syndrome X (*CSX*), in 49 patients with obstructive coronary artery disease (CAD) and in 60 healthy controls (*HC*). Significantly higher levels of both inflammatory cytokines were detected in CSX patients, compared to HC, indicating an increased inflammatory state (Modified from Lanza et al. [77])

of silent ischemia remains largely unknown, but peculiar characteristics of pain generation and/or processing are likely to play a role.

In CSX patients, on the other hand, severe angina may occur despite mild degrees of myocardial ischaemia. This likely depends on an enhanced painful perception of cardiac

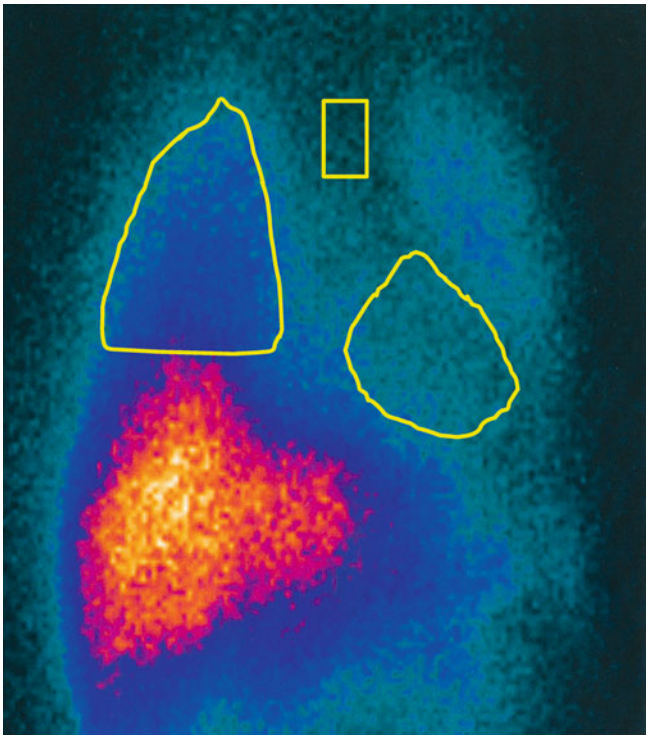

Fig. 7.11 Radionuclide image obtained 3 h after the injection of ^{123}I-metaiodobenzylguanidine (*MIBG*) from a patient with cardiac syndrome X. Cardiac MIBG uptake is totally absent, despite normal lung and liver uptake

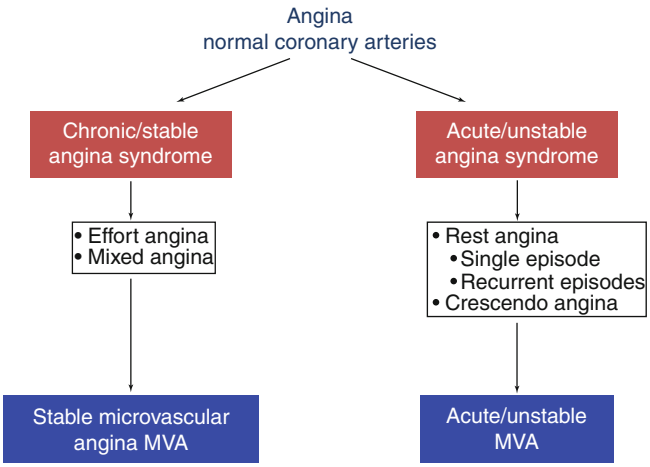

Fig. 7.12 Classification of microvascular angina according to clinical presentation (Modified from Lanza and Crea [6])

stimuli that has convincingly been demonstrated in several patients. The injection of saline or contrast medium in the cardiac chambers or in the coronary arteries, often causes pain in these patients, as also do pacing or intracardiac catheter manipulation [7, 8, 88].

The causes of the nociceptive dysfunction remain undefined. The considerable abnormalities of efferent cardiac adrenergic fibres [82] suggest possible alterations also in the function of afferent cardiac nerve fibres, and, using a randomized sham-controlled cross-over study, we have shown that the enhanced pain perception may mainly involve the ventricles [8]. Whether the neural abnormality is a cause or consequence of microvascular ischemia, however, remains to be ascertained [89].

On the other hand, other findings suggest that abnormalities in the central processing of peripheral stimuli may play a significant role at least in some patients [90, 91].

Independently of the etio-pathogenic mechanisms, the presence of the enhanced pain sensitivity helps to explain the development of angina, as well as the frequent relevant recurrence of angina symptoms, even for the low grade of myocardial ischemia occurring in MVA patients.

This is also supported by the fact that these patients show also an increased perception of typical pain when adenosine, the main mediator of myocardial ischemia-induced chest pain, is injected intravenously [92].

Beyond CSX

As recently highlighted, CMVD can be responsible for angina symptoms not only in patients presenting with the clinical features of CSX, but also in some other groups of patients, who have different clinical presentations [6] (Fig. 7.12). In some patients MVA can present as an acute/unstable form of angina, simulating non ST elevation acute coronary syndrome (NSTE-ACS). Again coronary angiography surprisingly shows normal coronary arteries.

While this clinical presentation concerns 5 % or more of NSTE-ACS patients [93] and can be attributable to various causes (either cardiac or non cardiac), some preliminary studies suggest that CMVD is the cause of angina in some patients [6].

In these patients with unstable primary MVA the basic clues to a myocardial ischemic origin of symptoms are the presence of transient abnormalities on standard ECG (i.e., ST-segment depression, negative T waves) and, in some patients, a mild elevation of serum markers of myocardial damage (mainly troponins).

The pathophysiological mechanisms responsible for CMVD in NSTE-ACS patients with normal coronary arteries are poorly known at present, as they have not been adequately investigated; however, intense vasoconstriction of prearteriolar and/or arteriolar coronary vessels is expected to represent the major mechanism of ischemia.

The detection at angiography of SCF has been suggested to be a clue to coronary microvascular constriction in some patients. The presence of SCF suggests basal increased constriction, which can be exacerbated by provocative stimuli, as cold pressor and/or acetylcholine [94, 95], while coronary vasodilator response may appear normal in these patients. The causes of coronary microvascular constriction in unstable

MVA remain also unexplored. Also in this case, however, the pathogenesis of CMVD is heterogeneous, and may involve a transient increase in neuro-humoral vasoconstrictor activity and increased susceptibility to vasoconstrictor agents.

Conclusions

The causes of CMVD in CSX are likely to be multiple and may result in a variable combination of impaired coronary microvascular dilation and increased vasoconstriction, with vasodilator abnormalities variably involving endothelium-dependent and endothelium-independent mechanisms. Furthermore, the role of structural vs. functional abnormalities remains to be better elucidated. Importantly, the mechanisms are likely to differ according to clinical presentation.

Efforts should be made to identify potential causes and mechanisms of CMVD in individual patients as this might point towards the most appropriate therapeutic approach.

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Endothelial Dysfunction in Microvascular Angina

8

Domenico G. Della Rocca and Carl J. Pepine

Abstract

A large proportion of patients with chest discomfort, thought to be angina pectoris, have "normal" or non-obstructive epicardial coronary arteries at angiography. However, absence of angiographic evidence of stenosis is not a sufficient criterion to fully determine the health status of the coronary vasculature as related to exclusion of ischemic heart disease (IHD). Endothelial and vascular smooth muscle dysfunction, at both the microvascular and macrovascular level, may negatively influence myocyte oxygenation and cannot be directly visualized by coronary angiography. Alternative techniques that measure coronary blood flow changes in response to stressors or resistance changes are required to more fully evaluate coronary microvascular function. Of the pathophysiological mechanisms proposed to explain functional impairment of the microvasculature as well as IHD, endothelial dysfunction is one central etiologic substrate. While dysfunctional endothelium clearly impacts coronary vasomotor properties and blood flow responses, endothelium-independent vascular smooth muscle dysfunction also has a role in the development of IHD and related symptoms like angina and is a predictor of adverse outcomes.

Keywords

Microvascular angina • Normal coronary arteries • Endothelial dysfunction • Vasoactive stimuli

Introduction

It is estimated that over nine million US patients have angina pectoris, which significantly impacts quality of life, ability to work, and costs to society [1].

Historical Considerations

An early report on the relationship between clinical manifestations and pathological findings noted that uncomplicated angina pectoris was often associated with occlusions of at least two of the main coronary arteries [2]. In the study, "no patient with angina pectoris failed to show a zone of old, complete occlusion in at least one of the major coronary arteries." With introduction of coronary angiography, this concept of occlusive stenosis in major coronary artery branches was reinforced by multiple reports correlating clinical manifestations (e.g., angina) with severe coronary artery disease (CAD) in living patients [3, 4]. Then in 1967 Likoff and colleagues first called attention to the "paradox of angina with unmistakable normal coronary angiograms" in a group of 15 women with ischemic electrocardiographic (ECG) abnormalities without diabetes or hypertension [5]. Many confirmatory reports followed in larger cohorts of women and men.

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Prevalence

Since then it has become accepted that among patients undergoing coronary angiography for evaluation of chest pain thought to represent angina pectoris, a large proportion has angiographically "normal" epicardial vessels or insufficient obstructive disease to explain ischemia [6–11]. The Coronary Artery Surgery Study (CASS) Registry found that among 25,000 patients with symptoms and/or signs of ischemia undergoing coronary angiography, 39 % of women and 11 % of men had what appeared to be "normal" epicardial arteries [12]. The American College of Cardiology-National Cardiovascular Data Registry (ACC-NCDR) database with several hundred thousand patients found "non-obstructive CAD" was considerably more frequent than that reported earlier from the CASS Registry with frequencies significantly higher among women (51 %) vs. men (32 %) [13]. The Women's Ischemia Syndrome Evaluation (WISE) found that 62 % of women referred to angiography for angina had none or non-obstructive disease.

Pathophysiological Mechanisms

The "Microvascular" Hypotheses

Likoff et al. proposed the presence of microvascular abnormalities as "pathophysiologic fault" (for IHD) hidden under the angiographic aspect of normal coronary arteries [5]. Kemp et al. documented myocardial lactate production in such patients during isoproterenol infusion [14]. In 1973, Kemp used the term "Syndrome X" in an editorial comment [7] on an article by Arbogast and Bourassa [15], in reference to features of their "Group X" patients with angina and normal coronary angiograms plus ECG and lactate evidence of myocardial ischemia. Cannon, Epstein and coworkers introduced the term "microvascular angina" in 1983, after documenting evidence for microvascular dysfunction as an inappropriate coronary flow response to various stimuli despite normal epicardial vessels by angiography [16]. They concluded that: (1) chest pain experienced by many of these patients is due to myocardial ischemia, (2) ischemia was caused by abnormal coronary dilator reserve (or constriction), and (3) this abnormal response may be due to reduced dilator response of small coronary arteries (presumably arterioles) to increased oxygen demand [16].

Evidence for Myocardial Ischemia

In addition to chest pain, the ECG ST-segment changes, myocardial metabolic abnormalities (e.g., lactate production, high-energy phosphate depletion, pH changes, etc.), perfusion abnormalities (SPECT, PET, cMRI), and transient alterations in left ventricular end-diastolic pressure have confirmed the presence of reversible malperfusion leading to myocellular hypoxemia and ischemia. Interestingly, we and others [16] have observed that in many of these patients there is wide variability in the ability to reliably reproduce symptoms and stress test findings during repeated testing. This within patient variability contributes to making these patients very difficult to evaluate for clinical and research purposes.

Role of Endothelium

Multiple pathophysiological mechanisms, operating above or in concept, have been proposed to explain development of microvascular angina [e.g., endothelial dysfunction (ED), reduced coronary flow reserve, impaired autonomic activity, altered platelet aggregability, diffuse atherosclerotic changes in epicardial vessels of medium diameter not visualizable by coronary angiography, ion imbalance in cardiomyocytes, hormonal imbalance and heightened pain perception] [17–24]. Mounting evidence indicates that ED underlies the pathophysiology of this disorder. Of note, most of the patients with this syndrome referred for invasive evaluation have multiple atherosclerosis risk conditions (increased LDL-C, hypertension, dysglycemia, obesity, diabetes, etc.) and these conditions alone in experimental models are associated with ED (Fig. 8.1). Additionally, endothelial function in patients with cardiac syndrome X (CSX) has been shown to be impaired similar to patients with CAD [25].

Endothelial cells (ECs) play a pivotal homeostatic role in vascular health, including vascular tone regulation, smooth muscle cell (SMC) growth inhibition, regulation of vessel wall remodeling, modulation of inflammatory responses, and release of antithrombotic factors. Many of the above mentioned functions are accomplished by synthesis and metabolism of substances in response to chemical and mechanical stimuli. The endothelium is a dynamic and multifunction system that is an essential regulatory mechanism for myocardial blood flow and flow distribution via SMC contraction and relaxation at the microvascular level. These effects are mediated by a number of endothelium-dependent vasoconstrictor and vasodilator factors [26].

Endothelium-Dependent Vasodilators

Nitric oxide (NO) has a central role in endothelial function and vascular SMC tone regulation (Fig. 8.2). It is synthesized by ECs NO synthase (eNOS) through oxidation of L-arginine to L-citrulline and exerts potent vascular SMC relaxation. In normal vessels this relaxation overrides SMC activation resulting from acetylcholine-induced activation of muscarinic receptors. eNOS, product of the Nos3 gene located in chromosome 7 (7q35—q36), is constitutively

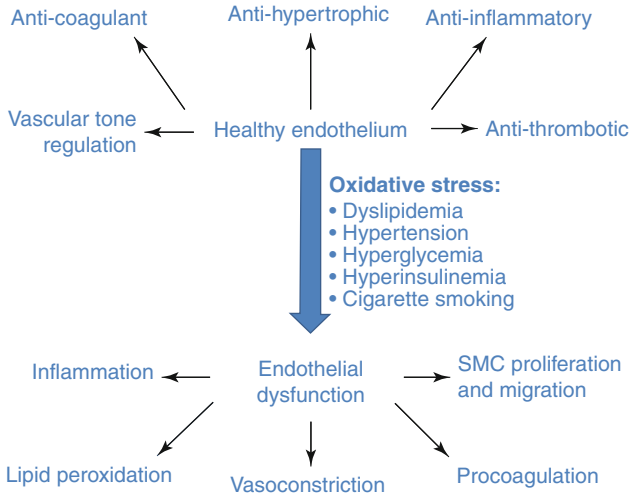

Fig. 8.1 Pathophysiology of endothelial dysfunction. *SMCs* smooth muscle cells

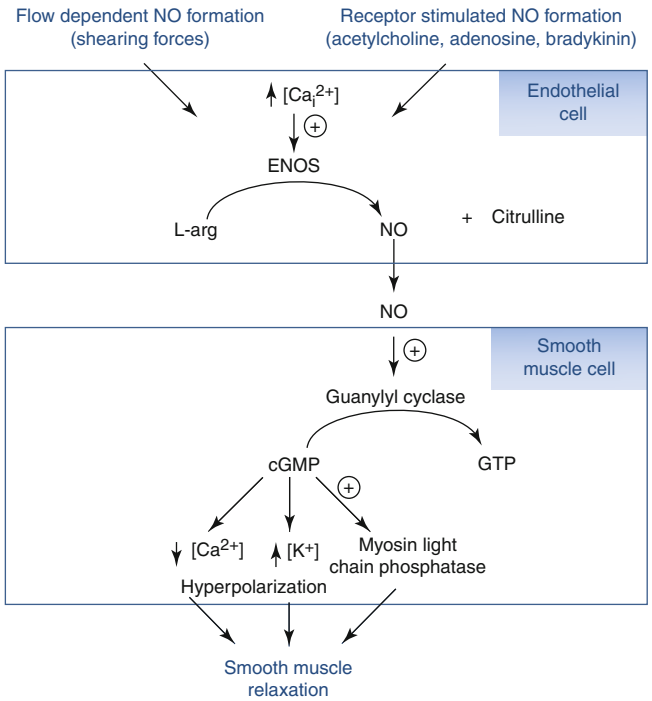

Fig. 8.2 Nitric oxide mediated vasodilation. *NO* nitric oxide, Ca_i^{2+} intracellular calcium; *eNOS* endothelial NO synthase, *L-arg* L-arginine, *cGMP* cyclic guanosine monophosphate, *GTP* guanosine 5′-triphosphate, *K* potassium

expressed by ECs but is stimulated further by multiple receptor-dependent agonists (e.g. thrombin, adenosine 5′-diphosphate, bradykinin, substance P, muscarinic agonists), shear stress [27], and cyclic strain [28].

Shear stress can affect endothelial function by determining K^+ channel activation, as well as vasoconstrictor, vasodilator and growth factors secretion with influx of Ca^{2+} due to increased release of ATP-activated P2X4 receptors [29]. This causes SMC relaxation with dilation of large, medium and small (microcirculation) vessels to result in flow-mediated dilation.

An increase in *myocardial oxygen demand*, in response to stress (e.g., exercise, emotion, etc.), releases vasodilator factors from healthy endothelium with an increase in coronary blood flow.

Healthy endothelium can also release *prostacyclin* (PGI_2) and *endothelial-derived hyperpolarizing factor* (EDHF), which have a synergic effect with NO on SMC relaxation and vascular tone control. Additionally, PGI_2 inhibits platelet activation but not adhesion [30, 31]. Since NO is a key mediator of endothelial function and vascular homeostasis, and is synthesized by eNOS, the possible role of eNOS gene polymorphisms as susceptibility factors for microvascular angina have been examined. Studies have found a role for the Glu298Asp polymorphism as a risk factor for CAD and myocardial infarction [32, 33]. A recent report provided support for this gene's role in the pathogenesis of microvascular angina among hypertensive patients [34]. Patients with CSX and genotype T/T Glu298Asp show lower levels of NO, compared to patients with genotype G/G [35]. They also experience lower fasting NO levels and an abnormal oral glucose tolerance test at 1 h (higher level of insulin) and oral lipid tolerance test (high levels of triglycerides and free fatty acids). The metabolic abnormality represented by high postprandial levels of free fatty acids may promote oxidative stress and apoptosis of ECs [36] and lead to coronary atherosclerosis and microvascular dysfunction. Three other polymorphisms of the eNOS gene (VNTR in intron 4, T786C polymorphism in the promoter region and G894T polymorphism in exon 7) have been studied [37]. Only the intron 4aa polymorphism has displayed a protective effect against CSX disease, independent of age, sex, hypertension and hyperlipidemia and has been associated with left ventricular hypertrophy in patients with CSX [38].

Endothelium-Dependent Vasoconstrictors

Counter-regulatory factors of endothelial function include endothelin-1 (ET-1, the most potent endogenous vasoconstrictor) thromboxane (TXA_2), transforming growth factor-β (TGF-β) and angiotensin II (ATII). *Endothelin* constitutes a three member family (ET-1, -2 and -3) of 21-aminoacid peptides produced by many cell types [39]. ET-1 is produced by EC and SMCs, airways epithelial cells, macrophages, fibroblasts, cardiac myocytes, brain neurons and pancreatic islets and contributes to vascular tone control with NO. In contrast with the vasoconstrictor effects exerted by ET-1, ET-3 is a product of vascular and intestinal endothelial cells and mediates release of vasodilator substances, especially NO and PGI_2. Three isoforms exert their effects through at least two seven-transmembrane G-protein couple receptors, ET(A) and ET(B) [40, 41]. ET(A) is expressed on vascular

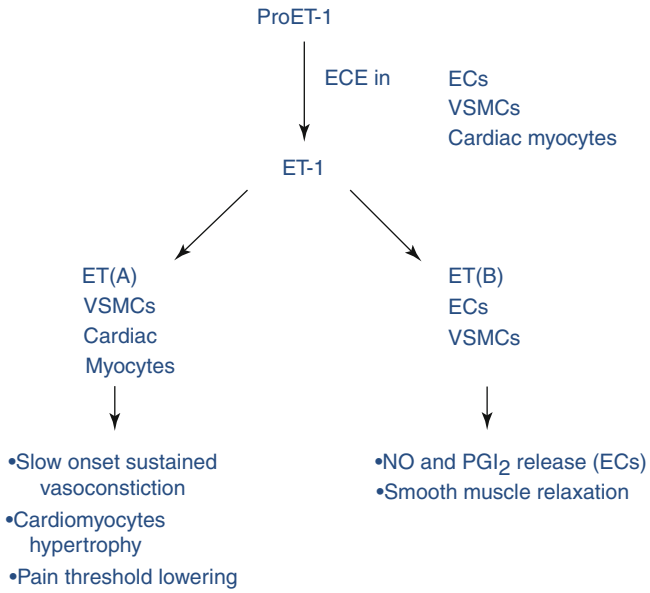

Fig. 8.3 Endothelin biosynthesis and cardiovascular effects. *ET-1* endothelin-1, *ProET-1* precursor peptides of ET-1, *ECE* endothelin-converting enzyme, *ECs* endothelial cells, *VSMCs* vascular smooth muscle cells, *ET*(A) and (B) endothelin receptors, *NO* nitric oxide, PGI_2 prostacyclin

SMCs and exerts a slow-onset sustained vasoconstriction (Fig. 8.3). ET(B) is located on ECs and vascular SMCs. Its activation promotes release of vasodilator substances (NO and PGI_2) by endothelium and relaxation of SMCs with consequent vascular dilation [42]. ECs are a rich source of *angiotensin converting enzyme* (ACE) to generate ATII, a vasoconstrictor which stimulates production of endothelin, among others. Both endothelin and ATII contribute to the pro-oxidant status and promote SMC contraction and proliferation, which lead to vascular remodeling and atherosclerotic plaque formation and growth. ATII also shows a pro-oxidant activity, which determines oxidative modification of low-density lipoprotein (LDL) cholesterol.

The gene for ACE has been investigated as a possible candidate in the pathogenesis of ED and microvascular angina. The enzyme is mainly expressed in lung and endothelium but is also found in heart and other organs (kidney, brain, bone marrow). It may exhibit an insertion (I) or deletion (D) polymorphism in intron 16, resulting in three genotypes (II, DD and ID). The heterozygous genotype I/D represents the most common genetic variant (47 %). Compared with the other two genotypes, the DD variant is associated with higher plasma ACE levels. Studies have reported a higher risk of CAD (Nakai 1994), left ventricular hypertrophy [43], arterial thickening [44, 45], and renal disease [46–48] among patients carrying the D/D genotype. The allelic variant was associated with impaired microvascular structure of the kidney in patients with non-diabetic renal disease [49]. The I allele frequencies have resulted to be significantly higher among elite distance runners, rowers and mountaineers, presumably a result of superior microvascular function in skeletal muscle [50–52].

We have shown that microvascular function improves with ACE-I therapy (quinapril, 80 mg/day) using a randomized, double blind, parallel design in 78 women with signs and symptoms of ischemia without obstructive CAD. Improvement of (CFR) coronary flow reserve was associated with reduction in angina. The beneficial response of the coronary microvasculature was limited to women with lower baseline CFR values (≤2.5), suggesting that the renin-angiotensin system is more involved among women with more severe microvascular diathesis [53]. Our findings extend data available on blocking effects of AT-II in microvascular angina among women. Kaski et al. [54], in a randomized, single-blind, crossover study of ten patients (seven women), found after 2 weeks of enalapril (10 mg/day) versus placebo that exercise duration and time to ischemia increased as ST depression decreased. Chen et al. [55] studied 20 patients (5 women) randomized to enalapril (5 mg twice daily, n = 10) or placebo (n = 10) (double blind design). After 8 weeks, exercise duration and CFR improved as endothelial markers (e.g. plasma von Willebrand factor and NO) increased with enalapril versus placebo.

Additionally, an association between ACE I allele and better muscle fatigue resistance has been reported [56]. In spite of the critical role of the renin-angiotensin-aldosterone system (RAAS) in vascular biology, there is insufficient evidence supporting ACE genetic variability as a determinant in the pathogenesis of microvascular angina.

Endothelial Dysfunction

When the balance is disrupted between vascular relaxing (e.g., NO, PGI_2 and EDHF) and contracting factors (e.g., ETI, ATII, TXA_2 and TGF-β), between growth inhibiting and promoting mediators, between antiphlogistic and prophlogistic substances, and between anticoagulant [e.g., NO, PGI_2, tissue plasminogen activator (tPA)] and procoagulant factor [e.g., tissue factor (TF), von Willebrand factor (vWF), TXA_2, plasminogen activator inhibitor (PAI), thrombomodulin (TM)], ED occurs. The disturbance of the antioxidant/oxidant balance results in an excess of reactive oxygen species, which contribute further to endothelial and vascular dysfunction. This provokes arterial wall damage and structural changes with proliferation of SMCs in the tunica intima and subintima, platelet and leukocyte activation, and adhesion and synthesis of cytokines, which increase endothelial permeability (e.g., VEGF) to oxidized lipoproteins. ED is considered the cornerstone in the pathogenesis of CAD. It is present at the earliest as well as the latest stages of the atherosclerotic process.

Patients with microvascular angina are often women, presenting with severe, chest discomfort typical for angina pectoris and lack of evidence of flow-limiting stenosis on coronary angiography. An impaired CFR, attributable to a

reduced microvascular dilatory response and realistically due to ED, has been proposed as the pathogenetic mechanism. ED is a systemic disorder, affecting large, medium and small vessels in various vascular beds and linked with levels of CAD risk factors (e.g., aging, male gender, obesity, hypertension, hypercholesterolemia, diabetes, smoking, systemic chronic inflammatory processes, estrogen deficiency in women) that are frequently present in patients with CSX.

Role of Vascular Smooth Muscle Cells

Mounting evidence supports the model of an active and synergistic interaction between ECs and SMCs for vascular tone control and homeostasis [57–61]. A cell-to-cell interaction, observed in vivo as myoendothelial bridges, has been proposed to regulate cellular growth, migration, differentiation and function in addition to the intricate paracrine regulation [62, 63]. In light of these findings, vascular SMC dysfunction results from a generalized, coexisting abnormality involving both ECs and SMCs. Several studies have shown evidence of a generalized disorder of smooth muscle tone regulation in patients with microvascular angina as well. In 1987, Sax et al. observed an impaired hyperemic response to forearm ischemia in patients with angina like chest pain, normal angiograms and a limited coronary flow response to atrial pacing and the vasodilator dipyridamole [64]. In 1990 Cannon et al. reported a high incidence of abnormal esophageal motility in patients with chest pain and normal coronary angiograms [65].

About 20 % had their typical chest pain during motility testing; angina-like chest pain was evoked in about half of those tested during intraesophageal balloon distention and in about 10 % during Bernstein testing, consisting of instillation of a weak solution of hydrochloric acid into the lower esophagus. These results suggest a possible combined role of esophageal dysfunction, abnormal visceral nociception and chest pain perception by patients with microvascular angina. On the basis of the high incidence of shortness of breath experienced by the majority of patients with microvascular angina, coronary microvascular dysfunction was linked with abnormal airflow resistance at rest and after inhalation of methacholine [65].

Structural and Functional Vascular Abnormalities

Although there is strong evidence supporting the role of microvascular coronary dysfunction in the pathogenesis of the disorder, several reports have suggested also a structural and/or functional involvement of large systemic and coronary vessels. Patients with typical, angina-like chest pain and angiographically "normal" coronary arteries exhibit increased carotid intima-media thickness, arterial stiffness and elastic module values than control subjects [66]. Although the epicardial vessels are apparently unaffected in the structure and non flow-limiting atherosclerotic lesions observed on coronary angiograms, a functional impairment of large coronary vessels has been reported. In 1989 two studies observed abnormal large coronary vasomotor responses in patients with CSX during exercise [67] and after calcium antagonist therapy (nefedipine) [68]. Additionally, patients without obstructive CAD, who exhibit ED assessed by intracoronary acetylcholine infusion, are at higher risk of cerebrovascular events [69].

More recently, we found that microvascular flow limitations [70] as well as macrovascular ED were highly prevalent among women in the WISE cohort and also independent predictors of adverse outcome [71]. In microvascular angina, SMCs show an enhanced Na^+-H^+ channel activity that can result in cellular alkalinisation with increased susceptibility to vasoconstrictors [72]. Abnormalities of NO generation, secretion and activity have been observed. Lerman et al. reported a decrease in coronary cGMP, the second messenger for NO activity, when the coronary endothelium is dysfunctional [73]. Patients with CSX also exhibit lower nitrate/nitrite systemic concentrations resulting from impaired NO production and secretion [55]. Egashira described a normalization of endothelium-dependent vasodilation after intracoronary infusion of the precursor of NO, L-arginine, in these patients [74]. Intravenous infusion of L-arginine can also restore insulin-mediated NO release [75]. Kolasin'ska-Kloch and colleagues reported a lower basal concentration of NO in patients with CSX, not observed at peak exercise and during recovery [76]. They also observed a lower basal NO/ET-1 ratio. Higher concentrations of estradiol were found in male patients.

Other levels of sex hormones (e.g., LH, FSH, testosterone) were comparable with controls in both sexes (estradiol only in women). Interestingly, in their study on "biochemical parameters of ED in cardiological syndrome X" they also observed a decrease in concentration of tPA during exercise and high blood levels of vascular endothelial growth factor (VEGF). VEGF promotes angiogenesis, vascular permeability and dilation and is released in response to hypoxia or ischemia. This finding is compatible with the results of other studies, which observed higher levels of endothelial progenitor cells (EPCs) in patients with CSX [77]. However, in vitro studies demonstrated a significant impairment of proliferative capacity, tube formation and adhesiveness of circulating EPCs. Other studies reported decreased levels and adhesive functions of EPCs in the same patients. High levels of ET-1 are a common finding in patients with chest pain and normal coronaries [78, 79]. ET-1 is the most powerful vasoconstrictor and also exhibits mitogenic [80] and algogenic [81] properties. Recent studies have observed a correlation between plasma ET levels and scintigraphically determined myocardial perfusion reserve [82]. Moreover, a relationship between high ET levels and impaired coronary vasomotor responses

has been reported. The algogenic properties of ET-1 may lead to pain threshold lowering and contribute to pain perception and anginal pain development. Inflammation is considered to have a central role in the pathogenesis of microvascular dysfunction. High levels of circulating forms of intracellular cell adhesion molecules (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1), molecules implicated in leukocyte adhesion, were observed in patients with chest pain and normal coronary arteries [83]. Additionally, these patients exhibit high blood levels of C-reactive protein (CRP) [84]. CRP levels have been demonstrated to correlate to CSX clinical activity [85]. High levels of CRP are related to frequent and prolonged angina symptoms, positive exercise stress test responses and ischemic episodes at 24-h ECG recordings. An inverse association was also reported between CRP levels and coronary blood flow response to acetylcholine [86].

With regard to the dysfunctional coronary microvascular bed that is thought to be the pathogenetic factor contributing to the onset of CSX, contrasting histologic data have been reported. The presence or the absence of non-specific histologic abnormalities have been suggested by different investigators [87–90]. The main findings in patients with CSX undergoing endomyocardial biopsy revealed interstitial fibrosis, hypertrophied myocardial fibers, mitochondrial swelling, small myelin figures and Z-band abnormalities [87–89]. In 1986, Mosseri et al. performed right ventricle endomyocardial biopsy in six patients with angina-like chest pain and normal coronary arteries, also suffering from congestive heart failure (2 pts), supraventricular tachyarrhythmias (3pts), or conduction disturbances (3pts) [91]. Histologic examination revealed hypertrophy of myocardial fibers, lipofuscin bodies, myofibrillar degeneration, interstitial fibrosis and significant thickening of the intramural coronary arteries with fibromuscular hyperplasia and hypertrophy of the media and mild intimal changes. Capillaries were contracted with markedly swollen, degenerated ECs with loss of pinocytic vesicles and organelle. In 2003, intravital videocapillaroscopy in peripheral (hands and feet nailfold, gingival edge, labial mucosa) and conjunctival observation sites were used to study microvascular structural changes in CSX [92]. The examination revealed markedly morphological abnormalities and severe quantitative alterations of the microcirculation (capillary redistribution, low capillary density, devascularization, wall profile alterations). Since ED is considered a systemic disorder, it may be assumed that the morphological abnormalities observed in the peripheral microvasculature mirror those in the coronary microvasculature.

Myocardial Perfusion and Coronary Blood Flow Assessment

Absence of angiographic evidence of atherosclerotic lesions is not a sufficient criterion to determine the health status of a coronary artery: angiographic normality does not necessarily correspond to functional normality. In 1981 Opherk et al. reported for the first time a significant decrease of coronary blood flow in patients with typical angina-like pain on effort but normal angiograms, compared to a group of patients without heart disease, after administration of dipyridamole [88]. In 1986, Yasue and colleagues observed a vasoconstrictor response in 27 of 70 arteries in 28 patients with variant angina who had no angiographic evidence of coronary artery stenosis or stenosis less than 25 % [93]. In 1989 Werns et al. showed that intracoronary infusion of acetylcholine in angiographically normal coronary arteries of patients with angiographic evidence of CAD results in vasoconstriction [94]. Multiple studies have linked ED with the burden of cardiovascular risk factors (e.g., aging, male gender, family history of premature CAD, high levels of LDL-cholesterol, hypertension, diabetes, smoking, estrogen deficiency and chronic inflammatory disease). ED is present at the late stages of CAD, when mostly atherosclerosis represents the pathologic substrate contributing to clinical sequelae related to tissue damage (e.g., ischemia, infarction) as well as the earliest stages when there is no angiographic evidence of coronary disease.

Coronary artery functionality can be assessed by invasive and non-invasive methods. Coronary artery assessment in the catheterization lab setting represents the reference standard for vascular function testing. Since microvascular angina mainly involves small resistance coronary vessels which cannot be studied directly because they are not visible at coronary angiography, microvascular dysfunction is assessed through the response of coronary blood flow to endothelial-dependent and endothelial-independent vasoactive stimuli. When dilation of the coronary microvasculature occurs, coronary vascular resistance decreases and coronary blood flow increases.

Different techniques have been used for the measurement of coronary blood flow [e.g., thermodilution, intracoronary Doppler ultrasound, positron emission tomography (PET), magnetic resonance imaging (MRI)]. Coronary endothelium-dependent vasodilation can be evoked by rapid atrial pacing or intracoronary acetylcholine administration. Different vasoactive stimuli are used for the assessment of endothelium-independent coronary vasodilator function (sodium nitroprusside, adenosine, dipyridamole, papaverine). Furthermore, pharmacological and physical coronary vasoconstrictor stimuli may unmask or exacerbate signs and symptoms of a myocardial ischemic insult in a proportion of patients with angina-like chest pain and normal coronary angiograms (acetylcholine, cold pressor test, ergot-alkaloids like ergonovine or methergine, handgrip). Tachycardia, produced by rapid atrial pacing, promotes a decrease in coronary vascular resistance secondary to flow-dependent release, mainly promoted by an increase in both myocardial oxygen demand and endothelial shear stress.

Acetylcholine is another endothelium-dependent vasodilator, which promotes NO release through the activation of muscarinic receptors expressed on the membrane of ECs. The common physiological and pathophysiological substrate driving endothelial-dependent vascular response to acetylcholine and rapid atrial pacing explains the similarity of results. Acetylcholine exerts a complex dual action that can result in vascular dilation or constriction depending on injected dose and vascular health status. Indeed, high concentration of the mediator can induce vasoconstriction through a direct activation of muscarinic receptors on the surface of SMCs. Additionally, a paradoxical vasoconstrictor response may be observed as low doses may result in vasoconstriction if endothelium is dysfunctional [95–99]. Experimental data documented that when endothelium is removed acetylcholine exhibits only vasoconstrictor properties by a direct action on SMCs. In light of these findings, stimulation of healthy endothelium and resulting physiologic increase in coronary flow are achieved when intracoronary doses of acetylcholine are lower than those required for a direct activation of SMCs as long as endothelium is functional (e.g. NO release).

Endothelium-independent vasoactive stimuli elicit vasodilation via direct SMCs relaxation. Sodium nitroprusside activates vascular SMCs guanylate cyclase that increases intracellular levels of cGMP. This results in a decrease of intracytoplasmatic calcium available to bind with calmodulin. Adenosine promotes SMCs hyperpolarization through the activation of A_1 and A_2 adenosine receptors and ATP-sensitive K^+-channels. Hyperpolarization leads to voltage-dependent calcium channels closure and a decrease in intracellular Ca^{2+} levels. Dipyridamole inhibits adenosine reuptake and catabolism resulting in increased extracellular levels of the nucleoside and increased intracellular levels of cGMP produced by NO through cGMP-phosphodiesterases inhibition.

In 1983 Cannon et al. studied the effect of rapid atrial pacing and ergonovine in patients with insignificant or no evidence of CAD [16]. The nine patients experiencing chest pain exhibited a lower increase in coronary blood flow than that of the remaining 13 patients who did not develop pacing-induced chest pain. Administration of the vasoconstrictor ergonovine elicited chest pain at rest in 2 of 20 patients and in 10 others during rapid atrial pacing. Legrand et al. reported abnormal exercise scintigraphic findings (regional exercise thallium-201 perfusion, regional exercise wall motion) and low coronary flow reserve in male patients with chest pain and normal coronary artery angiography [100]. Greenberg et al. studied the response of coronary blood flow to incremental atrial pacing in two groups of patients with angina-like pain and normal coronary arteries, selected on the basis of normal lactate extraction (group 1) or lactate production (group 2) at high pacing rate [101]. The latter showed a decreased coronary vasodilation and no difference in coronary vascular resistance in response to pacing stress. In 1989 Bortone and coworkers observed that some patients with microvascular angina can develop vasoconstriction of the distal coronary segments responsive to sublingual nitroglycerin and a vasodilation of the proximal coronary segments during exercise [67]. These patients also showed an impaired coronary flow response to dipyridamole. In 1991 Motz et al. studied the coronary flow response to acetylcholine and dipyridamole in 23 patients with clinical evidence of CAD and normal coronary angiograms [102]. They suggested for the first time the critical role of ED in the pathogenesis of CSX. Only six patients experienced an increase in coronary blood flow after administration of acetylcholine and dipyridamole. Eleven patients exhibited an abnormal vasomotor response to acetylcholine (no increase in coronary flow in eight patients, vasoconstriction in three patients). In six patients both acetylcholine and dipyridamole did not elicit an increase in coronary blood flow. In 1992 Vrints and colleagues examined the response of coronary blood flow to acetylcholine in 24 patients with typical (12 patients) and atypical (12 patients) anginal pain and normal coronary arteries [103]. The hemodynamic data were compared to those from 36 patients with flow-limiting stenosis (>50 % lumen diameter narrowing) in at least one major coronary artery and different degrees of atherosclerosis of the left anterior descending artery. In all the patients with CAD, intracoronary infusion of acetylcholine resulted in dose-dependent vasoconstriction (Fig. 8.4). The response was independent of the degree of atherosclerosis affecting the left anterior descending artery. Acetylcholine-induced vasoconstriction was observed in the 12 patients with typical chest pain and smooth coronaries. Nine of these patients experienced also typical chest pain during the infusion of acetylcholine.

Conversely, vasodilation was observed in patients with atypical chest pain and normal arteriograms. In 1993 Egashira et al. compared the responses of coronary blood flow between nine CSX patients and ten control patients after infusion of the endothelium-dependent vasodilator acetylcholine and the endothelium-independent vasodilators papaverine and isosorbide dinitrate [20]. Increasing doses of acetylcholine resulted in an increase in coronary blood flow in both groups. However, the degree of vasodilation was significantly lower in CSX group. High dose of the drug caused vasoconstriction in both groups. No differences were reported in coronary artery dilation and blood flow between the groups after administration of the two endothelium-independent vasodilators. Myocardial lactate production followed the infusion of papaverine and six of the nine patient developed anginal chest pain with ischemic ST-segment depression. The presence of myocardial perfusion defects within the territory of the left anterior descending coronary assessed by ^{99m}Tc-sestamibi SPECT imaging was associated with a decrease in coronary artery diameter by quantitative coronary angiography and coronary blood flow by intracoronary flow Doppler

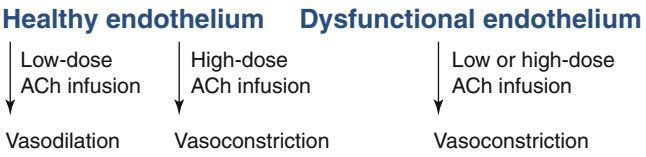

Fig. 8.4 Dose-dependent effects of acetylcholine on healthy and dysfunctional vascular endothelium. *ACH* acetylcholine

in response to acetylcholine in patients with mild atherosclerosis and angina [104]. No impairment of endothelium-independent vasodilation was observed in the same group. Using PET, which permits non-invasive assessment of regional perfusion with [15] O-labeled water or [13] N-labeled ammonia, Geltman et al. reported abnormal myocardial perfusion reserve with higher perfusion at rest and lower maximal flow after intravenous administration of dypiridamole in 8 of 17 patients with CSX compared to 16 normal subjects [105]. With the same technique Galassi et al. observed a lesser increase in myocardial perfusion in subjects with CSX who also developed chest pain and ST-segment depression after dipyridamole, compared to normal subjects or CSX patients without chest pain and ECG changing in response to the drug [106]. According to Geltman's findings, these patients showed higher resting perfusion than the other two groups. The endothelium-independent vasodilator dypiridamole only (without cold pressor testing), an endothelium-dependent vasodilator, resulted in a lesser increase in cardiac blood flow documented by PET in a population of 25 women with CSX compared to controls [107].

Using cardiac MRI, which provides superior resolution to evaluate perfusion, Panting, Pennell and coworkers documented a relative failure of subendocardial perfusion to increase with adenosine infusion in patients with microvascular angina that could also account for absence of major changes in LV wall motion [108]. However, Vermeltfoort and colleagues observed that adenosine infusion evokes significant perfusion response, not compatible to subepicardial and subendocardial hypoperfusion in patients with CSX studied by adenosine-stress cardiac MRI [109].

All of their patients did show initial subendocardial signal reductions of the first pass visual analysis of LV contrast similar to that described Panting et al. [108], but this was considered an artifact related to the first-pass sequence and not typical for an ischemic related perfusion defect. But there are considerable differences between these two studies, so addition work is needed. Lanza, Crea and coworkers have confirmed MRI perfusion deficits (with dobutamine stress) linked with abnormal CFR to adenosine [114]. Because ED is systemic, less invasive techniques have been applied in the effort to assess endothelial and vascular function in microvascular angina patients. Brachial artery ultrasound measures flow-mediated dilation of brachial artery after occlusion-release. Patients with microvascular angina show a flow mediated vasodilation comparable to that in patients with CAD and lower than that in healthy subjects [25]. Conversely, carotid intima-media thickness values were comparable between patients with microvascular angina and healthy subjects. In both groups intima-media thickness was lower than in patients with CAD, suggesting a potential use of the parameter in distinguishing patients with chest pain and normal coronary arteries from those with coronary atherosclerosis.

Summary and Conclusions

In 1991 Maseri et al. [110] proposed that coronary microvascular dysfunction might involve the prearteriolar vessels that have been demonstrated to be the site of greatest endothelium-dependent releasing factor activity [111, 112]. The dysfunction might be patchily distributed in small regions throughout the myocardium and determine focal ischemic events of the inner layers of the ventricular wall, generally inadequate to affect LV wall motion. Although the entity of ischemia appears to be ineffective on LV function, other factors (esophageal acid stimulation, sympathetic tone, and insulin resistance, abnormal pain perceptions) may intervene and interact in the development and determination of anginal syndrome. Camici and Crea have recently refined the definition of coronary microvascular dysfunction as " a dysregulation of coronary blood flow, not attributable to obstructive CAD that results from either structural and functional mechanisms in the coronary microvasculature" [113]. They also developed a clinical classification and summarized the possible pathogenetic mechanisms based on alterations observed and their possible causes (Tables 8.1 and 8.2). Analysis of the results of microvascular responsiveness to endothelial-dependent and –independent vasodilators highlights four different response patterns: (1) normal vasodilator response; (2) endothelium-dependent vasodilation impairment; (3) endothelium-independent vasodilation impairment; (4) coexisting endothelium-dependent and endothelium-independent vasodilation impairment.

Whatever the results, microvascular angina is a complex disorder affecting small cardiac and systemic artery vasculature and very likely encompassing several different pathophysiological entities. EC, and SMC dysfunction represent a predominant etiologic substrate for the development of angina-like chest pain in patients without flow limiting obstruction on angiography and likely also underlies the vasculopathy associated with IHD among patients with flow limiting obstructive disease.

Table 8.1 Clinical classification of coronary microvascular dysfunction

Coronary microvascular dysfunction in the absence of obstructive CAD and myocardial diseases	This type represents the functional counterpart of traditional coronary risk factors (smoking, hypertension, hyperlipidemia, and diabetes and insulin-resistant states). It can be identified by noninvasive assessment of coronary flow reserve. This type is at least partly reversible, and coronary flow reserve can also be used as a surrogate end point to assess efficacy of treatments aimed at reducing the burden of risk factors
Coronary microvascular dysfunction in the presence of myocardial diseases	This type is sustained in most instances by adverse remodeling of intramural coronary arterioles. It can be identified by invasive or noninvasive assessment of coronary flow reserve and may be severe enough to cause myocardial ischemia. It has independent prognostic value. It remains unclear whether medical treatment may reverse some cases. It is found with primary (genetic) cardiomyopathies (e.g., dilated and hypertrophic) and secondary cardiomyopathies (e.g., hypertensive and valvular)
Coronary microvascular dysfunction in the presence of obstructive CAD	This type may occur in the context of either stable CAD or acute coronary syndromes with or without ST-segment elevation and can be sustained by numerous factors. It is more difficult to identify than the first two types and may be identified through the use of an integrated approach that takes into account the clinical context with the use of a combination of invasive and noninvasive techniques. There is some early evidence that specific interventions might prevent it or limit the resultant ischemia
Iatrogenic coronary microvascular dysfunction	This type occurs after coronary recanalization and seems to be caused primarily by vasoconstriction or distal embolization. It can be identified with the use of either invasive or noninvasive means on the basis of a reduced coronary flow reserve, which seems to revert spontaneously in the weeks after revascularization. Pharmacologic treatment has been shown to promptly restore coronary flow reserve, and it may also change the clinical outcome. The likelihood of distal embolization can be reduced by the use of appropriate devices during high-risk procedures

Reprinted from Camici and Crea [113]

Table 8.2 Pathogenetic mechanisms of coronary microvascular dysfunction

Alterations	Causes
Structural	
Luminal obstruction	Microembolization in acute coronary syndromes or after recanalization
Vascular-wall infiltration	Infiltrative heart disease (e.g., Anderson–Fabry cardiomyopathy)
Vascular remodeling	Hypertrophic cardiomyopathy, arterial hypertension
Vascular rarefaction	Aortic stenosis, arterial hypertension
Perivascular fibrosis	Aortic stenosis, arterial hypertension
Functional	
Endothelial dysfunction	Smoking, hyperlipidemia, diabetes
Dysfunction of smooth-muscle cell	Hypertrophic cardiomyopathy, arterial hypertension
Autonomic dysfunction	Coronary recanalization
Extravascular	
Extramural compression	Aortic stenosis, hypertrophic cardiomyopathy, arterial hypertension
Reduction in diastolic perfusion time	Aortic stenosis

Reprinted from Camici and Crea [113]

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The Pathogenesis of Vasospastic Angina

9

Satoshi Yasuda and Hiroaki Shimokawa

Abstract

Coronary artery spasm plays an important role in the pathogenesis of ischemic heart disease presentations, including sudden cardiac death, and thus could be one of the most important functional abnormalities of the coronary artery. Coronary spasm is caused primarily by smooth muscle hypercontraction whereas the contribution of endothelial dysfunction may be minimal. Rho-kinase is a downstream effector of the small GTP-binding protein Rho and consists of two isoforms, Rho-kinase α/ROCK2 and Rho-kinase β/ROCK1. Accumulative evidence have demonstrated that Rho-kinase plays a central role in the molecular mechanism of coronary spasm through vascular smooth muscle cell hyperconstriction. Furthermore, in the recent era of percutaneous coronary intervention with drug eluting stents (DES), Rho-kinase pathway also plays a crucial role in the pathogenesis of DES-induced coronary hyperconstricting responses. In this article, we will briefly review the current knowledge about the pathogenetic significance of the Rho-kinase pathway in coronary spasm and address the therapeutic potential of Rho-kinase inhibitors.

Keywords

• Myocardial ischemia • Rho-kinases • Vascular smooth muscle cell • Vasospasm

Introduction

Coronary spasm is defined as a condition in which epicardial coronary arteries transiently exhibit abnormal contraction (Fig. 9.1) [1, 2]. Coronary spasm is not always preceded by elevations of blood pressure or heart rate, and is not associated with increased myocardial oxygen consumption. In coronary spasm, sudden excessive coronary vasoconstriction produces a transient reduction in blood flow, resulting in myocardial ischemia (supply ischemia/primary angina). Several lines of evidence indicate that coronary spasm is caused primarily by vascular smooth muscle cell (VSMC) hypercontraction, for which Rho/Rho-kinase pathway plays an important pathogenetic role [3, 4].

In this article, we will briefly review the recent research progress on coronary spasm, with a special reference to the Rho/Rho-kinase pathways [5].

Rho/Rho-Kinase Signaling Pathway and VSMC Hypercontraction

Rho-kinase (ROCKs) belongs to the family of serine/threonine kinases and is an important downstream effector of the small GTP-binding protein RhoA [5]. There are two isoforms

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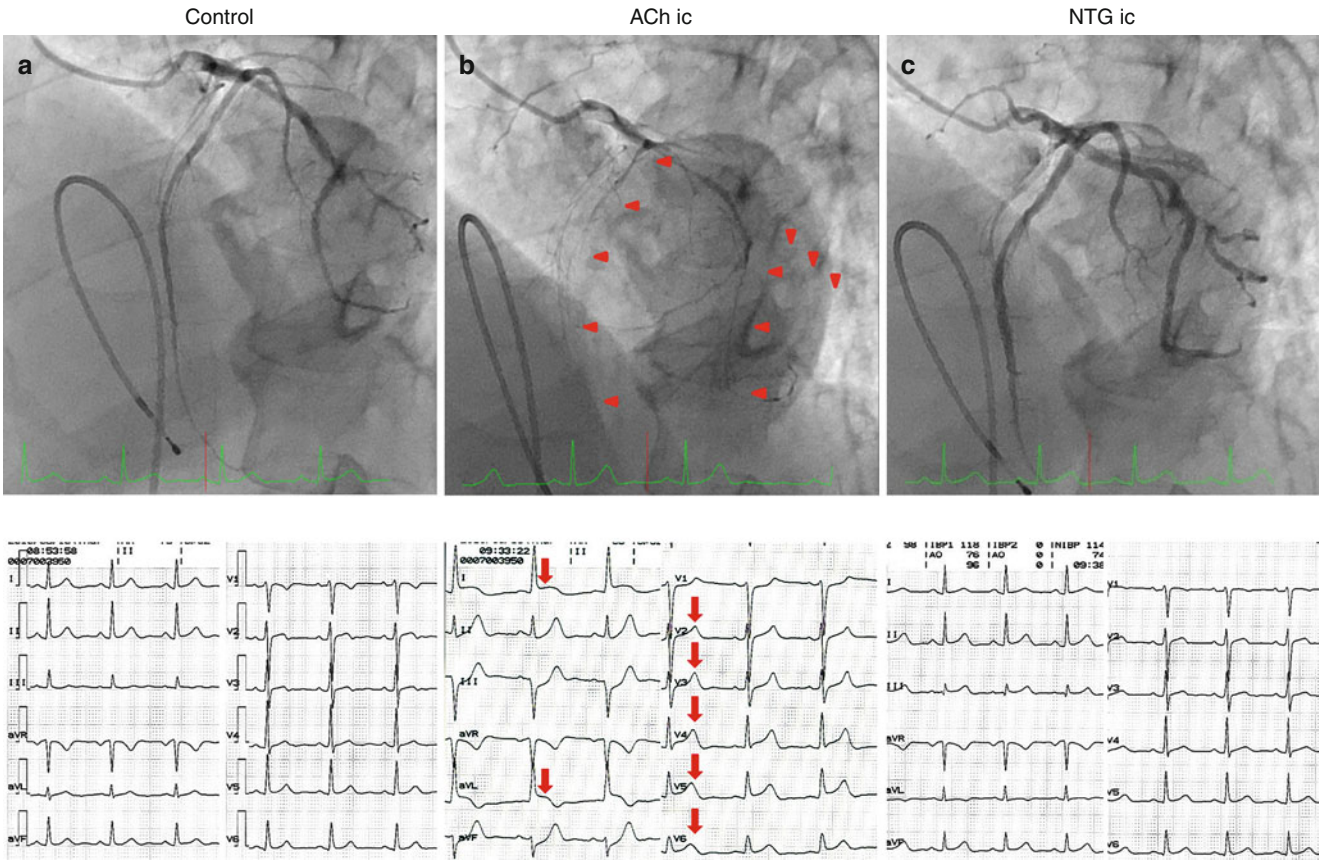

Fig. 9.1 Representative case of coronary spasm induced by acetylcholine provocation test. Although no significant coronary stenosis was found in control coronary angiography (**a**; *upper panel*), severe and diffuse coronary spasm was induced in both the left anterior descending and circumflex coronary arteries (*red triangles*) by intracoronary (*ic*) administration of acetylcholine (ACh) (**b**; *upper panel*). Coronary spasm and ST-segment elevation (*red arrows*) in electrocardiography (**b**; *lower panel*) were disappeared following ic nitroglycerin (*NTG*) (**c**; *upper and lower panels*)

of Rho-kinase, ROCK1 and ROCK2, and they have different functions with ROCK1 for circulating inflammatory cells and ROCK2 for vascular smooth muscle cells [6, 7]. It has been demonstrated that the RhoA/Rho-kinase pathway plays an important role in various fundamental cellular functions, including contraction, motility, proliferation and apoptosis, leading to the development of cardiovascular diseases [5]. Fasudil and hydroxyfasudil have been developed as a pharmacological inhibitor of Rho-kinase [8, 9].

Phosphorylation of myosin light chain (MLC) is a key mechanism in the regulation of vascular smooth muscle cell (VSMC) contraction. MLC is phosphorylated by Ca^{2+}-calmodulin-activated MLC kinase and dephosphorylated by MLC phosphatase. Agonists bind to G protein-coupled receptors and induce contraction by increasing both cytosolic Ca^{2+} concentration and Rho-kinase activity through mediating guanine nucleotide exchange factor. The substrates of Rho-kinase have been identified, including MLC, myosin binding subunit or myosin phosphatase target subunit 1, ezrin/radixin/moesin family, adducin, phosphatase and tensin homolog on chromosome 10, and LIM-kinases (Fig. 9.2) [4, 5]. Rho-kinase enhances MLC phosphorylation through inhibition of myosin-binding subunit of myosin phosphatase and mediates agonists-induced VSMC hypercontraction (Fig. 9.1) [4, 5].

The Important Role of Rho-Kinase in the Pathogenesis of Coronary Spasm

Accumulating evidence indicates that Rho-kinase plays a crucial role in the pathogenesis of coronary spasm. Intracoronary administration of fasudil or hydroxyfasudil, Rho-kinase inhibitors, markedly inhibits epicardial coronary spasm in porcine models with various inflammatory stimuli in vivo [8–13]. Indeed, the inhibition of Rho-kinase with fasudil/hydroxyfasudil is associated with the suppression of enhanced myosin light chain (MLC) phosphorylations (both MLC monophosphorylations and diphosphorylations) at the spastic coronary segments in those models [9, 10].

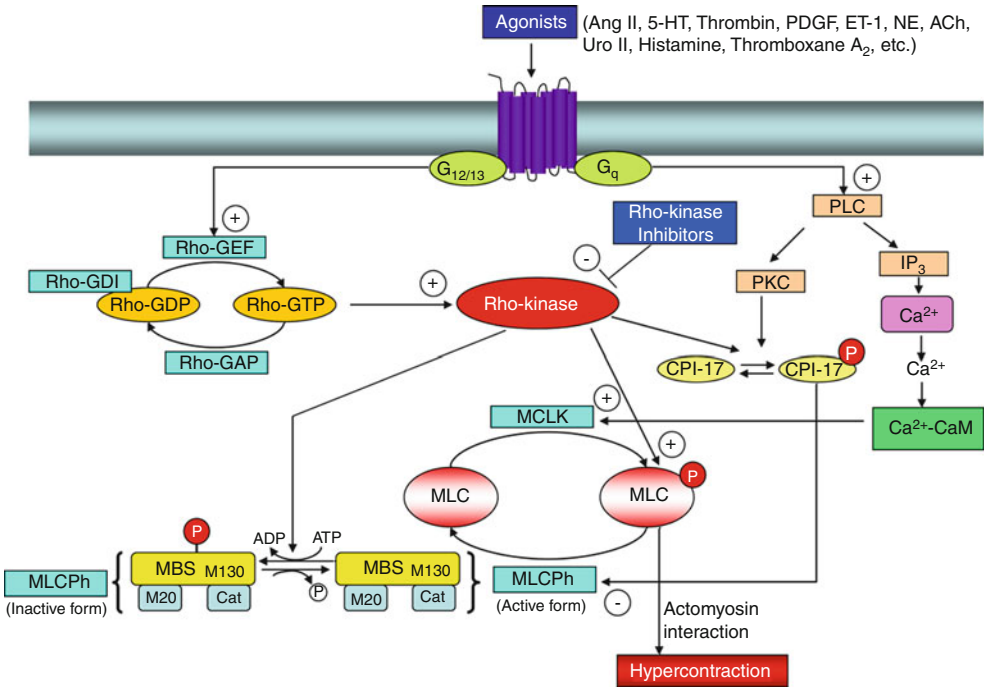

Fig. 9.2 Crucial role of the Rho/Rho-kinase signaling pathway in vascular smooth muscle cell hyperconstriction. Vascular smooth muscle contraction is induced by increased phosphorylation of myosin light chain (*MLC*). The agonist-induced activation of G-protein-coupled receptors leads to the stimulation of MLC kinase (*MLCK*) through an increase in intracellular Ca^{2+} concentration, and inhibition of MLC phosphatase (*MLCPh*). Following stimulation by various agonists, the Rho/Rho-kinase pathway is activated, resulting in the inhibition of MLCPh (through phosphorylation of its MBS), with a resultant increase in MLC phosphorylation. This Rho-kinase-mediated contraction of VSMC can occur independently of intracellular Ca^{2+} levels and is known as "calcium sensitization". Rho-kinase can also increase MLC phosphorylation and contractility by inactivating MLCPh after phosphorylation of CPI-17. *ACh* acetylcholine, *Ang II* angiotensin II, *Cat* catalytic subunit, *CPI-17* collapsin response mediator protein 2, *ET-1* endothelin-1, *IP3* inositol (1,4,5)-trisphosphate, *M20* 20-kDa subunit, *MBS* myosin binding subunit, *MLC* myosin light chain, *MLCK* myosin light chain kinase, *MLCPh* myosin light chain phosphatase, *NE* norepinephrine, *PLC* phospholipase C, *PDGF* platelet-derived growth factor, *Uro II* urotensin II, *VSMC* vascular smooth muscle cell. Stimulation is denoted by +; inhibition is denoted by − (Modified from Shimokawa and Yasuda [4] with permission from Elsevier)

We have demonstrated that fasudil is effective in preventing coronary spasm and resultant myocardial ischemia in patients with vasospastic angina [14, 15]. The clinical trials using fasudil for Japanese patients with stable effort angina demonstrated that the long-term oral treatment with the Rho-kinase inhibitor is effective in ameliorating exercise tolerance [16]. In patients with microvascular angina/spasm, pre-treatment with intracoronary infusion of fasudil effectively prevented acetylcholine (ACh)-induced angina and myocardial ischemia (myocardial lactate production), indicating that inhibition of Rho-kinase by fasudil suppresses ACh-induced coronary microvascular hyperconstriction [15]. Recently, we have demonstrated that Rho-kinase activity in circulating neutrophils, determined by the extent of phosphorylation of myosin binding subunit, a substrate of Rho-kinase, is a useful biomarker for the diagnosis and disease activity assessment in patients with vasospastic angina (Fig. 9.3) [17]. Also, the Rho-kinase activity was significantly decreased after 3-month medical treatment with calcium channel blockers (CCB) [17]. In the recent double-blind, randomized study of hypertensive patients [18], after 4 and 12 weeks of treatment, Rho-kinase activity in circulating neutrophils was significantly decreased in the CCB group but not in the renin-angiotensin system inhibitor group, whereas the antihypertensive effects were similar in the two groups. Although the precise mechanisms remain unclear and further studies are needed, long-term treatment with CCB may have potential inhibitory effects on Rho-kinase.

Drug Eluting Stent-Induced Coronary Hyperconstricting Responses

Drug-eluting stents (DES) have been widely used and have dramatically reduced restenosis after percutaneous coronary intervention [19, 20]. The first generation of DES, such as silorimus-eluting stent (SES) and paclitaxel-eluting stent (PES) have already been deployed in millions of patients worldwide. However, their use has raised the safety issue

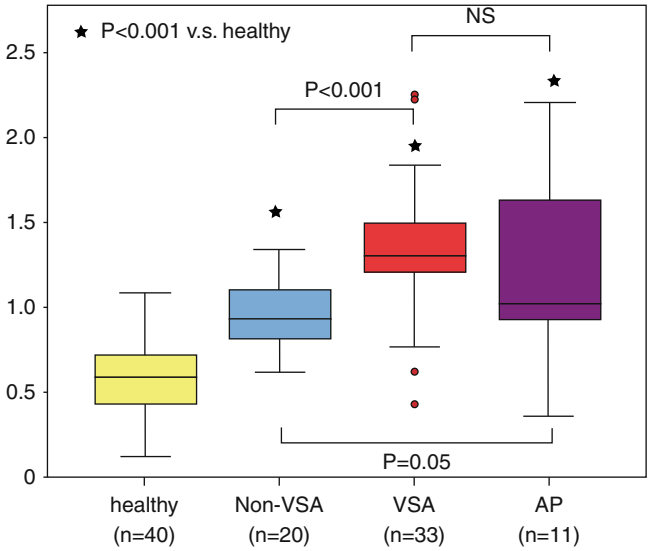

Fig. 9.3 Increased Rho-kinase activity in circulating leukocytes of patients with vasospastic angina. Rho-kinase activity was determined by the extent of phosphorylation of MBS, a substrate of Rho-kinase, and was expressed as the ratio of phosphorylated (p-MBS) to total (t-MBS) form. Results are expressed as *box* and *whisker plots*; the *central box* covers the quartile range with the median indicated by the *line* within the *box*. The *whiskers* extend to the most extreme values within 1.5 inter-quartile ranges of the quartiles. More extreme values are plotted individually. We examined 53 consecutive patients with chest pain who underwent acetylcholine provocation test for coronary spasm. They were divided into the two groups, depending on the response to the test; VSA (n = 33) and non-VSA group (n = 20). We also studied 40 healthy subjects and 11 patients with stable effort angina pectoris (AP) due to severe organic stenosis who required coronary stent implantation (Modified from Kikuchi et al. [17] with permission from Elsevier)

concerns, including late stent thrombosis [21] and impairment of coronary vasomotion [22–24]. Indeed, enhanced coronary vasoconstriction in response to ACh (Fig. 9.4) [22, 23] or exercise [24] has been demonstrated in the coronary segments adjacent to DES, but not in those to bare-metal stents (BMS).

By using porcine models in vivo, we have previously demonstrated that (a) DES enhance coronary vasoconstricting responses as compared with BMS (Fig. 9.5), (b) the coronary hyperconstricting responses are abolished by a Rho-kinase inhibitor, hydroxyfasudil, and (c) Rho-kinase expression and activity were increased at the peri-stent sites of DES, where inflammatory cell accumulation and microthrombus formation are enhanced [25, 26]. Recent study from our laboratory demonstrated the cardioprotective effects of long-acting CCB in the coronary arteries implanted with the first generation of DES [27]. Chronic treatment with long-acting nifedipine suppresses DES-induced coronary hyperconstricting responses and inflammatory changes, at least in part, through Rho-kinase pathway inhibition in pigs in vivo (Fig. 9.6) [27]. Inflammatory responses to DES could be due to a local hypersensitivity reaction to a non-bioresorbable durable polymer [28]. To avoid such an undesirable effect of polymers, biocompatible and bioresorbable polymers have recently been developed [29]. In fact, a recent study demonstrated that coronary vasomotion was preserved in a new-generation biolimus-eluting stent with bioresorbable polymers as compared with SES [30].

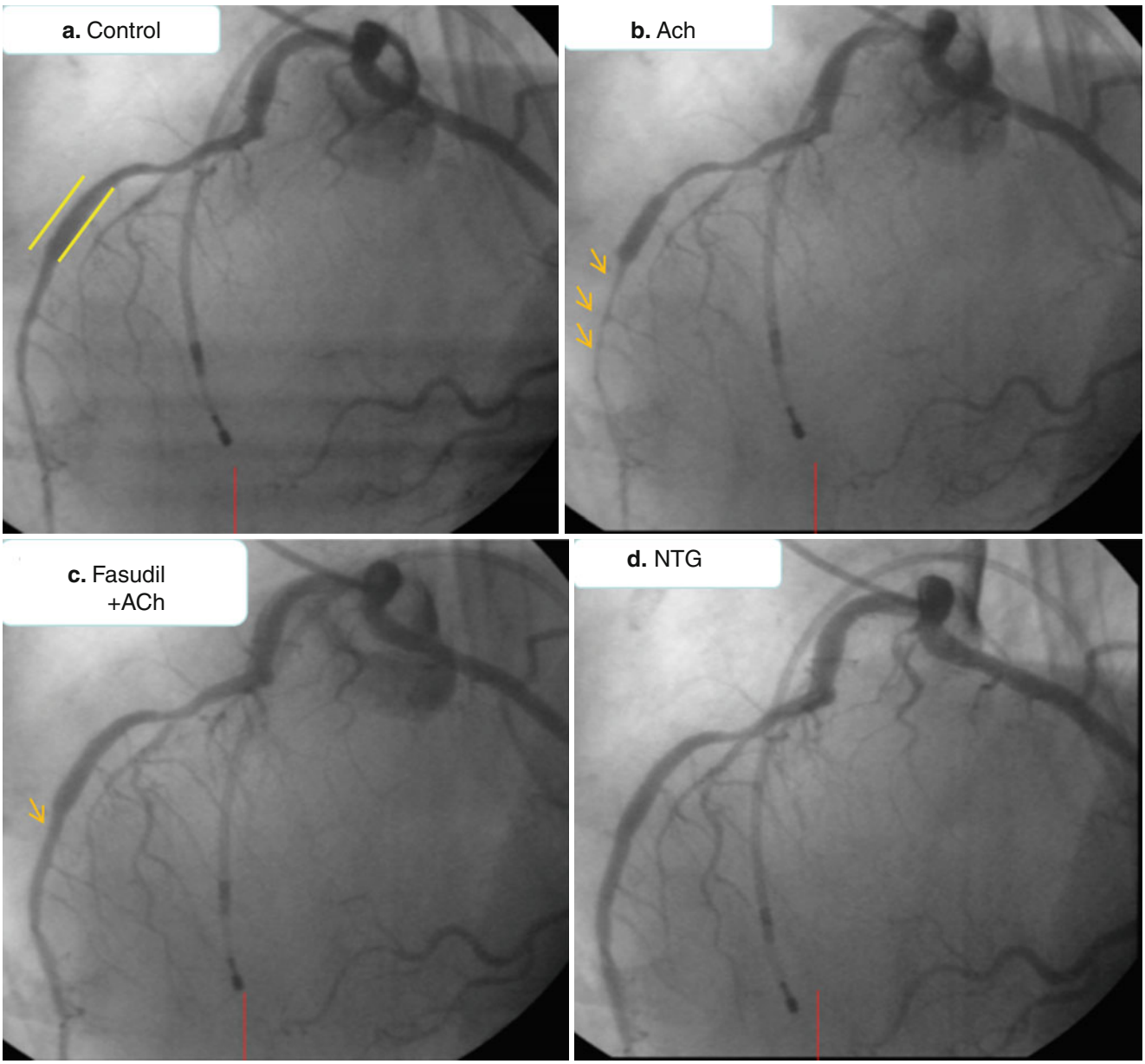

Fig. 9.4 Representative coronary angiogram in a patient with drug-eluting stent. Left coronary angiograms under baseline control condition (**a**), after intracoronary administration of ACh (100 μg) without (**b**) and with fasudil (F, 300 μg/min, ic) (**c**), and after intracoronary administration of NTG (**d**). *Yellow lines* indicate the site of drug eluting stent (Cypher™) implantation. The angiogram after ACh infusion (**b**) shows severe coronary spasm at the distal segment adjacent to the stent (*yellow arrows*), and the pretreatment with fasudil prevented it (**c**)

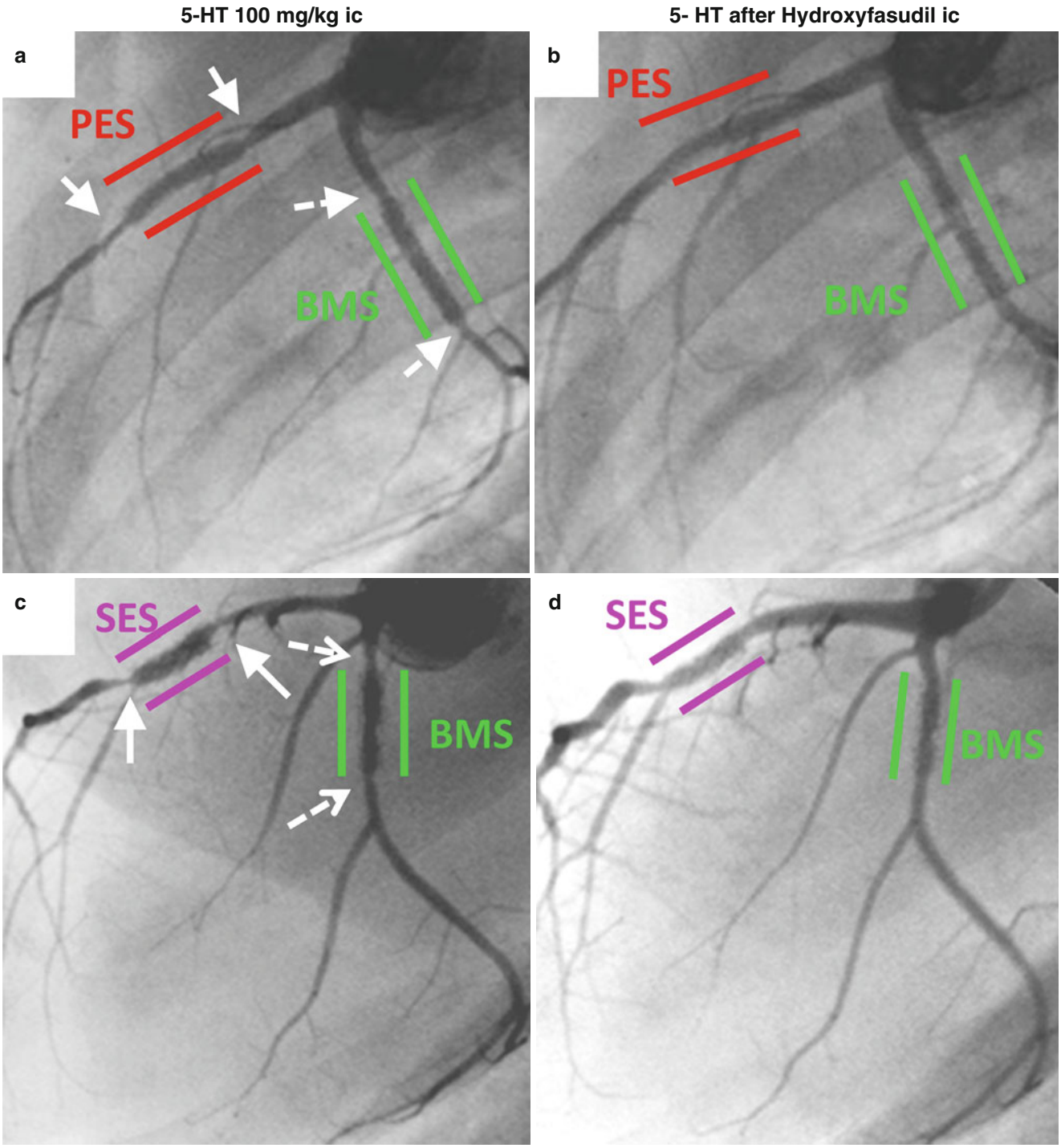

Fig. 9.5 Paclitaxel-eluting stent (*PES*) and sirolimus-eluting stent (*SES*) enhances coronary vasoconstricting responses in pigs in vivo. Representative left coronary angiograms after intracoronary serotonin (5-HT 100 μg/kg) without (**a**, **c**) and with (**b**, **d**) hydroxyfasudil (300 μg/kg intracoronary administration). The *red lines* indicate the site of paclitaxel-eluting stent (*PES*) implantation, *purple lines* indicate the site of sirolimus-eluting stent (*SES*) implantation, and *green lines* indicate the site of bare-metal stent (*BMS*) implantation. *Arrows indicate* the *proximal* and *distal* edges of stents (Modified from Shiroto et al. [25] with permission from Elsevier)

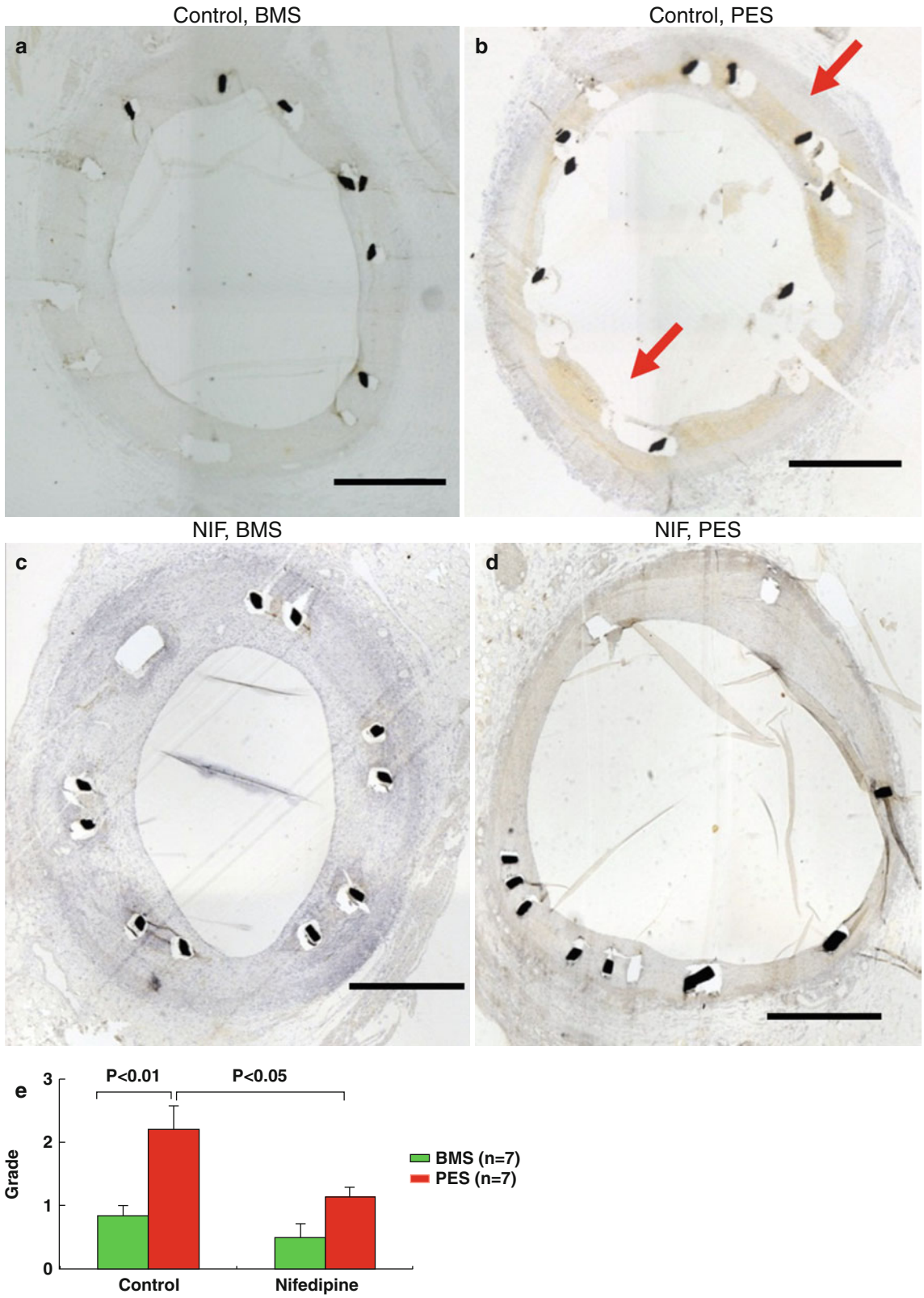

Fig. 9.6 Representative pictures of immunohistochemistry for Rho-kinase activity of stented porcine coronary arteries with and without long-acting nifedipine (4 mg/kg/day) for 4 weeks. Representative immunohistochemistry (*upper panels*) of phosphorylated myosin binding subunit (*MBS*) in the bare-metal stent (*BMS*)-treated arteries and paclitaxel-eluting stent (*PES*)-treated arteries in the control (**a**, **b**) and the long-acting nifedipine (*NIF*) groups (**c**, **d**). *Scale bars* represent 1 mm. We also semi-quantitatively assessed the extent of phosphorylated MBS (**e**), using the following scale: *0*, none; *1*, slight; *2*, moderate; and *3*, high. In the control group, the expression of Rho-kinase activity evaluated by the expression of phospho-MBS was enhanced at the PES sites. In contrast, in the NIF group, those changes were abolished (Modified from Tsuburaya et al. [27] with permission from Oxford University Press)

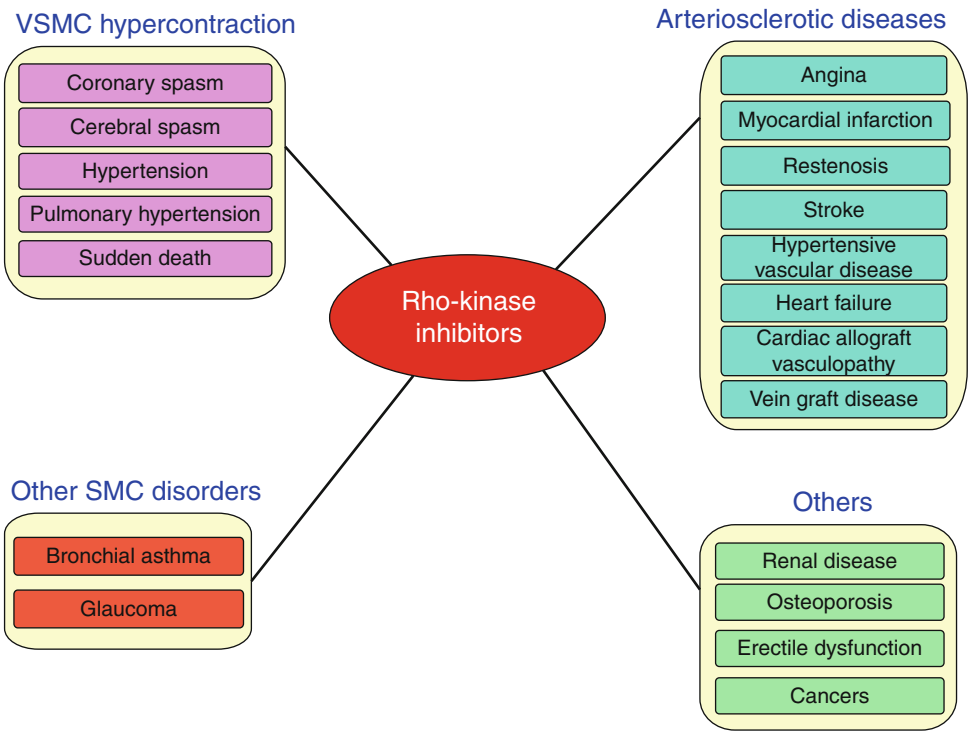

Fig. 9.7 Possible indications of Rho-kinase inhibitors. Rho-kinase inhibitors may be useful for the treatment of a wide variety of cardiovascular diseases with various etiologies, including VSMC hypercontraction, arteriosclerosis, other smooth muscle cell (*SMC*) disorders, and others (Modified from Shimokawa and Yasuda [4] with permission from Elsevier)

Conclusions

In the pathogenesis of coronary vasospasm, activation of the Rho kinase pathways is involved to induce VSMC hypercontraction and thus its inhibition emerges as a key therapeutic target [4] (Fig. 9.7).

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The Coronary Slow Flow Phenomenon

10

John Beltrame and Peter Ganz

Abstract

The coronary slow flow phenomenon (CSFP) is a microvascular coronary disorder, characterised angiographically by delayed contrast opacification of the distal vasculature in the absence of obstructive coronary artery disease. Its prevalence has been reported as 1–3 % of coronary angiograms performed. It often presents initially as an acute coronary syndrome with 8 % of patients having positive cardiac markers for myocardial infarction. Although transient T wave changes are frequently observed during the acute episode, only a third of patients have clinical evidence of inducible myocardial ischaemia. Both structural and functional studies have demonstrated the presence of microvascular coronary dysfunction however the underlying cause remains elusive. Possible pathogenetic mechanisms include a defective endothelial nitric oxide pathway, excessive endothelin mediated vasoconstriction, autonomic dysfunction, platelet dysfunction, metabolic derangements (associated with the metabolic syndrome and hyperhomocystinaemia), and vascular inflammation. The risk of future cardiac events following the initial presentation appears low however many patients continue to experience recurrent chest pain. Further well-controlled therapeutic studies are required to identify effective therapies for this disabling condition.

Keywords

Coronary slow flow phenomenon • Microvascular coronary dysfunction • Slow flow Syndrome X • Syndrome Y • Microvascular angina • Coronary heart disease • Normal angiogram • Mibefradil • Nebivolol • Trimetazidine • Statins • Dipyridamole • Endothelin Endothelial dysfunction • Coronary flow reserve • Microvascular disease

The Coronary Slow Flow Phenomenon

The coronary slow flow phenomenon (CSFP) is an angiographic phenomenon characterised by the slow passage of angiographic contrast into the distal vasculature despite the absence of obstructive coronary artery disease. Since its first description some 40 years ago, it has transcended from an angiographic curiosity to an identified coronary disorder of clinical interest. Despite significant advancement in the understanding of this disorder, many aspects of the condition remain unknown or poorly understood. In this chapter, the contemporary knowledge of the CSFP will be reviewed including its (1) definition and nomenclature, (2) angiographic findings, (3) clinical features, (4) microvascular coronary

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dysfunction studies, (5) potential pathophysiological mechanisms, and (5) evidence-based therapies. At the conclusion of the chapter a synthesis of the data will define the current perspectives of this interesting condition.

Definition and Nomenclature

The CSFP was first described in 1972 by Tambe et al. [1], when they reported six cases with this peculiar angiographic finding and speculated that it reflected microvascular coronary dysfunction thereby accounting for the patient's angina symptoms. Interestingly, these findings were reported the year prior to the landmark paper by Arbogast and Bourassa [2] which gave rise to another microvascular coronary disorder, Cardiac Syndrome X. Whereas research on Cardiac Syndrome X has been prolific over the past 40 years, investigations of the CSFP has not attracted significant attention until recently. Indeed until the dawn of the new millennium, less than 25 papers had been published on the CSFP with many of these being case reports. However in the past 10 years there has been an exponential increase in publications relating to the CSFP, with well over 100 original manuscripts published.

Primary and Secondary CSFP

It is important to distinguish the above phenomenon described by Tambe and colleagues from other conditions where there is delayed distal vessel opacification. There is frequent confusion in the literature between the CSFP and the no-reflow phenomenon. The later occurs in the context of successful percutaneous coronary interventions when suddenly the patient becomes symptomatic with ischaemic ECG changes and delayed vessel opacification despite the absence of a residual epicardial coronary artery stenosis [3]. In this case the 'slow flow' also reflects microvascular coronary dysfunction but embolization from the angioplastied/stented lesion is likely to play a major role in its pathogenesis.

To distinguish the clinically distinct but angiographically similar conditions, the terms primary and secondary CSFP have been coined [4]. Accordingly, in '*Primary CSFP*' there is no obvious clinical cause for the delayed vessel opacification (as in the context of Tambe et al. original description) whereas in '*Secondary CSFP*' there is an identifiable clinical cause (such as the no-reflow phenomenon). In both forms, the condition is characterised by delayed vessel opacification in the absence of obstructive coronary artery disease and should be distinguished from the later where the impaired flow may be due to a tight stenosis.

The subsequent discussion within this chapter will be confined only to 'Primary CSFP'. Although some aspects of Primary CSFP may be applicable to the secondary form, readers should refer to other texts concerning the no-reflow phenomenon for a more in-depth discussion of that disorder.

TIMI Flow Grade or TIMI Frame Count

The CSFP is an angiographic phenomenon and therefore defined on the basis of angiographic methodologies, in particular those established by the Thrombolytic In Myocardial Infarction (TIMI) group. One approach utilises the TIMI flow grade classification [5] where TIMI-2 flow is defined as the delayed filling of the distal vasculature; conventionally this is considered as requiring 3 or more beats to fill the distal vessels (Fig. 10.1). Thus some researchers have defined the CSFP as the presence of TIMI-2 flow in the absence of obstructive coronary artery disease [4, 6].

An alternative approach utilises the TIMI frame count method (TFC). This technique counts the number of cine frames required to opacify the vessel using the method described by Gibson et al. [7]. This group established a 'reference range' based upon 78 patients who had not experienced a myocardial infarct and reported similar TFC in the right coronary artery (RCA, n = 38, 20 ± 3 frames) and circumflex (Cx, n = 21, 22 ± 4 frames) with delayed times for the left anterior descending artery (LAD, n = 19, 36 ± 3 frames) because of its longer length. Accordingly, they derived a correction factor for the left anterior descending artery, dividing the raw score by a correction factor to obtain a 'corrected TFC' of 21 ± 3 frames for this vessel [7]. Using these as "reference values", some researchers have defined CSFP as either any TFC value above these values [8], or one [9], or two [10]-standard deviations above the reference ranges, or their own specified TFC range.

The merits of using the TIMI flow grade or TFC to define the CSFP warrant further consideration. The TIMI flow grade is readily assessable and can be performed during the diagnostic procedure. Moreover, being defined by the number of heart beats, the index is normalised for heart rate. In contrast, the TFC is more quantitative and requires frame analysis, which is generally readily available on most contemporary diagnostic angiographic systems. Moreover, the TFC must be adjusted for the image acquisition rate (30 frames/s in the original study [7]). It is also noteworthy that TFC has been shown to be influenced by heart rate, timing of dye injection, age, gender, systemic arterial pressure and body surface area [11]. As a useful reference, in a study where TIMI-2 flow was required to define a CSFP population (mean LAD opacification rate = 3.4 ± 1.1 beats), the corresponding corrected TFC in the LAD of these patients was 69 ± 35 frames [4].

In addition to the variation in defining CSFP by either the TIMI flow grade or TFC with variable cut-off thresholds,

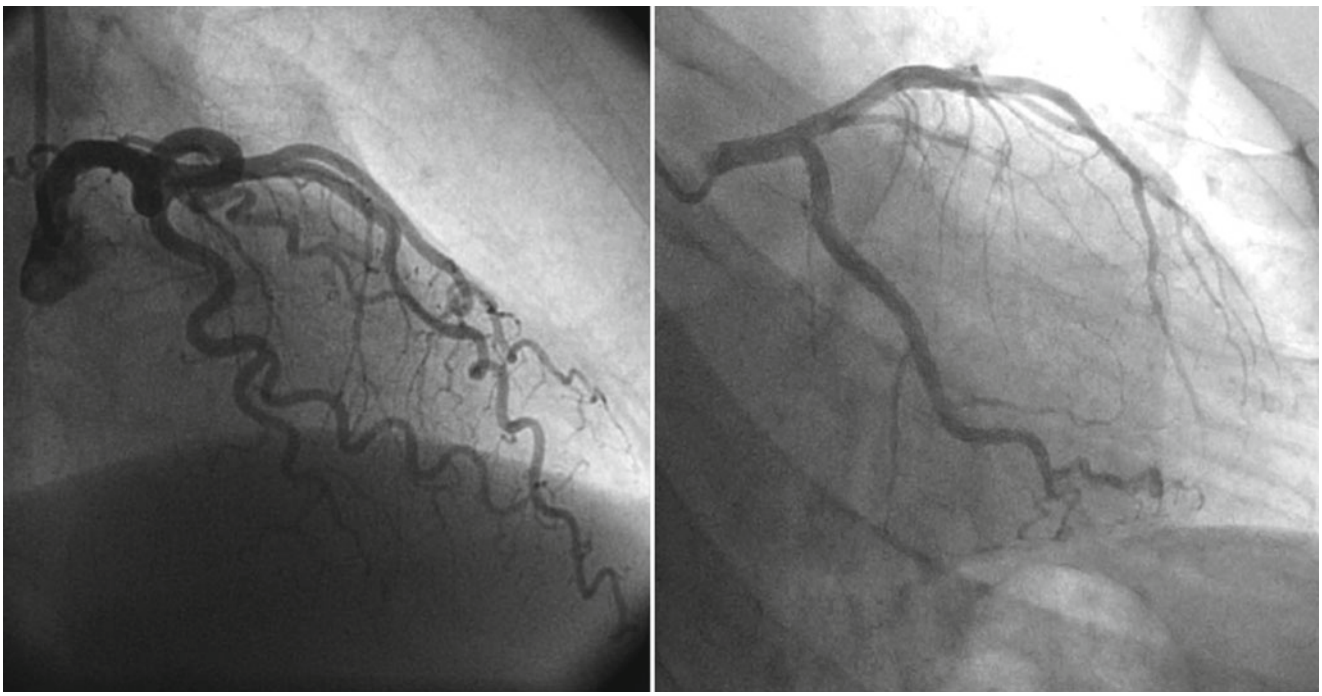

Fig. 10.1 Coronary slow flow phenomenon definition. The snapshot images below are taken at three heart beats from a patient without the CSFP (*left panel*) and with CSFP (*right panel*). The *left panel* demonstrates normal filling of the epicardial vessels whereas the *right panel* demonstrates incomplete filling of the left anterior descending artery (i.e. equivalent to TIMI-2 flow)

there is also variability in the definition as to the required number of vessels involved. Thus some researchers define CSFP on the basis that one or more of the epicardial coronary arteries exhibit the phenomenon. In contrast, other definitions require all three of the coronary arteries to exhibit the phenomenon. However as discussed later in this chapter, all three epicardial coronary arteries tend to show delayed opacification even if not all meet the CSFP criteria.

Near–Normal or Normal Angiography

There is also variation in angiographic coronary artery morphology in the various definitions of the CSFP. Since potentially a tight coronary artery stenosis may obstruct coronary blood flow and give rise to delayed distal vessel opacification, patients with obstructive coronary artery disease must be excluded from the definition since an identifiable cause for their chest pain and impaired angiographic flow is evident. In contrast, those without obstructive coronary artery disease do not have an obvious cause for their delayed angiographic flow or chest pain and warrant inclusion in the CSFP. Thus investigators have included patients with angiographically normal or near-normal coronary arteries (i.e. ≤40 % stenosis in any vessel) in the definition of the CSFP [4]. In contrast, other investigators have only included patients with angiographically normal (smooth) coronary arteries in the definition of the CSFP.

One note of caution – subjects with ectatic epicardial coronary arteries have reduced blood flow velocity, merely as a consequence of increased cross-sectional area. If absolute coronary blood flow is maintained, this reduction in flow velocity is appropriate. The diagnosis of CSFP based on slow flow velocity should only be entertained in patients without grossly dilated coronary arteries.

Final Thought

There is variability in CSFP definition in relation to (a) the assessment method (TIMI flow grade or TFC) and the extent of delay in angiographic contrast flow; (b) how many vessels need to exhibit the phenomenon – at least one versus all 3 vessels; and (c) the presence of angiographically normal epicardial vessels or minor non-obstructive disease only. Independent of the specific definition utilised, the CSFP patients all have delayed opacification of the epicardial arteries in the absence of obstructive coronary artery disease and no other obvious explanation for the chest pain which prompted the angiographic investigation. A plausible hypothesis is that the delayed vessel opacification reflects coronary microvascular dysfunction thereby accounting for the chest pain. The arguments whether CSFP can involve only one or must involve multiple coronary territories is misplaced as previous studies have shown that the vessels that do not fulfil

the CSFP criteria typically exhibit velocities slower than those of control patients without evidence of the CSFP [12].

Angiographic Findings

The CSFP has been reported to occur in approximately 1 % of diagnostic coronary angiograms [4]. More recent preliminary reports have suggested that this may be as high as 3 % of coronary angiograms [13] while others have reported a 7 % prevalence [14]. The findings in relation to co-existing coronary artery disease and the features of the delayed angiographic flow are summarised below.

Co-existing Atherosclerotic Coronary Artery Disease

As mentioned above, some investigators include both patients with angiographically near-normal and normal coronary arteries whilst others consider only those with entirely smooth coronary arteries on angiography. However, even this later group has been shown to have coronary atherosclerotic disease despite normal angiography. Cin et al. performed intravascular ultrasound on 19 patients with the CSFP and reported increased intimal and media thickness in the proximal, mid and distal arterial segments of these patients as compared with 14 controls who did not exhibit the CSFP [15]. Although there were no statistical differences in the individual risk factors between the groups (partly because of the small numbers), there appeared to be more atherosclerotic risk factors amongst the CSFP patients, which may have influenced the findings. The Cin et al. study [15], also reported "massive calcification" throughout the epicardial coronary artery in most of the CSFP; however a recent study showed no difference in coronary artery calcification as assessed by computerised tomography, compared with controls [16]. Despite these variable findings it would appear that most patients have co-existing atherosclerotic coronary artery disease despite the absence of obstructive lesions on angiography. Whether this contributes to the pathophysiology of the condition is open to speculation.

Angiographic Flow Features

The LAD artery is the most commonly affected vessel exhibiting delayed opacification, even when adjustment is made for its longer length [4]. Based upon the TIMI-2 definition, the LAD is involved in 85% of patients, the RCA in 45 % and the Cx in only 17 % [4]. However as mentioned above, even the vessels that do not fulfil criteria for TIMI-2 flow, typically have delayed opacification compared with controls [12].

In addition to the distribution of the 'slow flow', several noteworthy angiographic observations concerning the phenomenon may provide insights into its nature. Firstly, the angiographic finding of slow flow is typically observed during diagnostic angiography therefore suggesting there is a disturbance in resting blood flow. Whether the angiographic flow is further impaired with provocative manoeuvres such as tachycardia or administration of vasoconstrictor agents is unclear [12]. Secondly, serial studies of CSFP patients have shown that the angiographic phenomenon is persistent; even up to 10 years later [17]. This suggests that the phenomenon is inherent to the patient rather than an aberration occurring during the angiographic procedure. Thirdly, and perhaps most importantly, the phenomenon is modifiable despite its persistence. Several researchers have demonstrated that the phenomenon can be improved by vasodilatory agents [14, 18, 19]. Thus the underlying pathology responsible for the angiographic phenomenon cannot simply be structural but must involve a component of altered vascular tone.

Clinical Features

Following the recognition of the clinical features associated with this angiographic phenomenon, it was clear that a new distinct microvascular coronary disorder had been identified [4]. Several groups have also speculated that it is a unique disease entity [20–22] with some suggesting that is should be referred to as Cardiac 'Syndrome Y', to distinguish it from Cardiac Syndrome X [23].

Acute Coronary Syndrome Presentation

In a case–control study, Beltrame et al. [4] demonstrated that patients with the CSFP and normal angiography had different clinical characteristics to those without the CSFP. In particular, the CSFP patients tended to more often be younger, male, and current smokers but there was no statistical difference in the prevalence of hypertension, diabetes or hypercholesterolaemia (Fig. 10.2). However, what was more distinctive and striking was that the CSFP patients underwent coronary angiography because of an acute coronary syndrome (ACS) presentation. Specifically, the CSFP patients had recent onset angina (within the past month) and presented to the hospital emergency room with chest pain at rest. This acute presentation sufficiently alarmed the attending cardiologist to warrant admission to the coronary care unit and perform angiography urgently where-upon the CSFP was documented (Fig. 10.2).

Other researchers have also observed this association between the CSFP and an ACS presentation. Nava Lopez et al. [24], reported that 21 of their 23 CSFP patients

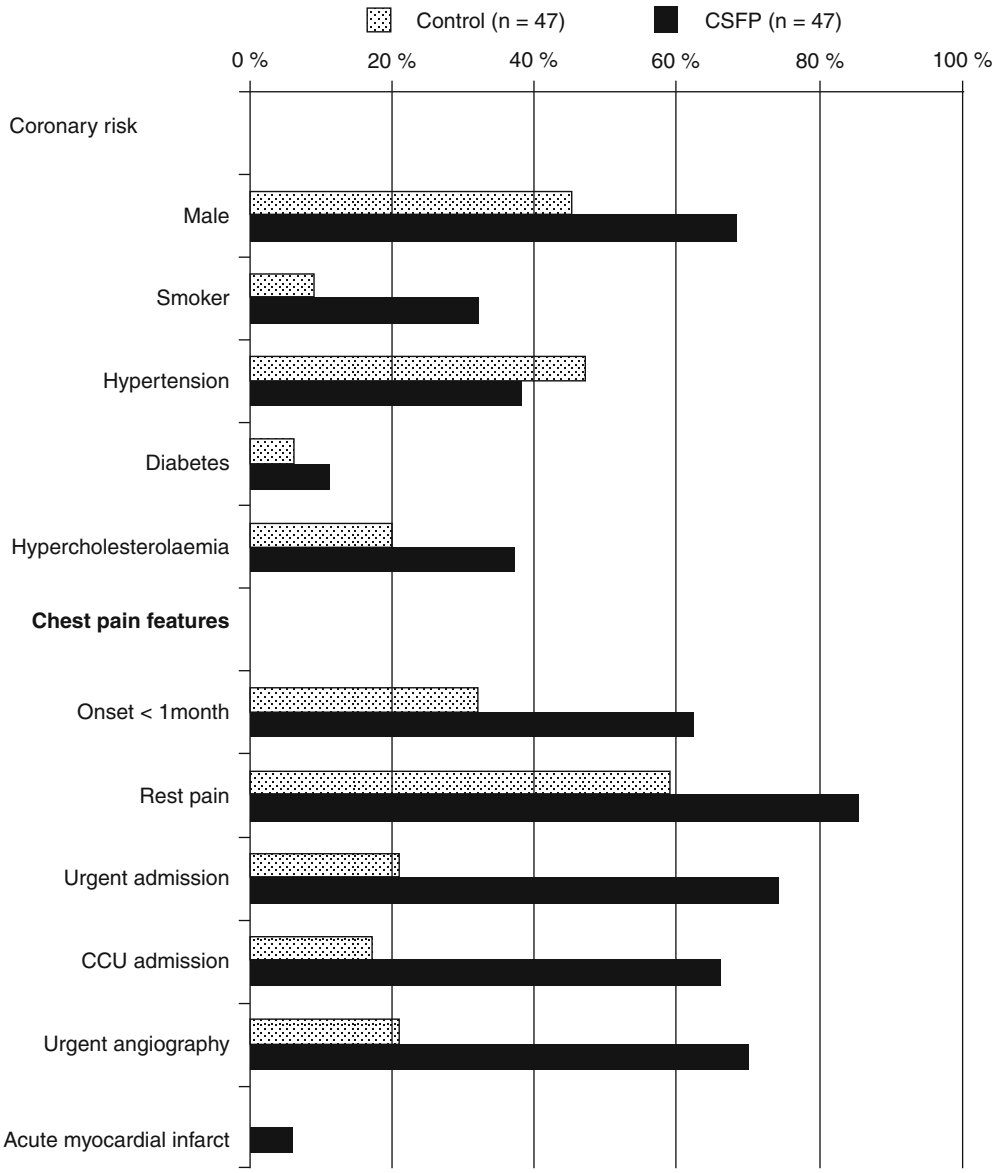

Fig. 10.2 Clinical characteristics of patients with the coronary slow flow phenomenon [4]. *$p<0.05$ compared with control group

presented with unstable angina and the remaining 2 with an acute myocardial infarction. Bencze et al. reported that 34% of CSFP patients presented with an ACS as compared to only 9% of those without the CSFP [25]. A number of case reports have also reported the CSFP on angiography in patients with an acute myocardial infarction and normal angiography [26–28].

An interesting parallel observation can be found in the landmark TIMI-IIIB study [29]. Whereas the above studies noted an ACS presentation in patients with documented CSFP, Diver et al. [29] reported delayed vessel opacification in half of the patients enrolled into an ACS study who had no obstructive coronary artery disease on angiography; hence independent verification of this relationship between the CSFP and ACS. Also, it may not be just a coincidence that the no-reflow phenomenon is more commonly observed in patients undergoing percutaneous coronary intervention for an ACS rather than those undergoing an elective procedure.

Clinical Profile Compared with Other Coronary Disorders

The CSFP has clinical attributes that place it in a clinical continuum between Cardiac Syndrome X and Prinzmetal variant angina (Table 10.1). Similar to Cardiac Syndrome X it is a microvascular coronary disorder but whereas the CSFP is associated with an ACS presentation prompting angiography, patients with Cardiac Syndrome X typically experience exertional angina and undergo coronary angiography following a positive exercise stress test [30]. In contrast, many patients with the CSFP have normal exercise stress tests [1, 4, 24].

Table 10.1 Clinical continuum of coronary vasomotor disorders

Clinical syndrome	Cardiac syndrome X	CSFP	Variant angina
Putative vasomotor mechanism	Microvascular coronary dysfunction	Microvascular (spasm) coronary dysfunction	Coronary artery spasm
Nature of angina	Exertional	Rest	Rest
Angina duration	Typically prolonged	Usually prolonged	Usually short duration
Positive exercise test	Always (by definition)	Infrequently	Seldom
Transient ST elevation	Rare	Case reports	Classical
Ergot-induced spasm	Exclude	Exclude	Typically (by definition)
Response to nitrates	Limited	Variable	Prompt response
Myocardial infarction	Rare	Seldom	Occasional

Moreover, although few patients with the CSFP experience a myocardial infarct, this is rare in Cardiac Syndrome X [30]. These important differences have led many investigators to speculate that the CSFP is distinct form Cardiac Syndrome X [4, 20–23, 25, 31–33].

Prinzmetal variant angina is classically characterised by rest angina associated with transient ST segment elevation (mimicking an ACS) attributable to epicardial coronary artery spasm. The coronary spasm is inducible with ergonovine provocation and promptly relieved with nitrate therapy, however exercise testing is frequently negative. Although the CSFP typically manifests as rest angina and has been associated with episodes of ST elevation [12, 27, 34–37], provocative spasm testing has failed to induce coronary artery spasm [12, 35, 38]. Thus as summarised in Table 10.1, the CSFP is a microvascular coronary disorder that has some attributes similar to Cardiac Syndrome X but more characteristics akin to variant angina and thus warrants consideration as a distinct disorder.

Coronary Risk Factors

In the above case control study [4], the only risk factor that was significantly associated with the CSFP was smoking; curiously, this is also a significant risk factor for variant angina. In other case–control studies, hypercholesterolaemia [39], increased body mass index [39], and the metabolic syndrome [40] have been associated with the CSFP. Larger systematic studies are warranted to further evaluate the predisposing risk factors.

Prognosis

An association between acute myocardial infarction and the CSFP has been established in case reports [27, 28] and case–control studies where a prevalence of up to 8% has been reported in the later CSFP cohorts [4, 24]. However this association requires further clarification before further implications can be considered. Firstly, in these reports the diagnosis of acute myocardial infarction involved the use of cardiac enzymes rather than the more specific troponin cardiac markers. Secondly, the CSFP was documented after the occurrence of the myocardial infarct, thus the relative cause and effect relationships are unclear. This is especially pertinent since delayed TFC have been reported in non-infarct related arteries of conventional atherosclerotic associated infarcts [41] and more recently delayed TFC have been shown in patients with acute myocardial infarction and normal coronary angiography [42]. However there is a case report of a patient with a documented 9-year history of the CSFP who subsequently experienced an acute myocardial infarct with repeat angiography demonstrating persistence of the angiographic phenomenon [26].

Sudden cardiac death and malignant ventricular arrhythmias have been reported in association with the CSFP [4, 43, 44]. Associated acute myocardial infarction was not documented in these isolated case reports. However QT interval prolongation has been documented in the CSFP [45] and in particular increased QT interval dispersion [45, 46], which may provide a basis for these events.

Follow-up studies of patients with the CSFP reveal a high prevalence of recurrent chest pain [4, 47]. With a median follow-up of 21 months, 84 % of CSFP patients continued to experience chest pain, with 33 % re-presenting to the emergency room with rest angina and 19 % requiring readmission to the coronary care unit [4]. Furthermore, Voelker et al. reported that patients with the CSFP were more likely to experience recurrent chest pain than those without this phenomenon [47]. Considering this increased morbidity, it is perhaps not surprising that patients with the CSFP have high anxiety scores [48].

Microvascular Coronary Dysfunction Studies

Since its inception, microvascular coronary dysfunction has been implicated in the pathogenesis of the CSFP. Intuitively, the delayed epicardial vessel opacification is believed to reflect increased resistance in the downstream microvasculature. However documenting microvascular coronary dysfunction

is challenging and often requires specialised approaches that include (1) indirect studies implicating microvascular coronary dysfunction in the absence of obstructive epicardial coronary artery disease (i.e. the presence of myocardial ischaemia or left ventricular dysfunction) or (2) direct structural (biopsy) and/or functional (coronary haemodynamic) studies of the microvasculature.

Myocardial Ischaemia Studies

A number of studies have focussed on evaluating the presence of inducible myocardial ischaemia in CSFP patients and encountered difficulties in establishing its presence. Exercise stress testing reveals ischaemic ST changes in less than half of the CSFP patients [1, 4, 49], although some report 70 % [33, 50] positive tests possibly reflecting a selection bias. Continuous ST segment monitoring during an ACS presentation demonstrate ischaemic ST segment changes in 24 % and T wave changes in 86 % of the CSFP patients [51]. Reversible myocardial scintigraphy defects indicative of ischaemia have been reported in 18–28 % of CSFP patients in the larger cohort studies [4, 9, 52]. Lactate production during rapid atrial pacing is considered the gold standard marker of myocardial ischaemia, yet this failed to identify any evidence of ischaemia in one study [12] and in only 18 % of CSFP patients in another study [9]. Thus ECG, scintigraphic and biochemical studies demonstrate evidence of ischaemia in less than a third of CSFP patients. Whether this reflects an absence of ischaemia in many patients or the insensitivity of the techniques utilised, remains to be defined. For example, one patient developed severe chest pain with ST elevation yet there was no evidence of lactate production on biochemical assessment [12].

Left Ventricular Function Studies

Regional wall motion abnormalities are seldom found in patients with the CSFP and no study has reported transient wall motion changes during stress imaging. However several studies have reported echocardiographic impaired diastolic filling indices in patients with the CSFP [53–55]. Recently, echocardiographic systolic strain imaging has demonstrated prolonged peak systolic strain times suggesting impaired longitudinal left ventricular systolic function also [56, 57]. These indices have correlated with the TFC suggesting a relationship with microvascular coronary dysfunction [53, 57].

Myocardial Biopsy Studies

Both right ventricular [58] and left ventricular [14] biopsy studies of patients with the CSFP have revealed structural microvascular coronary abnormalities. In both studies there was evidence of markedly thickened vessel walls with reduced luminal areas thereby contributing to the increased microvascular coronary resistance.

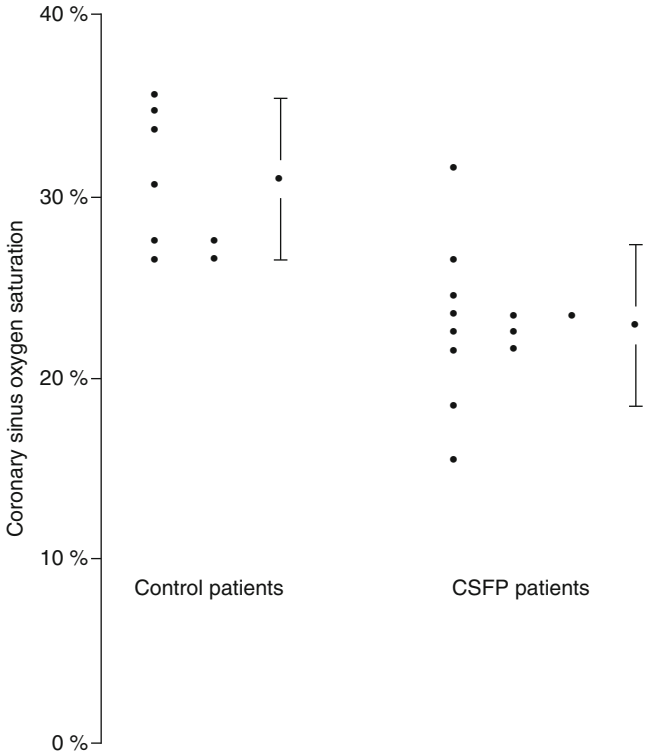

Fig. 10.3 Resting coronary sinus oxygen saturations for control (n = 8) and CSFP patients (n = 12)

Coronary Haemodynamic Studies

The above structural abnormalities must also have a dynamic component considering the associated ACS clinical presentation and the angiographic response to vasodilator stimuli, as previously discussed. The later findings are particularly pertinent since intracoronary administration of large vessel vasodilators such as nitrates have limited benefit in improving angiographic flow in the CSFP [14] and indeed may further delay vessel opacification [59]. In contrast, use of small vessel vasodilators such dipyridamole [14, 19], papaverine [59] or mibefradil [18] have been shown to improve the angiographic flow, supporting the concept that dynamic microvascular coronary dysfunction contributes to the phenomenon.

Evidence of an increased resting microvascular coronary resistance is well documented by measurement of coronary sinus oxygen saturation. As shown in Fig. 10.3, the resting coronary sinus oxygen saturation in CSFP patients (23 ± 4 %) is significantly lower than that of control patients (31 ± 4 %)

despite a similar myocardial oxygen demand (as reflected by the rate-pressure product) [12]. This higher myocardial oxygen extraction reflects the delayed myocardial perfusion and thus the increased resting coronary resistance.

Coronary flow reserve is calculated by assessing maximal coronary blood flow to a hyperaemic stimulus with reference to the baseline blood flow. An impaired coronary flow reserve is reflective of microvascular coronary dysfunction and referred to as 'microvascular angina' in the context of chest pain with normal angiography [60]. One study reported an impaired coronary flow reserve in patients with the CSFP [61] while others have noted a normal response [12, 31, 62]. The normal coronary flow reserve should be interpreted in the context of the other haemodynamic findings, namely an increased resting coronary resistance that can be alleviated by vasodilatory stimuli so that maximal blood flow can be achieved. This is consistent with the return of normal contrast flow with the administration of small vessel vasodilators and may also account for the frequent absence of inducible ischaemia on exercise. Hence it would suggest that the coronary resistance vessels are constricted at rest but can achieve maximal vasodilation with exercise.

One study has evaluated microvascular coronary endothelial function in patients with the CSFP [12]. In this study, intracoronary acetylcholine (1×10^{-4} M) was infused and changes in microvascular coronary resistance assessed in eight patients with the CSFP. The interpretation of the response to this nitric oxide dependent vasodilator are difficult, as the results were heterogeneous with one patient exhibiting a profound increase in resistance but most others showing little change or a fall in resistance. Overall there was no statistical change in microvascular coronary resistance to acetylcholine in this small study, underscoring the need for further studies.

Potential Pathophysiological Mechanisms

The mechanisms responsible for the microvascular coronary dysfunction are even more elusive to assess than ascertaining the presence of microvascular coronary dysfunction. Potential mechanisms include abnormalities in vasoactive autacoids, autonomic dysfunction, platelet dysfunction, metabolic derangements, inflammation and oxidative stress. These may all give rise to microvascular coronary dysfunction and warrant further consideration.

Vasoactive Autacoids

Local vasoactive substances may increase coronary microvascular resistance by either excessive vasoconstrictor forces or a failure of the compensatory vasodilatory mechanisms. The later mechanism is frequently described as endothelial dysfunction and considered to be mediated by nitric oxide; although other regulatory substances such as endothelium derived hyperpolarising factor may also play an important role in the microvasculature. In relation to the CSFP, impaired endothelial nitric oxide responses and the role of potent vasoconstrictors such as endothelin and neuropeptide Y have been investigated.

Brachial artery nitric oxide dependent flow mediated vasodilation has been reported to be impaired in CSFP patients [63, 64]. Furthermore, plasma levels of nitrite ions (a marker of nitric oxide production) are depressed [63, 65] and the endogenous nitric oxide inhibitor, asymmetric dimethylarginine (ADMA), elevated [64, 66] in patients with the CSFP. However, other researchers have shown flow mediated dilation to be intact [67, 68] and coronary sinus nitric oxide levels to be normal [69]. These disparate findings may be explained by differences in coronary risk factors, which may also contribute to endothelial dysfunction.

Endothelin is a potent vasoconstricting autacoid which mimics the angiographic phenomenon when administered in animal models [70]. Furthermore, both systemic and coronary sinus plasma endothelin levels have been reported to be elevated in patients with the CSFP, particularly during rapid atrial pacing [69]. This autacoid has a predilection for microvessels and warrants further investigation.

Other vasoconstricting autacoids that have been implicated in the CSFP include neuropeptide Y and Thromboxane A_2. In a unique study, neuropeptide Y administered to Cardiac Syndrome X patients (with normal contrast flow) induced the CSFP [71]. Thromboxane A_2 levels have been shown to correlate with contrast clearance in patients with chest pain and normal angiography [72].

Several studies have examined the association between polymorphisms for vasoactive compounds and the CSFP. The angiotensin converting enzyme deletion (DD) polymorphism has been shown to be associated with the CSFP, implicating the renin-angiotensin system in the pathophysiology of this condition [73]. Also the endothelial nitric oxide synthase polymorphism (T-786C) has been associated with the CSFP [74] whereas no association was found with the Glu298Asp variant [75].

Autonomic Dysfunction

Coronary pre-arteriolar microvessels are innervated and may be influenced by autonomic nerve fibres. Heart rate variability provides insights into the autonomic influences of the heart and has been investigated in patients with the CSFP. Two studies have demonstrated that the heart rate variability time domains are depressed in the CSFP suggesting a greater sympathetic neural influence [76, 77]. Further evidence for

increased adrenergic influences were reported by Yazici et al. [78], who demonstrated that plasma adrenaline and noradrenaline levels were increased in CSFP patients and that the levels were correlated with the TFC.

Platelet Dysfunction

Platelets may potentially cause microvascular plugging and thus increase microvascular resistance. Investigations in patients with the CSFP have revealed an increase in platelet number [79], mean platelet volume [80, 81] and platelet aggregation [82]. However, the relative role of platelets in this phenomenon requires further clarification.

Metabolic Derangements

Metabolic abnormalities such as the metabolic syndrome, increased homocysteine levels or increased oxidative stress have been associated with endothelial dysfunction and thus could potentially contribute to microvascular coronary dysfunction.

Various components of the metabolic syndrome have been described in patients with the CSFP including impaired glucose tolerance [40, 79], elevated plasma insulin levels [83], depressed high density lipoprotein levels [84], elevated triglycerides [84], elevated urate levels [85] and an increased body mass index [39]. Moreover Yilmaz et al. reported a 32 % prevalence of the metabolic syndrome (using the modified National Cholesterol Education Program's Adult Treatment Panel III report) in CSFP patients, as compared with 16 % in controls [39]. In contrast, Yazici et al. reported a normal insulin, glucose and lipid profile in the CSFP patients [86].

Elevated homocysteine levels in CSFP patients have been reported in a number of studies [87–90]. Several have observed a correlation between the plasma homocysteine concentration and the TFC [88–90] and one demonstrated a negative correlation with flow-mediated dilation [90]. Accordingly, homocysteine may contribute to the putative endothelial dysfunction and atherosclerosis observed in some CSFP studies. Interestingly, Evrengul et al. [88] reported positive urea breath tests implicating Helicobacter pylori infection in their CSFP patients who had elevated homocysteine levels and also noted reduced plasma folate levels. They therefore speculate that H pylori infections may impair folate absorption and thus increased homocysteine levels.

Markers of increased oxidative stress have been reported to be abnormal in patients with the CSFP. These include increased levels of serum malondialdehyde [90, 91] and erythrocyte superoxide dismutase [90, 91], as well as depressed levels of erythrocyte reduced glutathione [90, 91] and paraoxonase activity [92]. This increased oxidative stress may also contribute to the endothelial dysfunction and atherosclerosis and reflect concurrent inflammation.

Inflammation

Similar to oxidative stress, inflammation has been implicated in the pathogenesis of endothelial dysfunction, atherosclerosis and microvascular coronary dysfunction. Several studies have reported elevated high sensitivity C-reactive protein in patients with the CSFP and correlated these values with the TFC [93–95]. Furthermore, soluble adhesion molecules [96] have been shown to be elevated in the CSFP. In contrast to these findings, Yazici et al. reported normal high sensitivity C-reactive protein levels during a recent admission with chest pain and over the following 3-month period [97]. Hence the role of inflammation, as for many of these mechanistic studies, warrants further evaluation.

Evidence-Based Therapies

Arguably, the most important aspect of CSFP research is the identification of appropriate evidenced-based therapies. If an effective treatment is established, then the importance of making the diagnosis and especially distinguishing it from other forms of angina, is justified. Moreover, an effective treatment scientifically would strongly support the existence of this disease entity that some still consider largely an angiographic curiosity. Effective therapies may also potentially provide insights into the mechanism/s of this intriguing disorder.

Currently there are no established treatment guidelines for the CSFP. However, the fundamental principles in the management of coronary heart disease still apply and include, (1) the prevention of cardiac events (death and myocardial infarction) and (2) the control of disabling symptoms. Thus, in those patients who have an established myocardial infarct, secondary preventative measures should be considered including the use of aspirin, statins (especially in the presence of documented minor coronary artery disease), beta-blockers, and angiotensin converting enzyme inhibitors. However in the absence of a prior cardiac event (i.e. primary prevention), the benefit of these routine preventative therapies is less clear since there appears to be a low risk of future serious adverse events.

In the control of anginal symptoms, therapies must be titrated to the individual patient since those that are effective in one patient may not be beneficial in others. Conventional anti-anginal therapies used in various parts of the world for obstructive coronary artery disease include nitrates,

beta-blockers, calcium channel blockers, potassium channel openers (nicorandil) and metabolic agents (trimetazidine, perhexiline and ranolazine). These agents are effective in the treatment of epicardial coronary artery disease however their effectiveness in microvascular coronary disease may not be implicitly assumed. Therefore, it is important to consider the evidence available specifically in the treatment of the CSFP.

Table 10.2 summarises the published therapeutic studies in the CSFP. Several limitations are evident including (a) there are few studies assessing conventional anti-anginal therapies, (b) most studies are non-randomised, open-label in design and thus may be biased, (c) many studies are observational studies with serial endpoint assessment with only a few having a control group to determine the natural history of the study endpoint, and (d) many of the studies have focussed on surrogate endpoints rather than important health outcomes such as the control of angina. Despite these significant limitations, important insights have been gained from these studies that are summarised below.

Beta-Blockers

There are no clinical studies with conventional beta-blockers in the treatment of the CSFP however there are a number of studies utilising the novel agent, nebivolol. This agent not only blocks beta-1 receptors but also has a nitric oxide potentiating effect, thus any observed benefit may be from either or both of these mechanisms. Several independent Turkish research groups have investigated the role of nebivolol in the CSFP, demonstrating its benefit in improving flow mediated dilation [98, 99], mean exercise duration [99], oxidative stress markers [100] and left ventricular diastolic indices [109] (Table 10.2). These studies employed an observational, open-label study design with repeated assessment of the study endpoint. Thus although intriguing, the data require validation with rigorous randomised, double-blinded, controlled studies.

Calcium Channel Blockers

Intracoronary verapamil has been shown to improve angiographic flow in patients with the CSFP more effectively than nitrates. This is consistent with calcium channel blockade being more effective in vasodilating resistance vessels whereas nitrate therapy primarily targets the large epicardial coronary arteries. Furthermore the novel calcium channel blocker, mibefradil, improved angiographic flow in patients exhibiting the CSFP despite background verapamil therapy (Fig. 10.4). This may suggest that mibefradil is more effective in the treatment of the CSFP than verapamil. Of note, whereas conventional calcium channel blockers only block the long-acting calcium channel (L-channel), mibefradil blocks both the L-channel and the transit-acting calcium channel (T-channel).

Mibefradil not only improves the angiographic phenomenon but also symptoms. In a randomised, double-blind, placebo-controlled, cross-over study assessing the anti-anginal benefits of mibefradil in the CSFP, this agent was shown to reduce total angina episodes by 56 %, prolonged angina episodes by 74 % and sublingual nitrate consumption by 59 % [18]. The improvement in symptoms is well illustrated in Fig. 10.5, which documents angina frequency throughout the cross-over study. Considering the improvement in symptoms, it was not surprising that mibefradil was also shown to dramatically improve these patients quality of life [18].

Although there are no direct comparative studies of mibefradil with other agents in the treatment of the CSFP, personal experience in treating patients with this agent suggest it has exceptional efficacy. In an unpublished survey of 28 CSFP patients prescribed mibefradil, 95 % reported moderate-major anti-anginal benefits. Of the patients surveyed, 89% had previously experienced a poor response to other conventional anti-anginal agents including long-acting nitrates (89 %), other calcium channel blockers (78 %), and beta blockers (21 %). Thus it is noteworthy that conventional calcium L-channel blockers may be less effective than mibefradil in the treatment of the CSFP both in terms of symptoms and the angiographic response.

Considering the apparent relative clinical benefits of mibefradil over other calcium L-channel blockers, in-vitro studies were performed comparing the L-channel blockers (verapamil and nifedipine) with mibefradil and another combined L- and T-channel blocker, efonidipine. In isolated rat aorta segments (mean diameter = 2,055 ± 35 μm), i.e. conduit arteries, the four calcium channel blockers were equally effective in inhibiting endothelin constrictor responses [110]. However in mesenteric microvessels (mean diameter = 304 ± 7 μm), mibefradil and efondipine produced a greater inhibition of the constrictor responses compared with the conventional L-channel blockers. Figure 10.6 demonstrates that this more effective inhibition of endothelin constrictor response by combined L- and T-channel blockers compared to the L-channel blockers was also evident in human subcutaneous microvessels (mean diameter = 289 ± 14 μm) [110]. Furthermore, western blot quantification of the L and T-channels in the rat aorta demonstrated no difference in the abundance of these channels, whereas T-channels were more abundant than L-channels in the microvessels [110]. Hence mibefradil's greater efficacy in the CSFP may be due to its more effective inhibition of microvascular constrictor responses via T-channel blockade, which are more prevalent in the microvasculature.

Despite these clinically and biologically significant benefits of mibefradil in the CSFP, unfortunately the quest

Table 10.2 Therapeutic studies of the CSFP

Study	Therapy	n	Design	Study endpoint	Conclusion
Beta-blockers					
Albayrak [98]	Nebivolol 5mg/day, PO	42	Open-label, observ, serial study	FMD @ 12 weeks	Improves FMD
Tirakioglu [99]	Nebivolol 5 mg/day, PO	25	Open-label, case-ctrl, observ, serial study	FMD, MED & Duke Score @ 6 months	Improve FMD, MED & Dukes score @ 1 month with no further improve @ 6 months
Akcay [100]	Nebivolol 5 mg/day, PO	32	Open-label, case-ctrl, observ, serial study	Oxidative stress markers and NO @ 6-months	Restore oxidative stress markers and NO
Gunes [101]	Nebivolol 5 mg/day, PO	30	Open-label, case-ctrl, observ, serial study	P-wave duration & echo diastolic indices @ 3 months	Restore P-wave duration & diastolic indices
Calcium channel blockers					
Chang [102]	Verapamil or NTG 100-400mcg stat, IC	64	Open-label, case-ctrl, observ, serial study	TFC post-IC admin	TFC improve verapamil>NTG
Beltrame [18]	Mibefradil 50 mg stat, PO	10	Open-label, case-ctrl, observ, serial study	TIMI flow grade @ 30 min	Restore TIMI-3 flow in 72 % of vessels
Beltrame [18]	Mibefradil 100 mg/day, PO	22	Randomised, double-blind, placebo-ctrl, x-over study	Angina @ 4 week	improve angina x56 %
Other anti-anginal agents					
Sadamatsu [103]	Nicorandil 1mg stat, IC	11	Open-label, observ, serial study	TFC post-IC admin	nicorandil further improve TFC after NTG
Topal [104]	Trimetazidine 60 mg/day, PO	48	Randomised, double-blind, placebo-ctrl, serial study	HRV, stress test indices, NO, Endothelin-1	Improve HRV, stress test indices, NO, endothelin-1
Other agents					
Mangieri [14]	Dipyridamole	6	Open-label, observ, serial study	Angiographic flow	Restore 50 % to normal flow
Kurtoglu [19]	Dipyridamole 225 mg/day, PO	25	Open-label, observ, serial study	TFC @ 3 months	Restore normal TFC in 93 % of vessels
Guntekin [105]	Perindopril PO	32	Open-label, case-ctrl, observ, serial study	QT interval & echo diastolic indices @ 3 months	Restore QT interval & echo diastolic indices
Cakmak [106]	Simvastatin 40 m/day, PO	97	Open-label, observ, serial study	MPS Reversibility Score @ 6 months	Improve MPS Reversibility Score
Caliskan [107]	Atorvastatin 20 mg/day, PO	20	Open-label, observ, serial study	Echo diastolic indices and CFR @ 8 weeks	Improve echo diastolic indices (except E/A) & CFR
Fan [108]	Atorvastatin 20 mg/day, PO	91	Open-label, case-ctrl, observ, serial study	CFR @ 8 weeks	Improve CFR

PO oral administration, *IC* intracoronary administration, *n* number of CSFP patients, *Case-ctrl* case-control, *observ* observational study, *x-over* cross-over design, *TFC* TIMI frame counts, *NTG* nitroglycerin, *post-IC admin* post-intracoronary administration, *FMD* flow mediated dilation, *MED* mean exercise duration, Echo diastolic indices (E/A ratio, deceleration time, isovolumetric relaxation time), *HRV* heart rate variability, *Oxidative Stress Markers* malondialdehyde, superoxide dismutase, catalase, *NO* nitric oxide, *MPS* myocardial perfusion scintigraphy, *CFR* coronary flow reserve

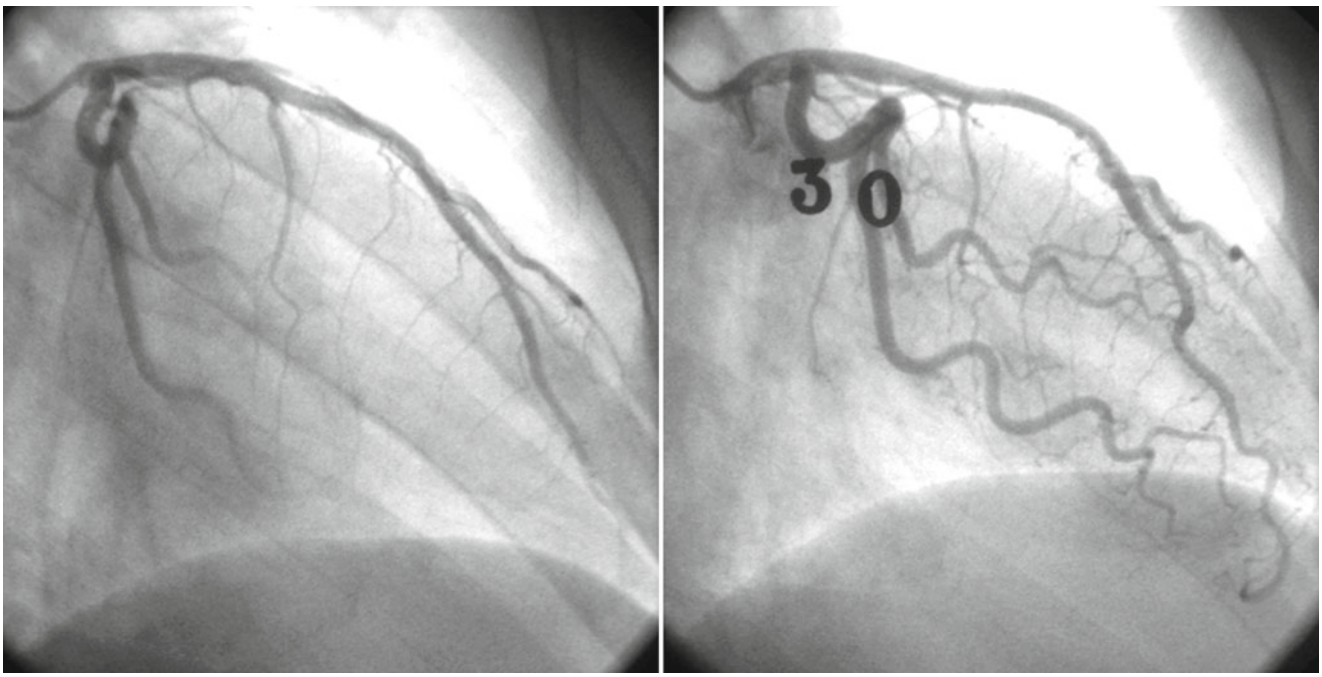

Fig. 10.4 Acute angiographic response to mibefradil. The snapshot images are recorded at three heart beats with the *left hand panel* showing delayed filling of the left coronary system which was improved 30 min after 50 mg of mibefradil as shown in the *right hand panel* (From Beltrame et al. [18] with permission from Elsevier)

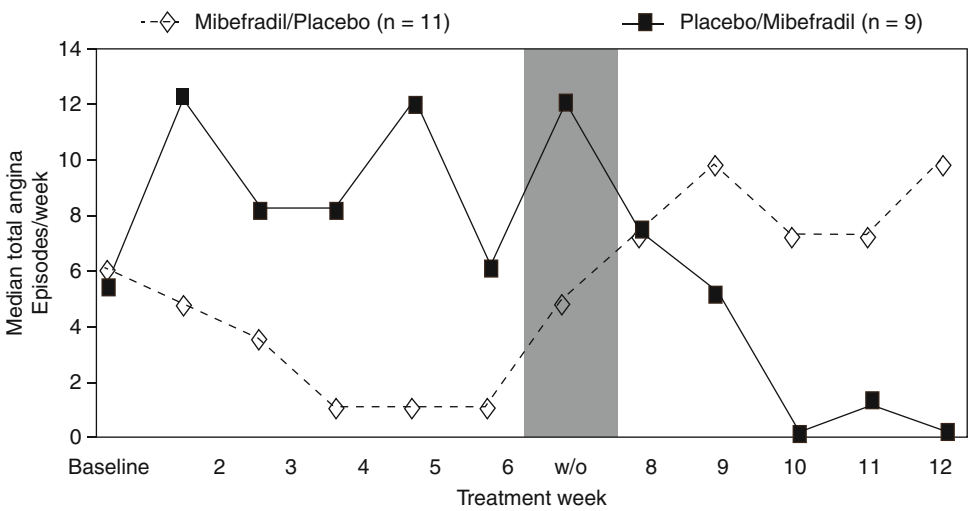

Fig. 10.5 Anti-anginal effects of mibefradil in the CSFP. Median weekly angina in 11 patients (*dashed line*) initially randomised to mibefradil for the first 6 weeks of the study, followed 1-week washout (*gray zone*) and then placebo for the remaining 6 weeks. The *solid line* shows the reverse for the nine patients randomised to placebo therapy first

for an effective agent in the treatment of this condition must continue since mibefradil has been withdrawn from clinical use due to extensive drug interactions. Despite this, the investigations into mibefradil have provided several important insights into the CSFP including, (1) reinforcing CSFP as a specific disease entity with an effective therapy, (2) providing supporting evidence for the pivotal role microvascular dysfunction plays in this disorder, and (3) provides proof-of-principle that therapeutic targets in the microvasculature may differ from that of large vessels.

Other Anti-anginal Agents

Nicorandil is a potassium channel opener that also has nitrate-like properties. In an uncontrolled, open-label study, intracoronary nicorandil was shown to further improve contrast flow in CSFP patients previously administered intracoronary nitrates [111]. However, the clinical efficacy of this agent requires further investigation. Trimetazidine inhibits fatty acid metabolism thereby improving glucose utilisation and thus reducing angina. In a randomised, double-blind,

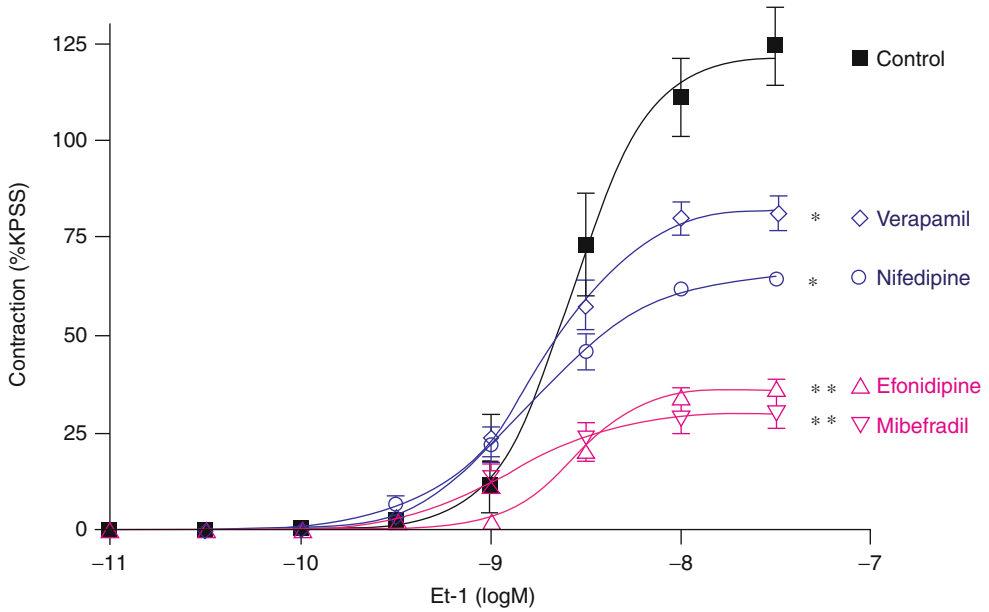

Fig. 10.6 Inhibition of endothelin constrictor responses by L-channel (verapamil and nifedipine) or combined L- and T-channel blockers (mibefradil and efonidipine) in human subcutaneous microvessels. *$p<0.001$ versus control, **$p<0.001$ versus L-channel blockers (n = 6) (Adapted from Ball et al (2009) [110])

placebo-controlled, sequential study, trimetazadine 20mg thrice daily was shown to improve heart rate variability, exercise stress test performance (time to angina and time to 1mm ST depression) and endothelin/nitric oxide levels in patients with the CSFP [104].

Other Therapeutic Agents

Dipyridamole is a potent small vessel vasodilator and has been shown to improve angiographic flow in patients with the CSFP. In contrast to patients with obstructive coronary artery disease where it has been shown to induce myocardial ischaemia by coronary steal, in the CSFP it appears to have anti-anginal benefits. Kurtoglu et al. assessed the anti-anginal benefits of dipyridamole 75 mg thrice daily in patients with the CSFP using a non-randomised, uncontrolled, open-label, sequential observational study-design [19]. After 3 months of dipyridamole therapy, repeat angiography demonstrated an improvement in the angiographic flow and 68 % of patients reported resolution of their angina with the remaining reporting a reduced angina frequency.

Angiotensin converting enzyme (ACE) inhibitors may potentially be of benefit in the CSFP. Guntekin et al. have recently shown that QT interval and echocardiographic left ventricular diastolic indices (potential markers of myocardial ischaemia) are abnormal in the CSFP. Following 3 months of perindopril therapy, heart rate slowed, the corrected QT interval returned to normal values in most patients and there was a significant improvement in echocardiographic deceleration time, E/A ratio and isovolumetric relaxation time [105]. However, there is no data whether ACE inhibitors alleviate symptoms in these patients.

Statins have been shown to inhibit constrictor responses in isolated microvessels [112] and thus may potentially be of benefit in coronary microvascular disorders. Several non-randomised, open-label, observational studies have demonstrated that statin therapy can improve ischaemia as assessed on myocardial scintigraphy [106], as well as echocardiographically assessed left ventricular diastolic indices [107] and the coronary flow reserve [107, 108].

A Synthesis of the Contemporary Data

Over the past 40 years the CSFP has evolved from an angiographic curiosity to an identified disease entity. The contemporary understanding of the CSFP can be summarised as follows:

- Conceptually, the CSFP is angiographically defined as delayed distal vessel contrast opacification in the absence of obstructive coronary artery disease. However, operational definitions of this phenomenon are variable with some studies utilising a TIMI flow grade scale and others the TIMI frame count. Furthermore, this angiographic phenomenon can be associated with secondary conditions such as 'no-reflow' however the discussions in this chapter were limited to primary forms of the disorder.
- The prevalence of the CSFP has been reported as 1–3 % of diagnostic angiograms.
- The CSFP is distinct from other microvascular coronary disorders in its clinical presentation since patients often undergo index angiography following an acute coronary syndrome presentation.
- In 8 % of CSFP patients, the phenomenon may occur in the context of acute myocardial infarction. Furthermore,

isolated case reports have associated it with malignant arrhythmias and sudden cardiac death. However follow-up studies report a low frequency of subsequent cardiac events but a high prevalence of recurrent chest pain (over 80 %) in patients with the CSFP.

- An increased resting coronary microvascular resistance has been demonstrated in the CSFP and presumably this is further increased during episodes of chest pain although this has not been conclusively demonstrated. Although microvascular coronary abnormalities have been noted in morphologic studies, the increased microvascular resistance is dynamic in nature as it is responsive to microvascular coronary vasodilators. Moreover, coronary flow reserve appears to be preserved in this condition.
- Myocardial ischaemia is documented in only a third of CSFP patients using conventional clinical ischaemic markers. Furthermore regional wall motion abnormalities are seldom observed. Whether this infers that the chest pain is not ischaemic in nature or the techniques are insufficient to detect the microscopic ischaemia, is open to speculation. Nevertheless, low coronary sinus oxygen saturation is a relatively consistent feature in CSFP and indicates that the coronary blood flow is inappropriately low for the level of myocardial oxygen demand.
- The mechanism/s responsible for the microvascular coronary dysfunction remain elusive. Whether the endothelial nitric oxide vasodilatory pathway is defective in this disorder is inconclusive. Endothelin is a potent vasoconstrictor and may potentially be involved in the disorder but further studies are required. The role of autonomic dysfunction, platelet dysfunction, hyperhomocysteinaemia, the metabolic syndrome and inflammation in the CSFP requires further investigation.
- Although a number of studies have examined various therapies for the CSFP, only two investigations have employed rigorous double-blind, placebo-controlled study designs to assess the clinical therapeutic impact. The benefits of the combined L-type and T-type calcium channel blocker mibefradil in this disorder have been confirmed by angiographic, clinical and basic laboratory studies but unfortunately this agent is no longer available. Trimetazidine has been shown to improve exercise stress test parameters (time to angina and 1mm ST depression) as well as biologic markers in patients with the CSFP.

Even though considerable advances in the CSFP have been made, substantial efforts are still required to further understand this intriguing disorder. Particular areas that warrant priority consideration are (a) larger studies investigating the prognosis in patients diagnosed with the CSFP, and (b) rigorous therapeutic studies identifying effective treatments for the recurrent chest pain experienced by these patients. Advances in these priority areas will further underscore the clinical importance in diagnosing patients with the CSFP.

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Part III

Microvascular Angina in Different Clinical Conditions

Microvascular Angina in Essential Hypertension

11

Tarek Francis Antonios

Abstract

Hypertension is the most important risk factor for cardiovascular morbidity and mortality worldwide. However, the mechanism whereby blood pressure is raised is not fully understood and it remains unclear how high blood pressure accelerates vascular disease and causes direct and specific end-organ damage such as nephropathy, retinopathy, lacunar infarcts and microvascular angina. There is now increasing evidence that microcirculatory abnormalities in essential hypertension are of paramount importance in the pathogenesis of this disorder. The microcirculation is responsible for the elevated peripheral vascular resistance in essential hypertension. Arterial hypertension is known to affect the coronary circulation through several mechanisms including coronary artery disease, left ventricular hypertrophy, and microvascular disease. Experimental and clinical data indicate that coronary microvascular disease exists in patients with essential hypertension in whom it can cause both a reduction of coronary flow reserve and a shift to the right of the coronary flow autoregulation curve. The role of microcirculatory abnormalities and, in particular, capillary rarefaction in the pathophysiology of hypertension and microvascular angina is discussed in this chapter.

Keywords

Microcirculation • Capillaries • Essential hypertension • Microvascular angina • Capillary rarefaction

Introduction

Systemic hypertension is the most important risk factor for cardiovascular morbidity and mortality worldwide [1]. Hypertension is present in 69 % of patients with a first myocardial infarction, 77 % of patients with a first stroke, 74 % of patients with chronic heart failure, and in 60 % of patients with peripheral arterial disease [2]. Hypertension is also a major risk factor for a dissecting aortic aneurysm, sudden cardiac death, angina pectoris, atrial fibrillation, diabetes mellitus, the metabolic syndrome, chronic kidney disease, thoracic and abdominal aortic aneurysms, left ventricular hypertrophy, vascular dementia, Alzheimer disease, and ophthalmologic disorders. However, the mechanism whereby blood pressure is raised is not fully understood and it remains unclear how high blood pressure accelerates vascular disease and causes direct and specific end-organ damage such as nephropathy, retinopathy, lacunar infarcts and microvascular angina. There is now increasing evidence that many of the abnormalities observed in essential hypertension involving the heart, large vessels and the microcirculation might precede the elevation of the blood pressure. The importance of the microcirculation in relationship to hypertension is that it is this particular section of the vascular system that determines the elevation of peripheral vascular resistance in

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essential hypertension. It is established that human essential hypertension and most forms of clinical and experimental hypertension are characterized by a normal cardiac output and an elevation in the peripheral vascular resistance. It is thought that the major site of vascular resistance is located in the small arterial and arteriolar beds. Recent studies have shown that the microcirculation may contribute between 40 and 90 % to pressure dissipation and therefore to vascular resistance [3]. The microvasculature in hypertension undergoes substantial structural changes and changes in physiological reactivity, which contribute directly to the elevation of vascular resistance [4, 5].

Microvascular Abnormalities in Hypertension

Several studies have shown a reduced blood flow in "maximally" vasodilated vascular beds in subjects with essential hypertension, consistent with a structurally based increase in flow-resistance [6]. Histological studies have also shown that in human essential hypertension, the media:lumen ratio of small arteries is increased in different stages of hypertension [7]. The increased vascular smooth muscle mass within small arteries in hypertension was shown to be due to hyperplasia rather than, as in the large arteries, to hypertrophy of vascular smooth muscle cells (VSMC). In certain small arteries the increased media:lumen ratio is due to *remodelling* of the same number of cells, either circumferentially or longitudinally. The processes of VSMC hyperplasia or vessel wall remodeling, while maintaining VSMC mass, may reflect events occurring at different levels of the vascular tree. There is considerable debate whether VSMC hyperplasia in small arteries precedes or follows hypertension. In primary forms of hypertension, small artery VSMC hyperplasia takes pace, in contrast to the VSMC hypertrophy observed in large arteries, and this may precede the development of hypertension.

Microvascular Rarefaction

The most consistent finding at the level of the microcirculation in primary hypertension in human and animal models of hypertension is the reduced number of arterioles and capillaries, as compared to normotensive controls. In humans with hypertension, Ruedemann [8] and Lack [9] reported rarefaction of capillaries in the conjunctival circulation and capillary and arteriolar rarefaction has also been described in other vascular territories in patients with essential hypertension such as the intestinal circulation, skeletal muscles, the myocardium and the stomach [10, 11].

Rarefaction of capillaries has been reported by several groups after the introduction of intra-vital capillary videomicroscopy [12]. Williams et al. [13] found that capillary density of the skin of the dorsum of fingers was significantly lower in hypertensive subjects than in normotensive controls. Of interest, however, they found no significant difference in capillary density between treated and untreated hypertensive patients. Gasser and Bühler [14] reported that nailfold capillary density was significantly lower in hypertensive subjects than in normotensive individuals. They also found a positive correlation between capillary density and mean diastolic blood pressure. Controversially, however, Duprez et al. [15] found no correlation between capillary number and either office recorded or 24-h ambulatory blood pressure measurements. Prasad et al. [16] examined the forearm skin in hypertensive subjects using intravital microscopy and fluorescein angiography and were able to confirm a 20 % reduction in capillary numbers in these individuals compared to controls. The mechanisms underlying arteriolar and capillary rarefaction are not well defined. It was proposed that there are at least two different mechanisms for microvascular rarefaction in hypertension: an early form related to primary defects in blood vessel growth and a later form, which is part of the adaptive remodelling of the vascular tree, due to altered mechanical stresses in hypertension. Studies in both genetic and renal animal models of hypertension point to a potential role of endothelial cell apoptosis during hypertension-induced microvascular rarefaction [17].

In primary hypertension capillary rarefaction may also be classified as structural, associated with impaired angiogenesis and diminished microvascular growth, and functional, associated with impaired recruitment of non-perfused capillaries due to severe upstream vasoconstriction or local capillary dysfunction.

Structural Capillary Rarefaction in Essential Hypertension

In many human tissues, capillaries work on a "rota system" i.e. some are perfused while others are shut down. As blood flow is controlled at the arteriolar level (pre-capillary resistance vessels), it can be hypothesized that by reducing pre-capillary resistance through reactive hyperaemia [18] or core heat load, most or practically all of the capillaries can "open up" thus maximizing capillary numbers.

In a series of studies we compared several techniques to try to maximize the number of visible capillaries during intravital capillary microscopy, including post-occlusive reactive hyperaemia, core-heat load test, venous congestion and combined reactive hyperaemia with venous congestion. Venous congestion was found to allow better visualization of the maximal number of perfused capillaries during intravital microscopy compared to post-occlusive reactive hyperaemia [19].

Using venous congestion to maximize the number of perfused capillaries we [20] studied 17 individuals with essential

hypertension who had not received treatment for their high blood pressure (mean age 53.5 ± 2.4, BMI 25.7 kg/m^2, blood pressure 155/96 mmHg) and 17 closely matched normotensive controls (mean age 53.9 ± 2.1, BMI 24.4 kg/m^2, blood pressure 127/77 mmHg). Mean functional capillary density (before venous congestion) was significantly lower (17 %) in the hypertensive subjects compared to the normotensive controls (62 ± 4 vs. 73 ± 3 per 0.68 mm^2 respectively) ($p = 0.049$ by ANOVA). With venous occlusion, capillary density increased significantly in both groups, however, maximal capillary density was significantly lower (19 %) in the hypertensive subjects (73 ± 5 in the hypertensives compared to 87 ± 4/field in the normotensive subjects) ($p = 0.0325$ by ANOVA) [20]. This study demonstrated that in patients with essential hypertension who have never received treatment for their high blood pressure, maximal (structural) capillary density is significantly lower compared to normotensive controls. The results of the study strongly suggest that much of the reduction in capillary density in hypertension is due to the anatomical (structural) absence of capillaries, rather than a 'functional' reduction caused by non-perfusion due to upstream vasoconstriction [20].

Rarefaction of Skin Capillaries in Patients with Pre-hypertension

Many vascular abnormalities have been reported in patients with pre-hypertension including elevated minimal forearm vascular resistance measured during maximal dilatation (indicating a structural decrease in cross-sectional area of the vascular bed or rarefaction) [21, 22]. We have assessed skin capillaries in subjects with intermittent mild essential hypertension to find out whether rarefaction antedates the onset of sustained blood pressure elevation. Our study included 18 patients (mean age 45.4 ± 3.4 years, BMI 26.1 ± 1.0 kg/m^2) with intermittent borderline hypertension (136/83 mmHg), 32 normotensive controls (mean age 51.5 ± 2.1 years, BP 126/77 mmHg, BMI 25.2 ± 0.6 kg/m^2) and 45 patients with established Grade 1 essential hypertension (mean age 47.0 ± 1.8 years, BP 156/98 mmHg, BMI 28.6 ± 0.9 kg/m^2). We found a significant reduction in functional capillary density at baseline, before venous congestion, in the borderline and established hypertensive subjects compared to the normotensive controls (57 ± 4 and 58 ± 3 compared to 76 ± 3 per 0.68 mm^2 respectively) ($p < 0.0001$). Maximal (structural) capillary density was also significantly lower (36 % in the borderline group and 30 % in the established hypertensive subjects) (63 ± 5, 70 ± 3 and 93 ± 3/field respectively) ($p < 0.0001$). We concluded that significant structural rarefaction of the skin capillaries occurs in the early stages of human essential hypertension with only mild intermittent elevation of blood pressure [23]. These results confirmed that patients with pre-hypertension have skin capillary densities as low as or even lower than patients with established hypertension. This indicates that capillary rarefaction may be a primary or a very early structural abnormality rather than a consequence of sustained hypertension.

Rarefaction of Skin Capillaries in Normotensive Offspring of Patients with Essential Hypertension

Both structural and functional abnormalities of the vasculature are present at an early stage in normotensive individuals with parental history not only of essential hypertension but also of other cardiovascular diseases. Abnormalities have been described in larger conduit arteries, such as increased arterial stiffness, as well as in smaller resistance arteries and arterioles. Children and adolescents with a parental history of hypertension had higher carotid stiffness and smaller carotid diameters compared to offspring of normotensive parents [24]. Minimal forearm vascular resistance was found to be 25 % higher in subjects with hypertensive relatives than in subjects with no family history [25], suggesting that there might be a structural abnormality in the forearm resistance vessels in normotensive subjects with family history of hypertension. Furthermore, flow-mediated vasodilatation was significantly lower in normotensive young subjects who had a family history of essential hypertension compared with offspring from normotensive parents [26]. Similar findings were also reported in normotensive offspring of individuals with premature myocardial infarction who were found to have a lower flow-mediated reactivity of the brachial arteries and greater mean intima-media thickness of the common carotid artery. Noon et al. found that offspring with high blood pressure whose parents also have high blood pressure had fewer capillaries on the dorsum of their fingers suggesting that defective angiogenesis may be an etiological component in the inheritance of high blood pressure [27]. This implies that capillary rarefaction does not necessarily represent an actual disappearance of blood vessels, but rather a decreased angiogenic capacity of the microcirculation of individuals predisposed to develop hypertension. It is as yet not known whether the decreased angiogenic potential of the microcirculation in essential hypertension is due to a genetic predisposition or whether it reflects an early, foetal or postnatal alteration in developmental programming. It is of interest to mention here that essential hypertension is associated with a reduced number of endothelial progenitor cells (EPCs) [28]. We studied 21 normotensive subjects with family history of essential hypertension (mean age 39.3 years, BP 124/79 mmHg) and 21 normotensive individuals with no family history of hypertension (age 46.3 years, BP 124/78 mmHg) [29]. As subjects with and without a family

history of hypertension were closely matched for blood pressure, it was necessary to recruit slightly older subjects in the control group (39.3 ± 2.8 vs. 46.3 ± 2.1 years, p = 0.052 by ANOVA). Consistent with findings in other studies, subjects with a family history of hypertension, had higher blood pressures (albeit in the normal range) as compared to age- and weight-matched individuals with no family history of hypertension. We found a significantly lower (15 %) mean functional capillary density in normotensive offspring of hypertensive parents compared to offspring with no family history of hypertension (67 ± 2 vs. 79 ± 4 per 0.68 mm^2 respectively) (p = 0.008 by ANOVA). After 2 min of venous congestion, maximal (structural) capillary density was also significantly lower (20 %) in offspring of hypertensive parents compared to offspring with no family history of hypertension (74 ± 2 vs. 93 ± 4 per 0.68 mm^2 respectively) (p = 0.0005, ANOVA).

It was concluded that normotensive individuals with history of essential hypertension in one or both parents have significant rarefaction of their skin capillaries [29]. As essential hypertension is, at least in part, an inherited condition, these results indicate that capillary rarefaction occur early in essential hypertension and would appear to be independent of the blood pressure readings i.e. a primary structural abnormality. This implies that capillary rarefaction in this setting does not represent a secondary disappearance of blood vessels, but reflects a decreased angiogenic capacity of the microcirculation of individuals predisposed to develop hypertension. This reduction in vascular growth may affect different organs and be expressed in divergent ways in distinct phenotypes of the cardiovascular risk syndrome. However, it is widely believed that capillary rarefaction in essential hypertension is not limited to the skin but represents a more generalized abnormality that affects different vascular beds.

Rarefaction of Capillaries in Patients with Microvascular Angina

Arterial hypertension is known to affect the coronary circulation through several mechanisms including coronary artery disease, left ventricular hypertrophy, and microvascular disease. Experimental and clinical data indicate that coronary microvascular disease exists in patients with essential hypertension in whom it can cause both a reduction of coronary flow reserve and a shift to the right of the coronary flow autoregulation curve [30]. Patients with anginal chest pain, positive exercise stress test and normal coronary arteriograms i.e. microvascular angina represent approximately 20–30 % of patients undergoing diagnostic coronary angiograms. Previous studies have suggested that patients with microvascular angina may not only have abnormalities of the coronary microvasculature, but also a more generalized systemic vascular involvement. These patients were found to have a significantly higher minimal forearm vascular resistance than normal controls indicating impaired vasodilator capacity [31]. Of particular interest is the observation that the magnitude of the vasodilator impairment of the peripheral bed correlated closely with that of the coronary bed indicating a relationship between the central and peripheral vascular abnormalities [31, 32].

We studied 49 patients with microvascular angina; 22 of these patients had treated essential hypertension (mean sitting blood pressure 138/80 mmHg) and 27 patients were normotensive (Syndrome X) (mean BP 125/73 mmHg). We also studied 29 age- and weight-matched normotensive controls (mean BP 122/75 mmHg) and 21 asymptomatic patients with essential hypertension who had not received any previous treatment for their hypertension (mean BP 156/97 mmHg) [33]. We used intravital video-microscopy to examine the skin of the dorsum of the middle finger of the non-dominant hand before and after maximization of perfused capillaries with venous congestion. Functional capillary density was significantly lower (17 %) in patients with asymptomatic essential hypertension than in normotensive healthy controls (54 ± 2 vs. 65 ± 2 capillaries per 0.56 mm^2 respectively, p = 0.001). After maximization with venous congestion structural capillary density was also significantly lower (62 ± 2 vs. 75 ± 3 capillaries per field, p = 0.0005). Patients with microvascular angina and hypertension had also a significantly lower capillary density than healthy controls both at baseline (51 ± 2 per field; p = 0.0001) and after maximization (57 ± 3 per field; p < 0.0001). Normotensive patients with microvascular angina (Syndrome X) had also a lower mean functional capillary density (52 ± 2 per field; p = 0.0001) and a lower structural capillary density (59 ± 2 per field; p = 0.0001) than healthy controls. There were no statistically significant differences between subjects with microvascular angina and asymptomatic patients with hypertension.

It was concluded that treated hypertensive patients with microvascular angina have significantly lower skin capillary density than matched healthy volunteers, both at baseline and after maximization with venous congestion. The pathophysiological importance of capillary rarefaction in patients with microvascular angina remains unknown. Capillary rarefaction cannot per se entirely explain the mechanism of chest pain in hypertensive patients with microvascular angina as these patients had a similar reduction in skin capillary density compared to asymptomatic hypertensive patients. It is intriguing that for a similar degree of capillary rarefaction, some hypertensive patients have chest pain whilst others do not. Nevertheless, structural rarefaction of capillaries in these patients suggests a generalized microvascular abnormality that may play a role in the pathogenesis of this syndrome. It has been recently suggested that patients

with microvascular angina may have insulin resistance [34]. Insulin resistance has been observed also in patients with essential hypertension, patients with diabetes mellitus and in obese individuals [35]. Reduction in microvascular density has been suggested to be a possible pathogenic link between these entities. In this study, patients with microvascular angina and successfully treated hypertension, had a level of capillary density similar to that of untreated asymptomatic hypertensives and significantly lower than that of healthy volunteers. This suggests that capillary rarefaction in hypertensive patients may not necessarily be improved or corrected by normalization of the blood pressure. Secondly, capillary rarefaction cannot per se entirely explain the mechanism of chest pain in hypertensive patients with microvascular angina as they had a similar reduction in skin capillary density as the asymptomatic hypertensive patients. This raises the question why for the same degree of capillary rarefaction patients with microvascular angina and hypertension have chest pain while patients with asymptomatic hypertension do not. One explanation may be that they have abnormal pain perception. Alternatively, it could be speculated that hypertensive patients with microvascular angina may have more microvascular rarefaction in their myocardium than at other sites. New therapeutic approaches for patients with microvascular angina targeting capillary angiogenesis and improving capillary reserve warrant future investigation.

Conclusions

The importance of microvascular rarefaction in the pathogenesis of essential hypertension raises the interesting question as to whether the induction of microvascular growth represents a future therapeutic option. Therapeutic angiogenesis is now intensively explored as a target for the treatment of ischaemia-related diseases [36]. In particular, myocardial ischaemia and peripheral ischaemia are two areas where angiogenic growth peptides are utilized experimentally. The use of such forms of therapy in both hypertension and microvascular angina represents a major challenge in view of the generalized nature of microvascular rarefaction. It would be of interest to investigate more classic antihypertensive drug treatment from the point of view of their effects on microvascular growth.

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Hypertrophic Cardiomyopathy

12

Vimal Patel and Perry Elliott

Abstract

Hypertrophic cardiomyopathy (HCM) is an inherited disorder of myocardial sarcomeric protein characterised by the presence of myocardial hypertrophy in the absence of any identifiable cardiac or systemic cause. Several sources suggest that myocardial ischaemia in the absence of obstructive coronary artery disease, plays an important role in the pathophysiology and natural history of HCM. Autopsy series have commonly shown left ventricular (LV) fibrosis and transmural scarring. Histological examination of these areas has revealed narrowed, small intramural coronary arteries that may be responsible for reduced coronary flow. Other mechanisms leading to ischaemia include systolic compression of epicardial arteries and an inadequate capillary density relative to muscle mass. Metabolic studies have shown abnormalities of lactate metabolism and coronary sinus pH consistent with the presence of myocardial ischaemia. Imaging studies with thallium-201 and position emission tomography (PET) have shown both reversible and fixed exercise-induced defects in myocardial perfusion. Although the presence of ischaemia is recognised and its pathophysiological importance assumed, the clinical and prognostic significance of ischaemia in individual patients with HCM is not yet known. Ischaemia may influence LV systolic function, ventricular relaxation, induce chest pain and be an important modulator of the arrhythmogenic substrate. There are also a minority of patients with HCM whose symptoms coincide with the development of systolic failure, progressive LV dilatation and wall thinning, and irreversible perfusion defects and diminished coronary flow reserve (CFR) have been demonstrated in this group.

The clinical evaluation of ischaemia in patients with HCM by conventional methods remains problematic. Technical difficulties with conventional techniques of assessing ischaemia are compounded by difficulty in interpreting the data obtained in relation to clinical findings. The presence of baseline electrocardiographic abnormalities in many patients complicates the interpretation of ST segment changes at rest and during exercise. ST segment depression during exercise also correlates poorly with symptoms, thallium-201 perfusion abnormalities and metabolic markers of ischaemia. Reversible defects on thallium-201 perfusion imaging correlate poorly with symptoms. Thallium imaging is further complicated by partial volume effects in the presence of asymmetric septal hypertrophy and a lack of data on the kinetics of thallium in hearts affected by HCM. PET has shown diminished

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CFR and hypoperfusion of the subendocardium in patients with HCM, but expense and the availability of this modality precludes its use to most physicians.

Keywords
Hypertrophic cardiomyopathy • Microvascular dysfunction • Ischaemia

Introduction

Hypertrophic cardiomyopathy (HCM) is the commonest inherited heart muscle disorder with a prevalence of approximately 1 in 500 adults [1]. It is defined clinically by the presence of left ventricular hypertrophy (LVH) in the absence of abnormal loading conditions [2–4]. In the majority of patients, HCM is inherited as an autosomal dominant trait, caused by mutations in genes that encode sarcomeric proteins [3]. Individuals with HCM can remain asymptomatic throughout their lives but many experience chest pain, symptoms of heart failure, syncope and sudden ventricular arrhythmias.

Chest pain in the absence of coronary artery disease is a common symptom in HCM. Although individuals may complain of atypical chest pain occurring at rest, exertion induced chest pain is a feature in as many as 50 % of individuals with HCM [5]. The aetiology of chest pain in HCM is complex and is likely to relate to myocardial ischaemia being precipitated by a combination of haemodynamic stress, increased metabolic demands and morphological abnormal blood vessels (Fig. 12.1).

Evidence Supporting Myocardial Ischaemia in HCM

Histology

Myocyte replacement and interstitial expansion with collagenous material results in myocardial fibrosis. The development

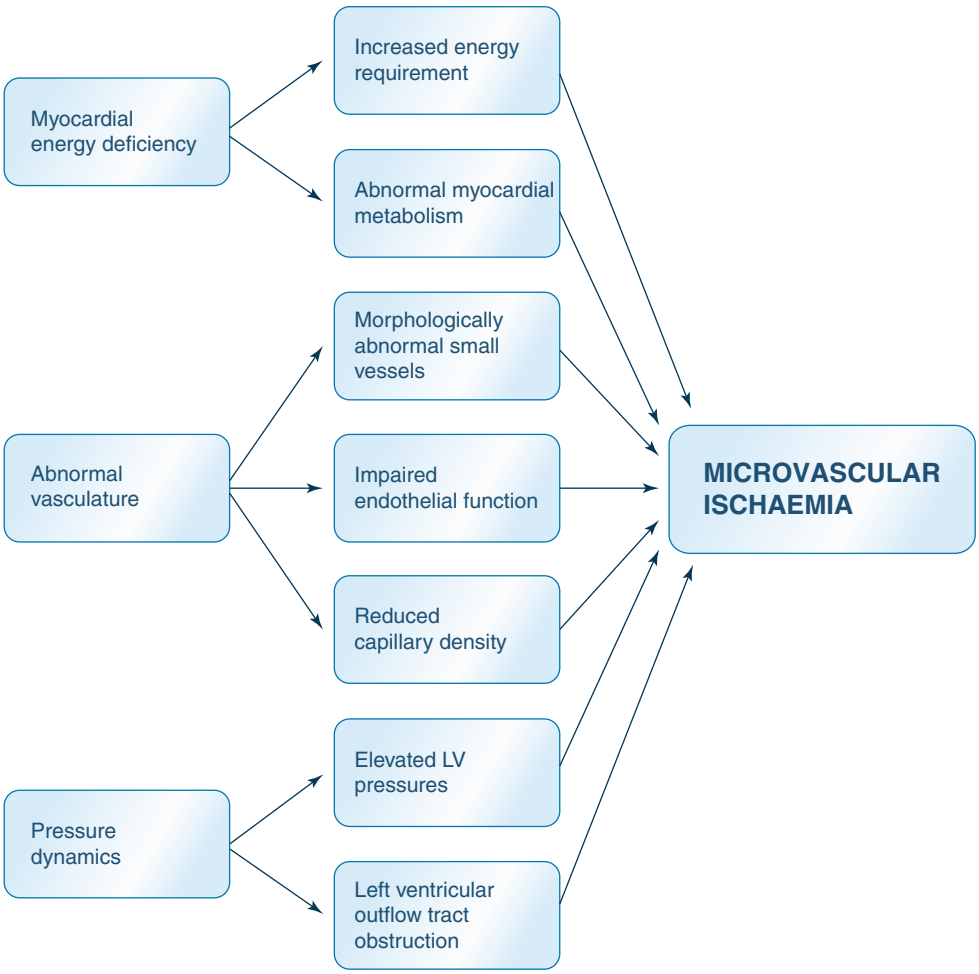

Fig. 12.1 Mechanisms contributing to microvascular ischaemia

of myocardial fibrosis in HCM is multifactorial and may precede phenotypic expression [6]. Genetic predisposition, abnormal molecular signalling and energy deficiency are intrinsic and fundamental drivers in fibrosis. However it is reasonable to presume that other factors including environment, haemodynamic stress and myocardial ischaemia are modifying factors.

Areas of coagulative necrosis, neutrophilic infiltrate, myocytolisis and granulation tissue healing consistent with subacute ischaemic injury as well as extensive chronic scar type replacement fibrosis, provided initial histological evidence to support the presence of ischaemia in HCM [7–9]. It has further been demonstrated that the distribution of the myocardial fibrosis is not uniform, and there is an increased in distribution towards the subendocardium [8, 10].

Coronary Sinus Sampling

Although the term ischaemia was first proposed by Virchow in 1858 [11]. There continues to confusion on the precise meaning of the term but common to all definitions is the phenomenon of inadequate oxygen delivery arising as a consequence of an absolute or relative reduction in myocardial blood flow (MBF). This in turn has biochemical consequences that impair energy homeostasis within myocardial cells and disrupt normal myocardial electrical-mechanical function. Until quite recently, the only practical way of detecting biochemical evidence of myocardial ischaemia was to measure coronary arteriovenous concentrations of a number of substances that reflect the state of myocardial metabolism. Of these, the most widely used method has been the assessment of myocardial lactate and pyruvate extraction of lactate and pyruvate. This technique is, however, subject to considerable sampling error, particularly when the myocardial substrate arterio-venous difference is small (i.e. approaches the limits of sensitivity of most methods for lactate determination). Absolute rates of lactate uptake or release can be determined using radio-labelled substrate, but this is expensive and difficult to perform. Several alternative methods have been employed including determination of oxygen extraction and measurement of coronary sinus pH using a hydrogen ion selective electrode.

Studies in patients with HCM have shown that a proportion of patients with HCM produce lactate under a variety of stress conditions [12, 13]. Several papers have reported reduced lactate consumption in patients with HCM in association with ST segment depression, reductions in coronary sinus blood flow and elevated left ventricular end-diastolic pressure (LVEDP). One of the most detailed early studies evaluating myocardial substrate extraction, coronary sinus flow and left ventricular (LV) haemodynamics in 13 patients with HCM identified that several had reduced cardiac efficiency in spite of normal oxidative metabolism at rest [12]. The findings of this study suggest that myocardial ischaemia might be caused by impaired utilisation of energy rather than reduced production. Five patients had progressive reductions in myocardial lactate and pyruvate extraction during pacing and although no single factor predicted which patients became ischaemic on pacing, each of the five had at least one of high resting myocardial oxygen consumption, low efficiency, and failure of coronary sinus flow to increase. The authors concluded that myocardial ischaemia in HCM is the consequence of either high myocardial oxygen demand disproportionate to the external work, or the inability of coronary flow to increase appropriately with heart rate.

In another study, dipyridamole stress generated a change in coronary sinus pH that was significantly greater in individuals with HCM compared to controls. In more than half the subjects with HCM, the development of chest pain was associated with a decline in coronary sinus pH [14]. This study provides direct in vivo confirmation of inducible myocardial ischaemia in individuals with HCM.

Electrocardiographic Evidence of Ischaemia

Individuals with HCM frequently have markedly abnormal resting electrocardiograms (ECG) with features that would usually be synonymous with myocardial ischaemia in the context of epicardial coronary artery disease. These changes include ST segment deviation and T wave abnormalities as well as pathological Q waves. Dynamic ST segment changes are also frequently observed during exercise testing and ambulatory monitoring. There is some evidence to suggest that a reduction in the amplitude of septal Q waves during exercise is a sensitive, although non-specific marker for regional septal or more global subendocardial ischaemia in those with asymmetrical septal distribution of hypertrophy [15]. The septal Q wave response during exercise has been shown to be a reliable indicator of coronary artery disease and may reflect abnormal septal activation, reflecting the loss of contraction associated with ischaemia [16]. However, so called “ischaemic” ST segment ECG changes” are unreliable markers of myocardial perfusion in the presence of myocardial hypertrophy and have been shown to correlate poorly with perfusion defects and impaired lactate consumption in response to pacing [17, 18]. This reflects other factors that can cause ST segment depression, most importantly ventricular hypertrophy but also heart rate dependent changes in ST segment depression (which are not necessarily indicative of ischaemia in the presence of resting ECG abnormalities) and exaggerated atrial repolarisation which can influence the ST segment.

Perfusion Imaging

Thallium^{201} scintigraphy is an established technique for the detection of myocardial ischaemia in patients with coronary artery disease, with a high sensitivity and specificity for predicting the presence and severity of atheromatous disease in epicardial vessels. A number of studies have examined thallium^{201} uptake in patients with HCM using a variety of protocols [17, 19–22]. The prevalence of perfusion defects has been reported to range between 10 and 100 % and although perfusion defects are primarily identified in the septum and anterior wall they can be more global [23].

Studies using planar and single-photon emission computed tomography (SPECT) thallium^{201} myocardial perfusion imaging have shown that fixed or partially reversible defects are associated with impairment of LV function, possibly relating to myocardial scar [21]. Although the prevalence of inducible perfusion defects is reported to be higher in symptomatic patients, evidence to support an association between perfusion defects and symptomatic status, including chest pain is limited [17–20]. It has been suggested that this paradox might be explained by a high prevalence of "silent" ischaemia in patients with HCM, but evidence that this is so is scant [17]. An equally plausible theory is that conventional thallium^{201} imaging is unable to reliably resolve differences in transmural MBF that result in subendocardial ischaemia. In this regard, it is of interest that some patients develop apparent stress induced LV dilation, which in fact represents global subendocardial hypoperfusion [17]. In the past, it has been suggested that the sensitivity of thallium^{201} imaging is improved by measuring thallium^{201} washout. However, the considerable overlap in values for total washout in patients with and without chest pain, and the potential influence of other technical and physiological factors on myocardial thallium^{201} clearance, means that the value of this additional analysis in the management of patients with HCM is questionable [24].

Positron emission tomography (PET) is theoretically superior to conventional single photon imaging in that it has better spatial resolution and can be used to quantitate MBF [25]. At rest subjects with HCM have a similar resting MBF compared to normal controls but, in response dipyradamole stress there is a generalised impairment in MBF and CFR compared to controls [26, 27] (Fig. 12.2). The reduction in CFR is not restricted to areas of hypertrophy and is greater in patients with a history of chest pain which is explained predominantly by higher baseline MBF [26]. Consistent with findings from thallium^{201} scintigraphy, pharmacological stress induces a transmural gradient in MBF generated by a reduction in the subendocardial to subepicardial MBF ratio [28].

Cardiac magnetic resonance (CMR) imaging offers better spatial resolution in patients with HCM compared to thallium^{201} scintigraphy and PET. Results of perfusion studies utilising this modality are consistent with those obtained from PET, demonstrating impaired coronary reserve in HCM with preferential reduction in the subendocardium [29] (Fig. 12.3). The utility of CMR provides further value in that contrast enhanced imaging allows in vivo estimation of myocardial fibrosis. There is strong correlation between late gadolinium enhancement (LGE) and *replacement* fibrosis in hearts with HCM analysed following autopsy or cardiac transplantation [30–33]. Several studies have demonstrated an association between myocardial fibrosis, MBF impairment and perfusion defects [29, 34–37].

Plasma Markers of Myocardial Necrosis

Cardiac biomarkers such as troponin are sensitive markers for myocyte injury and used in everyday practice for the diagnosis of acute coronary syndromes. In a cohort of 30 patients with HCM, levels of Troponin T (TnT) were elevated in 50 % of subjects and was sustained in the majority during the follow up period. Fractional shortening was significantly lower and the interventricular septum was significantly thicker in the group with elevated Troponin [38]. In a more recent study involving 162 individuals with HCM, serum Troponin I (TnI) ranged from 0.01 to 0.83 ng/mL (ref. ≤0.03 ng/mL). Levels of TnI were higher in males, individuals with atrial fibrillation and those with LV systolic dysfunction, and were an independent predictor for LV wall thickness and markers of diastolic dysfunction [39]. Transient elevations of serum troponin have also been demonstrated post exercise peaking at 6–9 h [40]. Although it would tempting to assume that elevations in cardiac troponin in HCM are secondary to myocardial ischaemia, it is essential to consider alternative mechanisms that may contribute to the systemic leakage of troponin including increased wall stress.

Mechanisms of Myocardial Ischaemia

Morphologically Abnormal Small Blood Vessels

At necropsy 83 % of individuals with HCM who experienced sudden cardiac death have morphologically distinct intramural coronary arteries characterised by a thickened vascular wall and decreased luminal area [41]. The vascular wall is characterised by expansion of the intimal and medial compartment secondary to proliferation of smooth muscle cells and the collagen network [41, 42]. These vascular changes are not specific to HCM but are 20 times more prevalent in HCM than in normal controls and their prevalence is similar

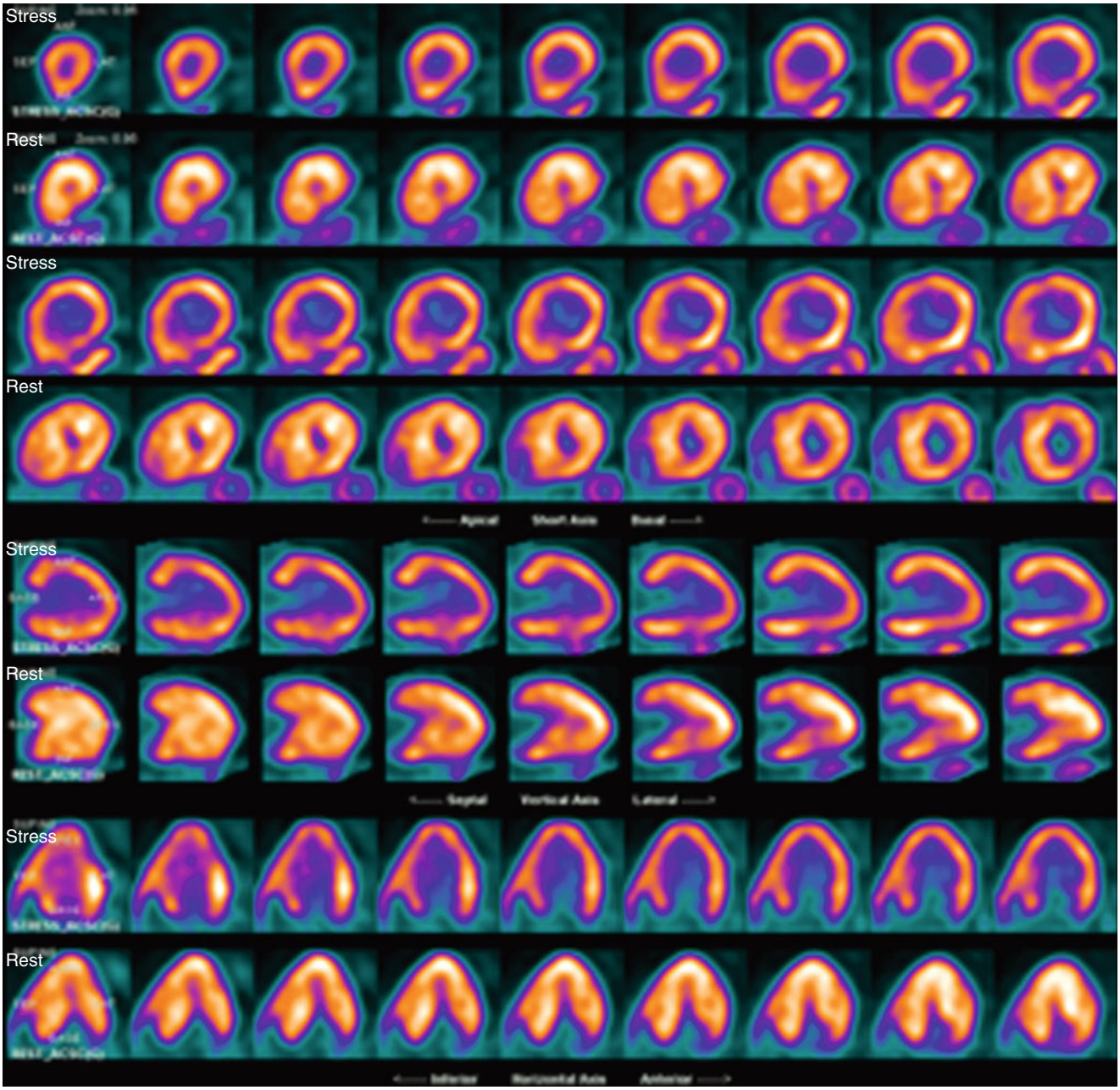

Fig. 12.2 PET imaging following dipyradamole stress in a patient with HCM demonstrating global subendocardial perfusion defect (Courtesy of Institute of Nuclear Medicine, University College London)

in those with or without a history of chest pain [41]. Abnormal small vessels are significantly more common in areas of extensive fibrosis and the extent of replacement fibrosis has been shown to correlate with small vessel disease [7, 41]. The extent of intraluminal narrowing normalised for total vascular area (%lumen) or wall area is lower in individuals with HCM and has been shown to correlate to coronary resistance reserve [43, 44]. The %lumen was shown to be 13 % lower in the subendocardium of individuals with HCM compared to normal controls and correlated with coronary vasodilatory reserve [45].

Endothelial Dysfunction

Myocardial ischaemia in response to pharmacological stress using adenosine and dipyridamole provide some evidence that endothelium independent coronary vasodilation is impaired in HCM. The role of endothelium dependent pathways in HCM in mircovascular dysfunction is less clear. Several studies demonstrate an abnormal vasoconstrictor effect to the cold pressor test in asymptomatic and symptomatic individuals with HCM [46, 47]. However, it has been shown that changes in coronary diameter and coronary blood

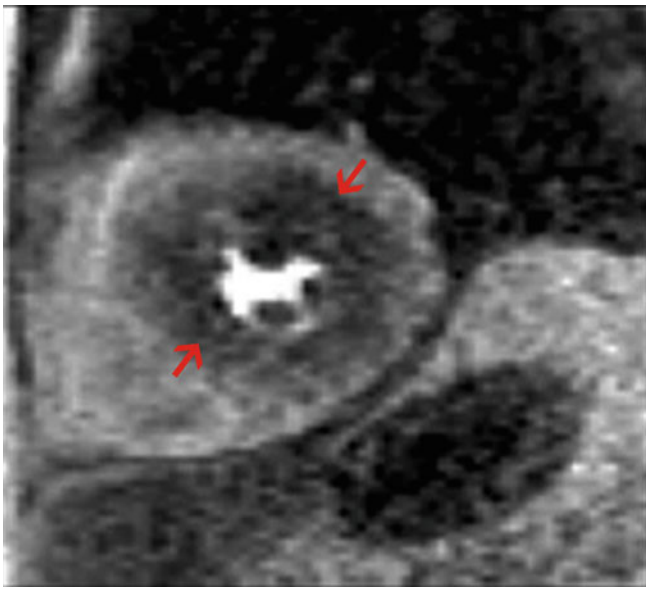

Fig. 12.3 CMR imaging following stress in a patient with HCM demonstrating subendocardial perfusion defects (*Arrows*) (Courtesy of Heart Hospital Imaging Centre)

flow do not differ significantly between the HCM and control groups in response to Bradykinin, an endothelial dependent coronary vasodilator [48].

Vascular Density

Subendocardial arteriolar density in HCM patients with a history of chest pain is reduced by 38 % compared to control values, correlates negatively with myocyte size and positively with coronary reserve [45]. Quantitative analysis of myocardial tissue obtained following surgical myomectomy from patients with obstructive HCM demonstrates that the number of capillaries per cardiomyocyte and overall capillary density are lower in individuals with HCM compared to controls [49]. There is a negative correlation between the degree of hypertrophy and both coronary resistance reserve and capillary density [44]. Together, the data suggest that perfusion abnormalities and the impairment of CFR seen in HCM reflect impaired compensatory vascular growth and a reduction in capillary density.

LV Haemodynamics

Diastolic dysfunction and LV outflow tract obstruction (LVOTO) are common features of HCM. The contribution of these factors to myocardial ischaemia remains uncertain but there is evidence that in obstructive HCM, hyperaemic MBF and CFR with a negative correlation to LVEDP [50, 51]. Hyperaemic transmural MBF ratio also negatively correlates with LVEDP and there is evidence that rapid cardiac pacing causes a substantial rise in LVEDP which is associated with a reduction of coronary flow and impaired cardiac lactate consumption [13, 50]. These findings suggest that LV filling pressure is a likely causative factor for the development of myocardial ischaemia, particularly in the subendocardium.

Myocardial Bridging

Myocardial bridging results from systolic compression of a coronary artery that runs an intramyocardial course and is more prevalent in HCM compared to other disorders [52]. Histological evaluation of HCM hearts with bridging have demonstrated the presence of scar in the perfusion territory of the bridged vessel suggesting that bridging can generate myocardial ischaemia [52]. Myocardial bridging in children with HCM has been associated with increased incidence of chest pain, impaired exercise tolerance, ST segment changes on ECG, increased magnitude of hypertrophy and increased risk of cardiac arrest or SCD [53, 54]. These findings have not been replicated in adults in whom there appears to be no association between bridging and long term outcome including sudden death [55].

Myocardial Energy Deficiency

The myocardium depends on oxygen for high-energy phosphate production by oxidative phosphorylation. In the normal heart, adenosine triphosphate (ATP) is produced primarily by the metabolism of free fatty acids (FFAs) and carbohydrates, with FFAs accounting for approximately 70 % of ATP production. When oxygen delivery to the myocardium is insufficient to meet the requirements of mitochondrial respiration, high-energy phosphate production falls and lactate, the end product of anaerobic glycolysis, accumulates. Animal and human studies suggest that HCM is characterised by a reduction in the concentration of high-energy phosphates in the myocardium [56]. One possible explanation is myocardial ischaemia caused by microvascular dysfunction, known to be present in many patients with HCM. An alternative hypothesis is that it is the direct consequence of sarcomere protein gene mutations on myocardial contractile efficiency [57].

Clinical Significance of Myocardial Ischaemia in HCM

Although the exact mechanism remains unclear, there is considerable evidence that myocardial ischaemia is an important aspect of the pathophysiology of HCM and a major

contributor to symptoms. However, the lack of reliable tools for noninvasive assessment of myocardial ischaemia in HCM is a substantial barrier to the determination of its significance in the natural history of the disease. Nevertheless, there are some data to at least support the hypothesis that that myocardial ischaemia influences outcomes. For example, histological studies have demonstrated that abnormal small vessels and areas of fibrosis are present from an early age in those experiencing premature death [7, 42, 58]. Furthermore, exertional angina is a feature in 48 % of individuals who experience sudden or heart failure related deaths [5].

In vivo assessment of myocardial ischaemia has provided further insight. A cohort study spanning 8 years determined the relation between coronary vasodilatory reserve with adverse LV remodelling. Although the prevalence of heart failure and death were low, individuals reaching this end point were in the lowest tertile of hyperaemic MBF. The relative hazard ratio following multivariate analysis for the development of systolic dysfunction was 7.5 in the lowest tertile [59]. Severe impairment of MBF following dipyridamole stress was associated with a relative risk of 9.6 from suffering a cardiovascular cause of death [27]. There are, of course, several limitations to these data, but they do provide some evidence that abnormal microcirculatory function is a component of disease progression.

Management of Microvascular Ischaemia

Pharmacological therapy in patients with HCM is usually administered on an empirical basis guided by subjective reporting of symptomatic improvement. In patients with symptomatic LVOTO, the main aim of treatment is gradient reduction by pharmacological, surgical or other means. Therapeutic options in patients without LVOTO are more limited, but drug therapy may improve chest pain and to a lesser extent dyspnoea.

Beta blockers and verapamil are currently recommended for the management of symptomatic individuals with HCM. Both drugs can lessen LVOTO, improve diastolic function and reduce myocardial oxygen demands. There are few studies that have examined the effect of either drug on myocardial perfusion and ischaemia, but those data that are available suggest that Verapamil may improve MBF.

In a study of asymptomatic or mildly symptomatic individuals with HCM, treatment with Verapamil for an average of 6.7 days resulted in a complete resolution of reversible thallium^{201} perfusion defects in 8 of 14 patients, with a partial resolution in another 2 [60]. Verapamil also reduces exercise induced subendocardial ischaemia, quantified using SPECT thallium^{201} perfusion imaging [61]. Studies utilising PET however have failed to demonstrate an improvement in resting MBF, hyperaemic MBF or CFR following treatment with Verapamil compared to baseline values and placebo treatment [28, 62]. Verapamil has also been shown to improve endothelium dependent function of the small arterioles in HCM, abolishing the abnormal vasoconstrictor effect to the cold pressor test [46, 47].

Patients with symptomatic obstruction may benefit from septal reduction therapy with alcohol septal ablation (ASA) or surgical myomectomy. Septal reduction has been shown to improve or eliminate reversible and even fixed thallium^{201} perfusion defects [63]. Other studies have demonstrated an increase in hyperaemic MBF, CFR and the hyperaemic transmural MBF ratio following septal reduction [64–66]. The reduction in LVOTO following septal reduction has also been associated with increased anginal threshold and a reduction in lactate production in some individuals [67]. The observed benefits following gradient reduction may relate to reduced myocardial oxygen requirements, increased systolic coronary flow and by a reduction in LV systolic and end diastolic pressure [66, 67].

Future Directions

Conventional treatment of myocardial ischaemia in patients with HCM aims to lower oxygen demand by decreasing heart rate and arterial blood pressure. An alternative approach to improving oxygen-demand imbalance is to stimulate glucose metabolism and reduce fatty acid oxidation.

In 1914, Budingen first suggested the metabolic approach to the treatment of angina, and gave intravenous glucose to eight patients [68]. As fatty acid oxidation strongly inhibits glucose and lactate oxidation, it follows that inhibition of fatty acid oxidation will increase the oxidation of glucose and lactate by the heart. Fatty acid oxidation is regulated by the concentration of free fatty acids in plasma, the activity of carnitine palmitoyl transferase-I (CPT-I), a mitochondrial enzyme that involved in the transport of long-chain acyl-CoA compounds into the mitochondria, and the activity of enzymes that catalyze fatty acid β-oxidation in the mitochondria. Drugs that inhibit cardiac fatty acid oxidation act in one of three ways: suppression of fatty acid release from adipocytes; inhibition of CPT-I and fatty acid uptake into the mitochondria; and direct inhibition of fatty acid β-oxidation. The last two are pertinent to a myocardial disease such as HCM.

A number of drugs inhibit CPT-I including perhexiline, etoxomir, and oxfenicine. Of these, perhexiline is the best studied in man. Perhexiline is an effective anti-anginal agent and improves ejection fraction, exercise capacity and symptomatic status in patients with heart failure of both ischaemic and non ischaemic aetiology [69]. Recent experience indicates perhexiline is also highly effective in HCM [70]. Compared to placebo, perhexiline therapy was associated

with improved symptom class, quality of life and exercise performance. A sub-study in the same cohort suggested this improvement may be due to improved myocardial energetics, however this inference is limited as measurements of cardiac energy status using ^{31}P cardiac magnetic resonance spectroscopy were made only under resting conditions and other mechanisms including the effect of perhexiline on myocardial substrate utilisation and blood flow were not assessed [70]. We speculate that its main effect appears to be mediated by reducing myocardial oxygen debt, but there may also be some contribution from improved myocardial perfusion due to its direct action on vascular smooth muscle and stimulation of platelet responsiveness to nitric oxide [71, 72]. An important limitation of the drug is its narrow therapeutic index and high individual pharmacokinetic variability, which arises because up to 10 % people carry a genetic polymorphism in the liver enzyme microsomal CYP2D6 resulting in slow drug hydroxylation. Excessive plasma levels can lead to peripheral neuropathy and hepatotoxicity, although these effects are virtually eliminated with close monitoring of plasma concentrations. As perhexiline is metabolised by CYP2D6, there is also potential for drug interactions (e.g. with SSRIs).

Direct inhibitors of ß-oxidation such as trimetazidine, a reversible competitive inhibitor of 3-ketoacyl-coenzyme A thiolase (3-KAT) also reduces fatty acid oxidation and increase glucose oxidation [73]. Because it operates downstream of CPT-1, trimetazidine is probably a weaker inhibitor of fatty acid oxidation than perhexiline, but in contrast, has a better safety and tolerability profile, has no known drug interactions and does not require plasma level monitoring. In placebo-controlled trials trimetazidine, either as monotherapy or in combination with beta-blockers or calcium channel blockers, has been shown to significantly improve exercise performance in patients with stable angina and ischaemic cardiomyopathy [74, 75]. Trimetazidine also appears to reduce free radical production and prevents accumulation of protons, sodium, and calcium in the myocyte [76]. Trials in HCM are currently underway.

Conclusion

There is strong evidence that myocardial ischaemia is an important component of the complex pathophysiology of HCM. The mechanisms for ischaemia relate to morphological abnormalities of the microvasculature, pathological hypertrophy and complex pressure dynamics. Accurate identification of ischaemia is challenging but dependent a number of imaging modalities can be used to identify impairment in MBF and its consequence, myocardial fibrosis. Therapeutic options in the management of myocardial ischaemia are limited and predominantly focused upon the use of negatively inotropic drugs, but modulation of metabolic pathways offers some exciting possibilities for the future.

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Microvascular Angina in Different Clinical Conditions: Diabetes and the Metabolic Syndrome

13

Isabella Tritto, Cinzia Zuchi, and Giuseppe Ambrosio

Abstract

Metabolic syndrome results in a pro-thrombotic, pro-inflammatory condition that markedly favours the development of diabetes and cardiovascular disease. In patients with metabolic syndrome, many interrelated factors are thought to contribute to the development of vascular alterations; however, insulin resistance is regarded as the most relevant. In fact, in addition to its well-known activity on glucose metabolism, insulin exerts a wide spectrum of non-metabolic actions, including vasodilation, inhibition of platelet aggregation and thrombosis, anti-oxidant and anti-inflammatory effects, which result in anti-atherosclerotic and vascular protective effects. In this setting, clustering of multiple cardiovascular risk factors may reinforce their pro-atherogenic potential. Metabolic syndrome is also accompanied by endothelial dysfunction, and it has become appreciated that microvascular damage is a common finding in these subjects. In diabetic patients, impairment of microcirculation is recognized at the level of all circulatory districts, including coronary microvessels, and it has an important prognostic impact. Diabetes is accompanied by profound changes in energy metabolism, increased oxidative stress, derangement of adipokines synthesis, reduced mobilization and function of endothelial progenitor cells, which may lead to microvascular dysfunction. Features of the insulin resistance syndrome, including altered glucose tolerance, are more frequent in patients with microvascular angina. Taken together, these observations suggest that diabetes, along with each of the various components of the metabolic syndrome, has the capability of profoundly altering coronary microvascular reactivity, thus predisposing to myocardial ischemia even in the absence of coronary artery stenosis. When these alterations combine in the same patient to give rise to full-blown metabolic syndrome, their negative effects on myocardial perfusion are synergistically potentiated. While the pathophysiology of this condition has become to be substantially unravelled, much research is still needed to achieve a tailored therapeutic approach.

Keywords

Microvascular angina • Microcirculation • Diabetes mellitus • Metabolic syndrome • Insulin resistance • Oxidative stress • Obesity

A possible link between microvascular angina (MVA) and insulin resistance and diabetes was first suggested by the observation that after an oral glucose load hyperinsulinemic response was greater in patients with microvascular angina in comparison with healthy subjects matched for age, sex, and body mass [1]; of note, patients with overt diabetes or hypertension were excluded. In these MVA patients, the degree of

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hyperinsulinemia after glucose load was similar to what observed in patients with coronary artery disease [2]. Similarly, during hyperinsulinemic euglycemic clamp, insulin-induced glucose uptake was significantly impaired in MVA patients compared with controls, while insulin-stimulated glucose uptake in the forearm was significantly reduced [3]. These observations suggested a role for increased concentrations of insulin in microvascular dysfunction.

Over the past decade, it has become evident that a growing number of adults in Western countries show multiple alterations of metabolism, which may have a strong pro-atherogenic effect. With a catchy term, this condition is now recognized as the "metabolic syndrome" [1–4]. Metabolic syndrome is specifically defined by the presence of at least three out of five risk factors, namely glucose intolerance, elevated triglycerides, low HDL-cholesterol level, hypertension, and abdominal obesity. This constellation results in a pro-thrombotic, pro-inflammatory condition that markedly favours development of diabetes and cardiovascular disease [5–7]. This condition is currently increasing in prevalence and it is associated with increase in adverse prognosis [8] in proportion to the number of risk factor components [9]. Evidence is also growing that the familial clustering of multiple cardiovascular risk factors may indicate that they may be the result of gene/environment interactions [10].

Metabolic Syndrome and Microvascular Dysfunction: A Pathophysiological Link

In patients with metabolic syndrome, many interrelated factors are thought to contribute to the development of vascular alterations; however, insulin resistance is regarded as the most relevant [1–3]. In fact, in addition to its well known activity on glucose metabolism, insulin exerts a wide spectrum of non-metabolic actions, which include vasodilation, inhibition of platelet aggregation and thrombosis, anti-oxidant and anti-inflammatory effects, which result in anti-atherosclerotic and vascular protective effects [3]. Insulin resistance may thus promote vascular inflammation and contribute to development of atherosclerosis and its complications. In this setting, endothelial dysfunction may also play a major role. Endothelial cell functions are impaired in many disease processes; this condition, termed "endothelial dysfunction" (ED), is characterized by decreased NO bioavailability, and imbalance in the endothelium-derived relaxing and contracting factors [11, 12], and it also implies a condition of pro-thrombotic and pro-inflammatory alteration of the endothelial layers, which favours atherogenesis and plaque complications. Alterations induced by the loss of normal endothelial function result in accumulation at the injured site of inflammatory cells, which in turn contribute to expand and perpetuate the inflammatory process through further release of oxidants, cytokines, proteases, and lipid mediators [13–15]. This conditions is thus viewed as a pre-atherosclerotic state of vascular endothelium, representing a marker of the action of cardiovascular risk factors on the vessel wall [12].

In the setting of metabolic syndrome multiple cardiovascular risk factors may reciprocally interact, and since each of them in its own right is capable of inducing vascular alterations, it easy to see how their clustering may reinforce their pro-atherogenic potential. Plasma lipids affect endothelial function, and there is a well-documented association between atherogenic lipoproteins (including low-density lipoproteins (LDLs), post-prandial chylomicron remnants and fasting triglyceride-rich particles), and endothelium-dependent responses [16]. Conversely, high density lipoproteins (HDLs) seem to modulate endothelial function in a beneficial manner. In hypertension, the structure, function and number of microvessels are altered [17]. Similarly, alterations in the microcirculation can be demonstrated in obese individuals [18]. Dysfunction at the level of both resistance vessels and capillary beds develops progressively along with an increase in adiposity [19–21]. This close association between measures of adiposity and microvascular dysfunction suggests that cross-talk pathways may exist between adipose tissue and the microvasculature. Adipose tissue, and particularly visceral adipose tissue cells, secrete a variety of bioactive substances, called adipokines, such as adiponectin, leptin, resistin, angiotensinogen, and tumor necrosis factor-α (TNF-α). Obesity-related endocrine signalling, together with resistance to vascular vasodilating effects of insulin, may lead to altered microvascular function observed in these subjects [18]. In this regard, obesity is independently predictive of coronary circulatory dysfunction as an early functional stage in the development of CAD, and obesity is associated with endothelial dysfunction of peripheral and coronary circulation [22–24]. As for diabetes, impairment of microcirculation is clearly recognized at the level of all circulatory districts, including coronary microvessels (see below).

Metabolic syndrome is also accompanied by ED [25–29]. Also in this case, insulin resistance and high systolic blood pressure are major determinants of ED [25], and generation of angiotensin II (angII) by adipose tissue might be involved [30, 31]. In addition to its direct effect on vascular smooth muscle cells, AngII may contribute to insulin resistance by decreasing plasma levels of adiponectin, an insulin-sensitizing adipokine [32, 33]; it may further contribute to ED by stimulating generation of oxidants (ROS), and inactivation of NO [11]. ROS, in turn, activate the transcription factor NF-kB, which stimulates the expression of pro-inflammatory and pro-thrombotic genes. It has become appreciated that microvascular damage is a common finding in subjects with the metabolic syndrome and, in particular, may constitute a pathogenetic link between hypertension and insulin resistance [34].

Obesity and Its Metabolic Effects on the Vasculature

With regard to specific biochemical alterations of obesity, recent findings point to some important antiatherosclerotic and antithrombotic effects of leptin through stimulation of endothelium-derived release of nitric oxide [35] that may possibly counteract the adverse effects of increases in body weight on coronary vasomotor function. Conceptually, the beneficial effects of leptin on endothelium-dependent circulatory function could be related in part to the negative regulation of adipose-derived endocannabinoids by increased leptin concentrations in obesity [36]. As endocannabinoids are upregulated in obesity, they stimulate adverse metabolic changes such as hyperlipidemia, hypoadiponectinemia and hyperinsulinemia, all of whom have been shown to promote the development of CAD. Of note, recent investigations indicate the presence of cannabinoid-1 (CB1) receptors on vascular endothelial and smooth muscle and endothelial cells, while CB2 receptors are also found in macrophages and T-lymphocytes within atherosclerotic lesions [36–38]. Increased plasma concentrations of endocannabinoid (anandamide and 2-arachidonoylglycerol) are associated with coronary circulatory dysfunction in obese individuals [39]. This observation might suggest increases in endocannabinoid plasma levels as a novel cardiovascular risk factor in obesity.

Other adipocytokines, such as visfatin or apelin, are also markedly increased in obesity, particularly when this is associated with insulin resistance and hyperinsulinemia [35]. There is some experimental evidence indicating that apelin may stimulate the release of endothelial-derived NO, while also counteracting angiotensin II-induced vasoconstriction. Interestingly, another adipocytokine -which is regarded as an atheroprotective- adiponectin, is paradoxically decreased in obesity. Adiponectin concentrations are inversely correlated with body fat mass and are also decreased in type 2 diabetes and in patients with CAD. Among important antiatherogenic effects of adiponectin are increase in insulin sensitivity, stimulation of endothelial NO production, and inhibition of the expression of cell adhesion molecules such as ICAM-1 and VCAM-1 [35, 40]. These adiponectin-related effects may reflect in part the underlying mechanisms of the anti-thrombotic and anti-atherogenic effects of adiponectin in vivo, which appear to be increasingly lost as adiponectin levels are diminished in obesity. At the same time, reduced ghrelin plasma levels in patients with metabolic syndrome were associated with endothelial dysfunction of the forearm vessels in response to acetylcholine stimulation, which could be restored by intravenous infusion of ghrelin. Taken together, the coordinated role of adipocytokines and endocannabinoids in the modulation of coronary vasomotor tone in overweight, obese and type 2 diabetic patients remains to be defined.

Role of Reactive Oxygen Species

Factors involved in alterations of coronary microvascular function [41], as indexed by coronary flow reserve (CFR) in response to vasodilating stimuli [42] share the ability to induce oxidant generation, which may also play a major role in diabetic microvascular dysfunction. Oxidants may react with nitric oxide and prostanoids: while inactivating these vasodilating mediators, reaction generates new molecules with different biological activities, such as peroxynitrite and isoprostanes [43, 44]. Peroxynitrite is a relatively stable, highly oxidizing species, that can thus oxidize soluble molecules and cellular components distant from its site of formation [43]. Isoprostanes are generated by non-enzymatic oxidation of lipids; some of them, like 8-epi-PGF-2α, are biologically active, and may induce vasoconstriction and platelet aggregation [44]. In addition, oxygen radicals activate the transcription factor NF-kB, and other intracellular pathways, such as protein-kinase C, thus stimulating the expression of pro-inflammatory and pro-thrombotic genes. Finally, reactive oxygen species may induce cell death: high amounts induce necrosis while low concentrations trigger apoptosis [45, 46]. These actions contribute to oxidant-induced endothelial and microvascular dysfunction [11, 12, 47].

Diabetes is accompanied by profound changes in energy metabolism, which include reduction of glucose uptake, glycolysis, carbohydrate oxidation, and switch from glucose oxidation to fatty acid oxidation [48, 49]. These changes are also accompanied by oxidative stress. Hyperglycemia increases glucose oxidation, NADH generation and mitochondrial generation of superoxide [48, 49]. Glucose utilization is diverted from its glycolytic pathway into alternative biochemical pathway: increased advanced glycation endproducts (AGEs) formation, increased hexosamine and polyol flux, and activation of classical isoforms of protein-kinase C [48, 49]. AGEs binding to their receptor on vascular cells generates ROS, probably via NADPH-oxidase activation. The increase in polyol flux is also accompanied by increased superoxide production by NADPH oxidase and mitochondria; in addition, increased glucose utilization through this pathway consumes NADPH, with subsequent impaired regeneration of reduced glutathione, and reduced activity of NO synthase, which also contribute to oxidative stress [48, 49].

Finally, plasma levels of free fatty acids (FFA) are elevated in diabetic patients. Excess FFAs enter the citric acid cycle and generate acetyl-CoA to produce excess NADH, which again increases mitochondrial superoxide production [48, 49]. Acute infusion of FFAs induces elevations in isoprostane concentrations, a marker of oxidative stress [48, 49], and impairs endothelium dependent vasodilation [50]. These data suggest that FFA modulate microvascular function, and that oxidant generation might be involved in this process.

Derangement of adipokines synthesis, particularly leptin, has been proposed to also play a role in oxidant generation that accompanies diabetes. Leptin is an adipokine that decreases food intake, and it may also modify the function of various cell types of the vessel wall, such as endothelial cells and vascular smooth muscle cells [48]. Endothelial cells incubated with leptin produce increased levels of reactive oxygen species [48].

Role of the Renin Angiotensin II System

The effects of angiotensin II (AngII) extend beyond its action on the vasculature, and several studies have demonstrated that an activated renin–angiotensin system (RAS) is implicated in the development of insulin resistance and type 2 diabetes [27–29]. AngII is known to activate NADPH oxidase in endothelial cells, with subsequent generation of reactive oxygen species (ROS), inactivation of nitric oxide, and vasoconstriction [11]. Obesity is associated with upregulation of Ang-II type 1 receptors [51], which mediates upregulation of proinflammatory and profibrotic pathways [52]. Interleukin-6, a pro-inflammatory cytokine, induces oxidative stress and endothelial dysfunction via overexpression of ang-II type 1 receptors [53].

Administration of AngII receptor blockers to patients with metabolic syndrome reduces plasma levels of Interleukin-6 and other inflammatory markers [54]. Elevated free fatty acid levels induce endothelial dysfunction in human forearm via RAS activation [55]. Ang-II may also influence adipokine levels. In rats, Ang-II infusion decreases plasma levels of the insulin-sensitizing adipokine adiponectin via activation of type 1 receptors and oxidative stress [32, 33]; in patients with essential hypertension and insulin resistance, RAS blockade with either an ACE inhibitor or an AT1 antagonist increased adiponectin secretion [56]. Taken together, evidence indicates that AngII generation largely contributes to oxygen radical generation and endothelial dysfunction.

Synergistic Effects of Multiple Factors

Because of the frequent association between diabetes, hypertension, and dyslipidemia in patients with metabolic syndrome it is important to consider their combined effect. Microvascular dysfunction contributes to both increased blood pressure and impaired organ perfusion. This decrease in blood flow leads in turn to impaired glucose uptake in muscle, contributing to increased insulin resistance and finally to diabetes [34]. In patients with both diabetes and hypertension, endothelial dysfunction and alterations in the vascular structure and function of microvessels may be found. Myocardial blood flow measured with positron emission tomography in various stages of insulin resistance (impaired glucose tolerance, normotensive and hypertensive type 2 diabetes) showed a progressive reduction of myocardial flow and of endothelium-dependent coronary vasomotion with worsening of insulin resistance in comparison with insulin-sensitive individuals [57]. Structural alterations of small arteries are present in both hypertensive and normotensive patients with NIDDM [58, 59], but these alterations are more pronounced in hypertensive patients with NIDDM than in patients with essential hypertension or normotensive diabetics [58]. Finally, in hypertensive patients free of coronary artery disease, the degree of impairment in coronary vasodilator capacity is independently associated with plasma cholesterol and LDL-cholesterol [60].

Metabolic Syndrome and Microvascular Dysfunction: Clinical Evidence

Features of the insulin resistance syndrome have been described in patients with microvascular angina more frequently than age- and gender-matched asymptomatic, healthy controls. Non-obese male patients had lower insulin sensitivity and higher insulin concentration, higher mean triglycerides, lower mean high density lipoprotein cholesterol concentration, higher systolic blood pressure [61]. Nondiabetic female patients also showed more frequently metabolic syndrome and related adiposity, as well as metabolic and inflammatory alterations, as indicated by higher levels of insulin and triglycerides, lower levels of HDL-cholesterol, increased plasma levels of von Willebrand factor and leptin [62]. Consistent with these data, 30 % of patients but only 8 % of controls fulfilled criteria for the metabolic syndrome as defined by the National Cholesterol Education Program [62]. Recently, angina in the absence of manifest atherosclerosis has been associated with clinical, inflammatory, and vascular factors that reflect endothelial dysfunction and vascular stiffness among the 1,480 women from the Dallas Heart Study [63]. Angina was not associated with coronary artery calcium deposition, but it was related to variables reflecting obesity and insulin resistance and was independently associated with African-American ethnicity, premature family history of myocardial infarction, and waist circumference. Such women with angina also had higher levels of soluble intercellular adhesion molecule-1 and vascular cell adhesion molecule-1 [63]. These data lend further support to the hypothesis that the insulin resistance syndrome might predispose to a spectrum of arterial disease capable of causing myocardial ischemia.

In addition, as a possible link between cardiac and metabolic syndrome X, enhanced activity of the sodium-lithium

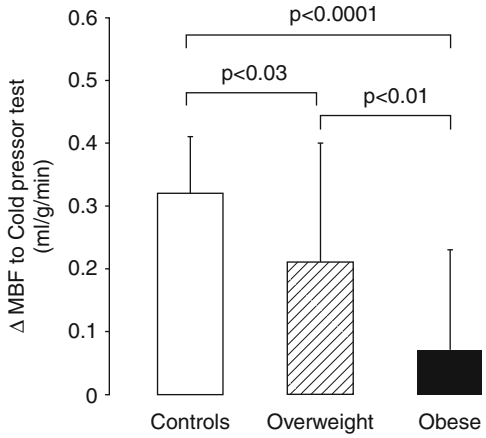

Fig. 13.1 Progressive worsening of coronary endothelium-dependent vasodilation with increasing body weight. *Graph* shows significant differences in myocardial blood flow (Δ *MBF*) during cold pressor testing (*CPT*) among normal overweight and obese subjects (Reprinted from Schindler et al. [24] with permission from Elsevier)

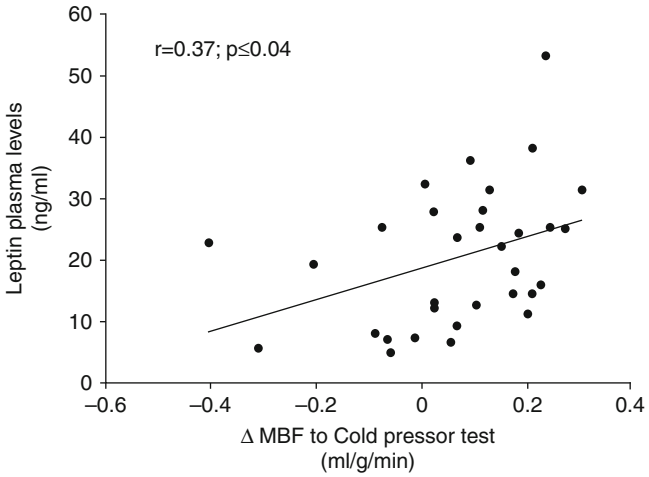

Fig. 13.2 In obese subjects, leptin plasma levels were correlated with changes in myocardial blood flow (Δ *MBF*) during cold pressor testing (*CPT*) (Reprinted from Schindler et al. [24] with permission from Elsevier)

countertransport was proposed, since it has the potential to cause both glucose intolerance and smooth muscle hyperactivity [64]. Taken together, these data suggest that insulin resistance may be a feature of patients with microvascular angina and that its related metabolic and inflammatory derangements and dysregulation may contribute to microvascular dysfunction and myocardial ischemia.

Since obesity is an independent predictor of coronary endothelial dysfunction [23, 24], it may act as a possible alternate mediator of coronary vascular disease rather than as an epiphenomenon related to other traditional coronary risk factors commonly associated with obesity. This is compatible with recent observations that increasing body weight in relatively young healthy individuals without traditional coronary risk factors [24] was paralleled by an increase in plasma markers of the insulin-resistance syndrome and chronic inflammation, and it was independently associated with coronary circulatory dysfunction that progressed from impairment only in endothelium-dependent coronary vasomotion in overweight to impairment of total vasodilatory capacity in morbid obesity (Figs. 13.1 and 13.2). This progressive worsening of the coronary circulatory function is likely to reflect a mechanistic link that confers an increased risk of adverse cardiovascular outcome in obesity [65]. Of particular interest, increased concentrations of the adipocytokine leptin were associated with relatively higher increases in endothelium-related and, thus NO-mediated, coronary flow in response to sympathetic stimulation with CPT [24], which might reflect a beneficial effect of leptin and/or leptin-related factors on the coronary vascular endothelium to counteract the adverse effects of increases in body weight on coronary vasomotor function [24, 57, 66].

In particular, the independent predictive value of obesity for coronary vasomotor dysfunction [23, 24] suggests direct mediators such as adipocytokines and/or endocannabinoids released from the adipose tissue to be involved in the regulation of coronary vasomotor tone and, thus, in the initiation and development of CAD. As already mentioned obesity is associated with alterations in adipocytokine and endocannabinoid concentrations that may affect coronary circulatory function [37]. There is some preliminary evidence of beneficial effects of adiponectin and ghrelin on endothelial function of the coronary and brachial artery, respectively, while it is currently unknown how altered adipocytokines and endocannabinoids concentrations may affect coronary vasomotor (circulatory) function in obesity in humans. In this regard, elevated plasma levels of the adipocytokine leptin were significantly associated with relatively higher endothelium-related MBF increases to cold pressor testing [24] (Fig. 13.2).

When the effects of insulin-resistance on coronary circulatory function were evaluated, progressive worsening of endothelium-dependent vasomotor function was found, which was paralleled by increasing severity of insulin-resistance and carbohydrate intolerance [57]. Conversely, attenuated hyperemic MBF response to pharmacologic vasodilation was accompanied by the more clinically evident metabolic abnormalities in type 2 diabetes [57].

In diabetic patients, impairment of microcirculation is recognized at the level of all circulatory districts, including coronary microvessels. The prognostic impact of microvascular alterations is further supported by the recent observation that, in patients with known or suspected coronary heart disease, and a negative dipyridamole stress echocardiography, a reduced CFR is associated with worse prognosis, both in diabetic patients and in the non diabetic populations [67].

In the absence of overt stenosis of epicardial coronary arteries, a reduction of CFR has been documented in both type 1 and 2 diabetes mellitus by multiple techniques. Several factors have been postulated to be responsible for this CFR alteration. First, blunted CFR can be a direct consequence of elevated glycemia [68, 69]. In fact, in patients with type 2 diabetes hyperemic myocardial flow were on average 27 % lower than in normal volunteers and the degree of impairment was related to the degree of glycemic control [70–72]. Glycemic control was independently related to the CFR, and appears to be essential for coronary microangiopathy in NIDDM [70–72], as also supported by the observation of marked and similar coronary microvascular dysfunction in response to both endothelium-independent and -dependent stimuli in young subjects with uncomplicated diabetes, either of type 1 or type 2 [69]. Given the notion that patients with type 1 diabetes are insulin-deficient while type 2 diabetes are insulin-resistant, this observation brings support to a key role for hyperglycemia in the pathogenesis of vascular dysfunction in diabetes.

As mentioned, another possible component of microvascular dysfunction in diabetic patients is insulin resistance, a feature of patients with type 2 diabetes mellitus or metabolic syndrome. In a non-randomized study, myocardial blood flow responses to dipyridamole were similar in the insulin-sensitive and insulin-resistant groups. However, myocardial blood flow response to cold pressor test was significantly greater in insulin-sensitive than in insulin-resistant patients [73].

Insulin resistance has been proven to alter PET-derived CFR during cold pressure test, an endothelium-dependent stimulus [57]. Endothelial function can also be impaired in early diabetes mellitus [74]. Flow mediated dilation of brachial artery, a reliable indicator of peripheral NO-mediated endothelial function, is significantly altered in patients with either glucose intolerance or overt diabetes, and also in subjects with normal glucose tolerance but with a parental history of type 2 diabetes [75]; micro- and macrovascular reactivities were reduced in these two groups compared with healthy controls but were at a better level than in those with clinically manifest type 2 diabetes [75]. Increased cardiac sympathetic activity, known to occur in diabetic patients, may contribute to abnormal CFR in this clinical setting [76]. Interestingly, this study compared three group of subjects: normal controls, subjects with type 1 diabetes but no evidence of microangiopathy at retinal evaluation, and patients with type 1 diabetes and early subclinical microangiopathy. Despite equivalent glycemic control, diabetic patients with evidence of early microangiopathy demonstrated exaggerated plasma norepinephrine excursions, impaired MBF regulation, and LV diastolic dysfunction. MBF reserve during adenosine stimulation was also reduced [76].

Another factor possibly influencing, or at least predisposing to, the impairment of diabetic CFR is represented by left ventricular diastolic dysfunction and its underlying mechanisms [77]. Left ventricular diastolic dysfunction is evident in type 1 diabetics without coronary artery stenosis when CFR is also impaired [76]. This association is not surprising, since coronary perfusion occurs predominantly during diastole. Even in patients without coronary artery disease, changes in the time constant of left ventricular isovolumic pressure fall (τ) is associated with decreased coronary flow [78]. It has to be pointed out that both reduced CFR and diastolic dysfunction are associated with insulin resistance [57, 79], left ventricular concentric remodeling/hypertrophy [80, 81], with disorders of sympathetic nervous system [76], abnormalities of angiotensin-renin system [82], and endothelial dysfunction [83]. Thus, it can be hypothesized that coronary microvascular damage at the same time may play a mechanistic role for diastolic dysfunction [84], while also being a possible consequence of it. Determinants of microvascular dysfunction in diabetes, such as hyperglycemia and insulin resistance, and factors including sympathetic overdrive, endothelial dysfunction and left ventricular concentric remodelling, may also contribute to the development of left ventricular diastolic dysfunction.

In ex vivo experiments, both the level and the activity of NADPH oxidase were significantly increased in veins and arteries harvested from diabetic patients. In these "diabetic vessels", the endothelium was an additional source of superoxide production because of dysfunctional endothelial NO synthase [85]. Although not obtained in microcirculation, these observations suggest important roles for NADPH oxidases and endothelial nitric oxide synthase uncoupling in mediating increased vascular superoxide production and endothelial dysfunction in patients with diabetes.

A correlation between oxidant stress and microvascular dysfunction has also been observed in subjects with diabetes and microangiopathy [76], in which urinary 8-epi $PGF_{2\text{-}\alpha}$ excretion (an index of oxidative stress) was increased, and plasma antioxidant capacity was decreased, in comparison with patients with diabetes but no evidence of microangiopathy; in addition, elevated CRP and plasma vWF antigen, and impaired MBF reserve, were also present, consistent with endothelial dysfunction [76]. In response to cold pressor test, plasma norepinephrine release was also greater. These findings suggest that augmented spillover of norepinephrine, increased oxidative stress and inflammatory status may contribute to abnormal vascular reactivity in this condition [76].

Other Consequences of Oxidative Stress on the Vessel Wall: Necrosis, Apoptosis, Altered Repair

In ventricular myocardial biopsies obtained from diabetic patients, diabetic status was accompanied by evidence of increased apoptosis and necrosis of endothelial cells, in

which levels of Angiotensin II and nitrotyrosine, an index of peroxynitrite generation, were also increased. Apoptosis and necrosis were detected only in cells containing nitrotyrosine, suggesting a correlation between oxidative stress and apoptosis/necrosis of cardiac cells [46].

Altered oxidant balance has also been involved in the reduced mobilization and function of endothelial progenitor cells (EPCs), which seems to accompany the diabetic condition [86]. EPCs are important regulators of vascular repair, and the number of circulating EPCs correlates with endothelial dysfunction and cardiovascular risk in humans [87] and it is reduced in metabolic syndrome [88] and diabetes [89]. eNOS is a key enzyme in the regulation of mobilization and function of EPCs. In diabetic patients EPC recruitment at sites of vascular injury is also impaired [86]. EPCs from diabetic patients produce excessive superoxide and show impaired migratory capacity compared with nondiabetic subjects [86]. Both alterations are paradoxically attenuated by NOS inhibition, suggesting that in diabetes uncoupling of eNOS, resulting in eNOS-mediated oxidant generation [90], with subsequent reduction of EPC levels and EPC function [86]. Thus, excess oxidative stress might not only induce microvascular inflammation, but it might also reduce the ability of tissue defences to repair vascular injury. Angiotensin II receptor antagonists increase the number of regenerative EPCs in patients with type 2 diabetes [89]. In a prospective double-blind parallel group study, the number of EPCs was significantly lower in diabetic patients as compared with age-matched healthy subjects; but it significantly increased in comparison with placebo treatment after 12 weeks of treatment with olmesartan or irbesartan [89].

Another factor which may contribute to myocardial ischemia in diabetic patients is myocardial insulin resistance: patients with coronary artery disease and heart failure exhibit myocardial insulin resistance, that is greater in those with type 2 diabetes. This may limit the ability of the myocardium in patients with type 2 diabetes to withstand ischemia and may contribute to the occurrence of angina [91].

Compensatory Mechanisms

The diabetic microcirculation also seems to have the ability to compensate for reduced NO generation, via mechanisms that are not entirely elucidated. It has recently been shown that in diabetic patients there is increased COX-2 expression and augmented prostaglandin-mediated bradykinin-induced dilation in coronary arterioles [92]. This mechanism may act to maintain adequate coronary flow. The mechanisms underlying COX-2 upregulation are unknown, but oxidative stress may be involved, since enhanced superoxide production was associated with increased COX-2 expression in high glucose–treated cultured endothelial cells [92]. The compensatory role of COX-2 mediated vasodilation in diabetic patients might also contribute to explain the controversial findings about the safety of use of selective COX-2 inhibitors in patients with high cardiovascular risk. It might be hypothesized that blockade of prostaglandin synthesis in the arteriolar wall may adversely affect coronary vasodilator responses in these patients.

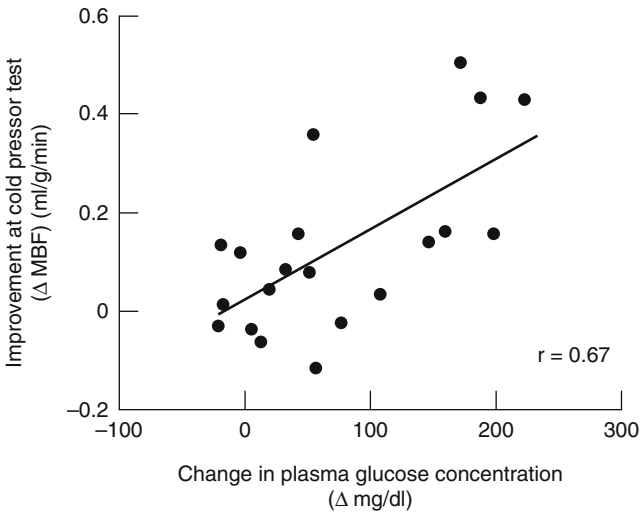

Fig. 13.3 Coronary endothelium-dependent vasodilation increases with improved glycemic control: correlation between decrease in plasma glucose concentrations and improvement in coronary vasomotor function in response to cold pressor testing (*CPT*), expressed as differences (Δ) between baseline and follow up (Reprinted from Schindler et al. [94] with permission from BMJ Publishing Group Ltd)

Possible Effects of Interventions

Improvement of altered coronary vasomotor function in patients with diabetes or alterations of metabolic syndrome has been sought through a variety of interventions, Some of them focused on counteracting "traditional" risk factors for atherosclerosis and endothelial dysfunction, while other interventions explored different strategies.

Results obtained in a small study in patients with impaired glucose tolerance, indicate that angiotensin II type-1 receptor blockade with Valsartan (160 mg daily for 12 weeks uptitrated to 320 mg daily for another 12 weeks) substantially improves coronary circulatory function as assessed by PET [93]. This same group has also reported that, in patients with type 2 diabetes, in whom MFR in response to CPT was significantly impaired, MFR could be significantly improved after treatment with oral glyburide and metformin, suggesting that effective glycemic control might improve coronary vascular function [94] (Fig. 13.3).

In the large randomized ADVANCE trial, antihypertensive therapy with a fixed combination of perindopril and indapamide in patients with type 2 diabetes showed favourable microvascular effects in noncoronary vascular districts, and reduced microalbuminuria and total renal events [95]. Since the same treatment also seems able to improve coronary microvascular dysfunction in hypertensive patients [96], it is tempting to speculate that it could also improve both coronary and noncoronary microvascular function in diabetics. This is suggested by a significant 14 % reduction in the risk of coronary events in patients who received treatment with perindopril and indapamide in the ADVANCE study. In that same trial, more intensive glucose control obtained with glicazide MR reduced glycated haemoglobin to 6.5 %, compared with 7.3 % in the standard control group. After a mean 5-year follow-up, intensive control reduced the incidence of combined major macro- and microvascular events by 10 %, and the incidence of new or worsening nephropathy by 221 % [97]. Similar findings have been reported in UKPDS (United Kingdom Prospective Diabetes Study), which showed that a more intensive hypoglycaemic therapy (resulting in a glycated haemoglobin level of 7 %), versus a less intensive one (resulting in a level of 7.9 %), reduced microvascular end points by 25 % and myocardial infarction by 16 % over the course of a 10 year follow-up [98]. A recent meta-analysis of 6 trials that included 4,472 diabetic subjects has substantially confirmed these results, showing a 19 % reduction of major cerebro-cardiovascular events [99].

Among approaches to reduce risk factors, it should be mentioned that flow mediated dilation can be restored by physical training programs in diabetic patients [100].

As less traditional approach one may consider interventions aimed at reducing oxidant stress. Given the involvement of oxidative stress in the pathogenesis of diabetic microvascular dysfunction, and also endothelial dysfunction, it would seem logical to administer antioxidant therapy to these patients. Initial studies have shown that acute administration of antioxidants may indeed restore endothelial function in diabetic patients; however, chronic administration of vitamin E or C in large clinical trials has failed to demonstrate beneficial effect on cardiovascular events or all-cause mortality, even when only diabetic patients were analyzed [49, 101, 102], and a recent meta-analysis of clinical trials with vitamin E has suggested that the use of high-dose vitamin E may actually be deleterious [103]. The bulk of evidence is actually against chronic antioxidant therapy to reduce cardiovascular mortality in these patients [104].

A possible alternative is represented by drugs currently in use, that also have ancillary antioxidant properties, and which have already demonstrated beneficial effects in large randomized controlled-trials. Certain ACE inhibitors may act as direct antioxidant, and they might also interfere with the pro-oxidant effects of Ang II. Statins have also been shown to exert vascular antioxidant properties [49]. Administration of angiotensin II receptor blockers to patients with metabolic syndrome reduces plasma levels of Interleukin-6 and other inflammatory markers [54]. In patients with essential hypertension and insulin resistance, RAS blockade with either an ACE-inhibitor or an angiotensin II receptor antagonist increased adiponectin secretion [56]. The FFA-induced impairment in the endothelial function was completely prevented by a single dose of either an angiotensin II receptor blockers or an ACE inhibitors, suggesting that an elevation of FFAs induces endothelial dysfunction through activation of the RAS [50]. A recent study in a small number of patients has suggested that the combination of these two type of drugs has additive effects [105]. Finally, thiazolidinediones or glitazones may improve endothelial dysfunction by decreasing oxidative stress via the peroxisome- proliferator-activated receptor γ [49].

While many such interventions have shown a beneficial effect on microvascular function, the lingering question is whether they may also improve symptoms in patients with microvascular angina. Interestingly, benefits on various parameters of exercise tolerance have been obtained in patients with microvascular angina through a substantially different approach, namely trying to influence microcirculation function, either via potentiation of endogenous adenosine (by aminophylline [106, 107]), or secondary to a putative increase in the activity of nitric oxide with ACE-inhibitors [108–111], or statins [112, 113] (see Table 13.1 for details). However, none of these studies went past the “proof-of-concept” stage, with only a handful women treated for a few weeks (see Table 13.1, also, [114–118]).

In conclusion, diabetes, along with each of the various components of the metabolic syndrome, has the capability of profoundly altering coronary microvascular reactivity, thus predisposing to myocardial ischemia even in the absence of coronary artery stenosis. When these alterations combine in the same patient to give rise to full-blown metabolic syndrome, their negative effects on myocardial perfusion are synergistically potentiated. While the pathophysiology of this condition has become to be substantially unravelled, much research is still needed to achieve a tailored therapeutic approach.

Table 13.1 Clinical studies on treatment of microvascular angina

Author	Year	N	W	Drug	Study design	Length	Effects
Elliot [107]	1997	13	11	Aminophylline 350 or 225 mg × 2/day	Randomized, double-blind, cross-over, placebo-controlled	3 weeks	↑ time to angina during exercise stress test
Kaski [109]	1994	10	7	Enalapril 10 mg/day	Randomized, single-blind, cross-over, placebo-controlled	2 weeks	↑ exercise duration and ↓ exercise-induced ischemia
Chen [110]	2002	20	5	Enalapril 20 mg × 2/day	Randomized, double-blind, placebo-controlled	8 weeks	↑ exercise duration, ↑ CFR, ↓ plasma vWF, ↓ ADMA, ↑NOx, ↑ ratio L-arginine/ADMA
Nalbantgil [111]	1998	18	15	Cilazapril 5 mg/day	Randomized, double-blind, cross-over, placebo-controlled	3 weeks	↑ exercise duration and ↓ ST-shift during exercise
Russel [114]	2007	28	25	Irbesartan 150 mg daily to 300 mg daily	Randomized, double-blind, placebo-controlled, two periods cross-over	1 week	No effect on exercise duration and on ischemia episodes at Holter ECG
Pizzi [108]	2004	45	40	Ramipril 10 mg/day and Atorvastatin 40 mg/day	Randomized, placebo-controlled	6 months	↓ SOD levels, ↑ exercise duration and improved SAQ
Fabian [112]	2004	40 C	15	Simvastatin 20 mg/day	Randomized, placebo-controlled	12 weeks	↓ exercise-induced ischemia
Kayikcioglu [113]	2003	40	22	Pravastatin 40 mg/day	Randomized, single-blind, placebo-controlled	3 months	Improvement of FMD, ↑ exercise duration and time to 1 mm-ST depression
Rosano [115]	1996	25 MI	25	17-beta-estradiol cutaneous patches 100 μg/day	Double-blind, placebo-controlled, cross-over	8 weeks	↓ chest pain episodes, no effect on exercise duration
Lerman[116]	1998	26	13	L-arginine 3 g × 3/day	Randomized, double-blind, placebo-controlled	6 months	↓ symptoms, ↑CFR, ↓ endothelin
Botker [117]	1998	16	14	Doxazosin 1–4 mg/day	Double-blind, cross-over, placebo-controlled,	10 weeks	No effect on angina, exercise duration and exercise-induced ischemia
Jadhav [118]	2006	33 ND	33	Metformin 500 mg × 2/day	Randomized, double-blind, placebo-controlled	8 weeks	Improvement in forearm (skin) endothelium dependent microvascular function, maximal ST-segment depression, Duke score and chest pain incidence

Abbreviations: *W* women, *C* Hypercholesterolemia, *MI* previous myocardial infarction, *ND* non diabetic, *CFR* coronary flow reserve, *CBF* coronary blood flow, *FMD* flow mediated dilatation, *SAQ* seattle angina questionnaire

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The Transplanted Heart

14

Giuseppe Vassalli, Augusto Gallino, and Pierre Vogt

Abstract

Transplanted hearts are susceptible to develop a unique form of accelerated coronary artery disease, termed coronary allograft vasculopathy. The disease is the main manifestation of chronic immune rejection and results from repeated inflammatory insults to the graft coronary arteries. Nonimmunological factors including hyperglycemia, dyslipidemia, hypertension, viral infections and drug toxicity play contributory roles. Despite improvements in pharmacological immunosuppression, graft vasculopathy continues to limit the long-term survival of cardiac transplant recipients. The disease affects both large epicardial arteries and small intramyocardial vessels. Microvascular endothelial dysfunction may represent an early yet potentially reversible stage of graft vasculopathy. In a significant proportion of patients, however, it is accompanied by progressive occlusive narrowing of small coronary vessels. As a consequence of cardiac denervation, typical angina is uncommon. Myocardial ischemia often is silent or manifested by atypical symptoms, shortness of breath, fatigue, syncope, arrhythmias, or sudden death. Therefore, patients should be monitored for progressive deterioration of left ventricular function by serial imaging studies. Intravascular ultrasonography (IVUS) studies at 1 and 12 months after heart transplantation (HTx) are important to detect intimal thickening and concentric luminal narrowing to identify patients at high risk for future cardiovascular events. Noninvasive modalities such as computer tomography and magnetic resonance coronary angiography and perfusion imaging will likely play increasing roles in the future. Recent therapeutic advances include the use of antiproliferative drugs such as sirolimus (rapamycin), 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, calcium channel blockers, and angiotensin converting enzyme (ACE) inhibitors. Unfortunately, these agents have slowed down the progression of graft vasculopathy but have failed to fully prevent it. Future development may target chemokines and adhesion molecules that mediate leukocyte accumulation in the vessel wall.

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Heart transplantation • Coronary graft vasculopathy • Microvascular disease

Heart transplantation (HTx) is the ultimate treatment for end-stage heart failure. Approximately 4000 HTx procedures are performed worldwide each year [1]. In a retrospective analysis of 14,401 patients who underwent first-time HTx between the years 1999 and 2006, survival at 30 days, 1 year, and 5 years was 94, 87, and 75 % for the young group (<60 years of age) and 93, 84, and 69 % for the older group [2]. The overall half-live of cardiac allografts approached 10 years [1].

Although immunosuppressive agents have been quite effective in preventing acute cardiac allograft rejection, chronic rejection has persisted as an unresolved problem. Chronic rejection is manifested primarily by a unique form of accelerated coronary artery disease, termed coronary allograft vasculopathy [3]. By the fifth post-transplant year, graft vasculopathy and ensuing graft failure accounts for 30 % of deaths in cardiac transplant recipients [1]. The disease affects both large epicardial arteries and small intramyocardial vessels. The present review discusses selected aspects of coronary allograft vasculopathy with a focus on microvascular disease. As a consequence of cardiac denervation, typical angina is rarely perceived in these patients. Instead, graft vasculopathy may be manifested by atypical symptoms including shortness of breath and fatigue.

Prevalence

In a multicentric study, 42 % of cardiac transplant recipients had abnormal invasive coronary angiograms and 7 % of them had severe graft vasculopathy by the fifth post-transplant year [4]. However, coronary angiography is an insensitive method in this population. Intravascular ultrasound (IVUS) imaging is more sensitive than invasive angiography, as it identifies early intimal thickening and concentric luminal narrowing. IVUS studies have revealed a high prevalence of graft vasculopathy up to 75 % by the first post-transplant year [5–7].

Pathogenesis

Coronary allograft vasculopathy is a complex disease that results from repeated immune and nonimmune–mediated injuries to the endothelium, which triggers inflammatory cascades, vascular cell proliferation, and fibrosis (Fig. 14.1). The pathogenesis of the disease has been discussed in detail elsewhere [8–12]. Donor-transmitted coronary artery disease is a significant contributory aspect. In an early study, pre-existing coronary artery lesions, as demonstrated by IVUS, were present in approximately half of donor hearts in a series of young donors aged 32 ± 12 years [13]. In another series of 171 transplant patients aged 53 ± 13 years, donor-transmitted coronary artery lesions were detectable by invasive coronary angiography in 4.1 % and by IVUS in 53.8 % of patients. In this study, however, donor-transmitted disease was not associated with an increased long-term incidence of cardiovascular adverse events [14]. Another pathogenetic factor is ischemic time. Data from the International Society of Heart and Lung Transplantation (ISHLT) registry indicate that ischemic times greater than 7 h for donor hearts increase the risk of both 1- and 5-year mortality [1].

The simple observation that while graft coronary arteries develop lesions the host's native arteries are spared indicates a key role for alloimmune responses in the development of graft vasculopathy. This is supported by animal data showing that while hearts transplanted into a genetically different recipient are affected, those placed in the original donor strain are spared [15]. Clinical data indicate that the extent of donor–recipient human leukocyte antigen (HLA) matching correlates directly with cardiac allograft survival [1, 16–18]. The relationship between acute rejection episodes and the development of graft vasculopathy is complex and still incompletely understood. Clinical correlations between the number of acute rejection episodes, both early and late after HTx, and graft vasculopathy have been reported [19–22].

Traditional cardiovascular risk factors such as hyperglycemia, dyslipidemia, and hypertension are highly prevalent in transplanted patients, in part as side effects of immunosuppressive drugs, and play contributory roles in the development of graft vasculopathy [23]. At necropsy, histological analysis of human cardiac allografts showed frequent coronary lesions with diffuse intra- and extra-cellular lipid accumulation in both intimal and medial walls [24]. Mean total cholesterol content in coronary arteries was more than tenfold higher than in comparable donor age-matched native vessels. Extent of lipids in the arterial walls was highly correlated with mean cumulative cyclosporine and prednisone doses. Cyclosporine was shown to induce endothelial injury, nephrotoxicity and hypertension [25–27]. Finally, infectious agents such as cytomegalovirus [28–32] and Chlamydia pneumoniae [33] have been implicated in the development of graft vasculopathy, but their roles are not firmly established.

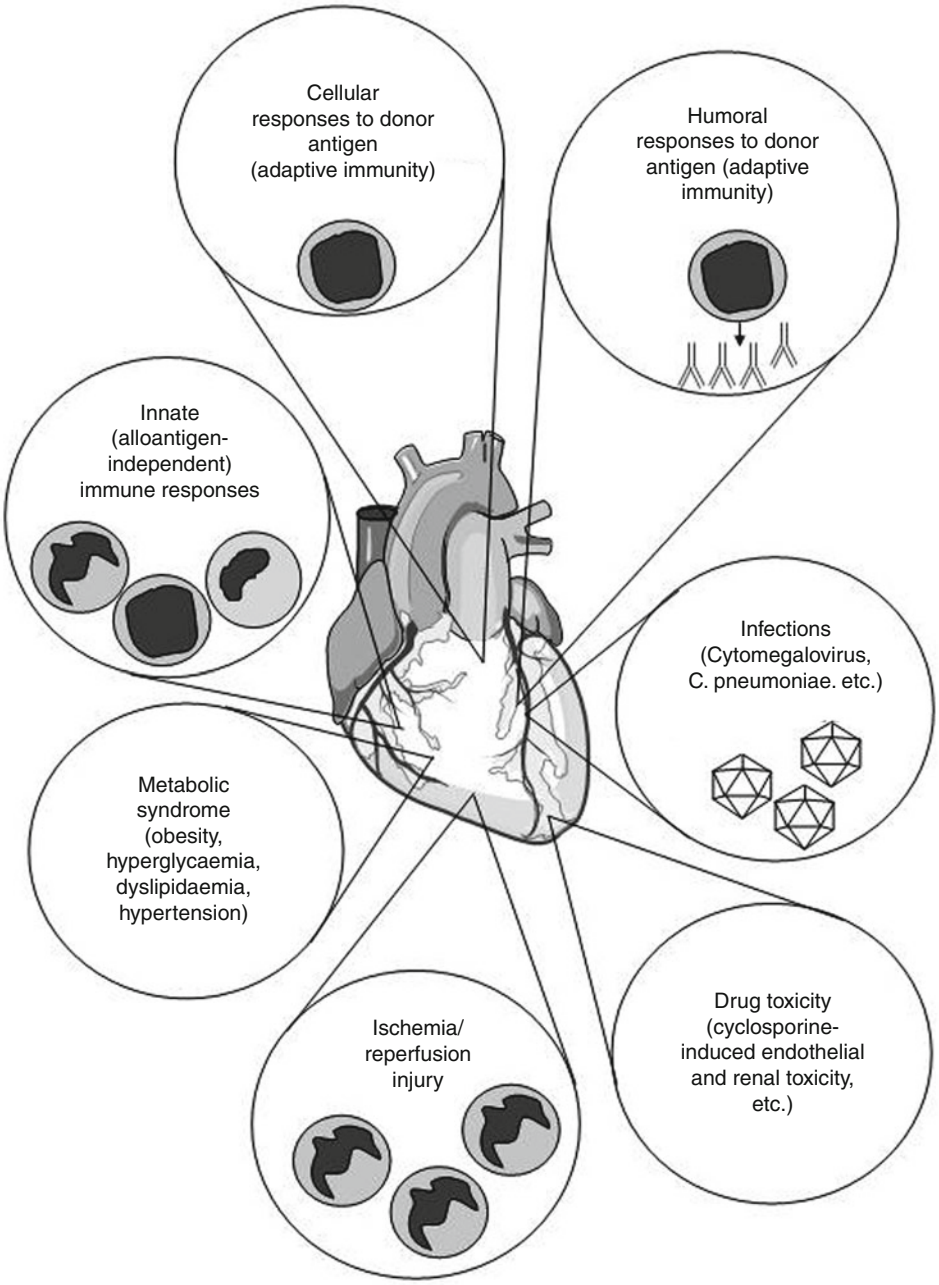

Fig. 14.1 Schematic of the major alloimmune-dependent and independent mechanisms participating in the pathogenesis of coronary allograft vasculopathy, including donor-antigen dependent (adaptive) cellular and humoral responses, donor antigen-independent (innate) responses, ischemia-reperfusion injury, classic cardiovascular risk factors (metabolic syndrome), infections and drug toxicity

Histology

By the fifth post-transplant year, virtually all graft recipients have histological evidence of graft vasculopathy including concentric fibrous intimal thickening, smooth muscle cell proliferation, and perivascular mononuclear cell infiltrates, eventually leading to destruction of elastic fibers and thinning of the media [34, 35]. However, complex atherosclerotic plaques closely resembling lesions in native vessels are frequent. Lipid accumulation in both intimal and medial walls is a common finding [24], as mentioned. Occlusion of small coronary branches often precedes that of the larger arteries, resulting in multiple microinfarcts.

Graft Coronary Microvascular Dysfunction

Coronary blood flow (CBF) measurement is an established method to evaluate the functional integrity of the microcirculation. A decrease in coronary flow reserve (CFR), the ratio of hyperemic to resting CBF, can reflect either structural changes of the myocardium as a result of rejection episodes and left ventricular hypertrophy, or microvascular disease in the context of graft vasculopathy [8]. In an early study by Treasure et al. [36], CBF was measured at constant arterial pressure with a Doppler catheter in the left anterior descending coronary artery in 29 transplant patients 1–3 years after HTx and in seven nontransplanted controls.

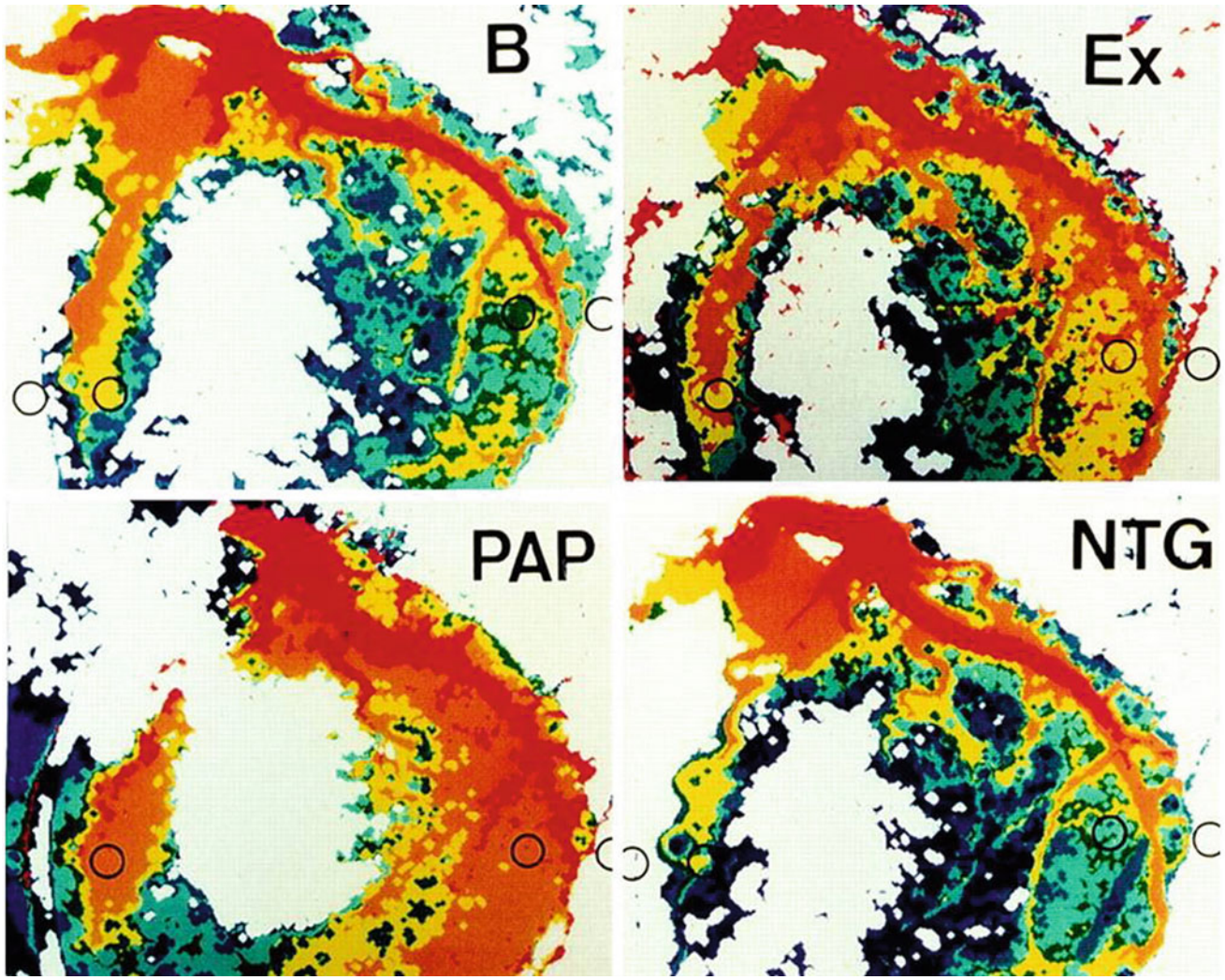

Fig. 14.2 Coronary angiography and parametric imaging in a patient 2 years after HTx at baseline (*B*), after intracoronary papaverine (*PAP*) administration, at the peak of supine bicycle exercise (*Ex*), and after sublingual nitroglycerin (*NTG*) administration. Contrast density and mean appearance time were determined in the perfusion territory (*open circles* indicate region of interest in respective background regions) of the left anterior descending coronary artery (*left in each image*) and the left circumflex coronary artery (*right*) as well as in neighboring background regions. The hyperemic response (*orange and yellow areas*) to exercise was decreased compared with that to papaverine (as opposed to nontransplant controls) (Reprinted from Vassalli et al. [37] with permission from Wolters Kluwer Health)

The endothelium-dependent agent acetylcholine (10^{-8} to 10^{-6} M) and the essentially endothelium-independent agent adenosine were used as vasodilators. The increase in CBF in response to acetylcholine was normal 1 and 2 years but impaired 3 years after HTx, whereas the increase in CBF in response to adenosine was essentially normal. These results suggest a progressive impairment of endothelial microvascular function occurring 2 to 3 years after HTx. We measured CFR with supine bicycle exercise as a physiologic hyperemic stimulus and parametric imaging in 10 asymptomatic cardiac transplant recipients 2 to 3 months after HTx, in 25 transplant recipients without angiographically significant coronary disease who were studied 1–6 years after HTx, and in 8 nontransplanted controls (Fig. 14.2) [37]. CFR measured during exercise was maintained 3 months after HTx but was significantly decreased in patients studied 1–6 years after HTx. To the contrary, CFR measured with intracoronary papaverine, a direct coronary vascular smooth muscle relaxant, was maintained up to 6 years after HTx. Because microvascular dilation during dynamic exercise depends on the release of nitric oxide (NO) by an intact endothelium, these findings are consistent with a progressive impairment of endothelial microvascular function after HTx. However, these studies measured CFR as a relative flow ratio, rather than absolute CBF. Using positron-emission tomography (PET), Krivokapich et al. [38] reported that reduced CFR during exercise in cardiac transplant recipients mainly resulted from an increased CBF at rest, as opposed to a decreased hyperemic response during exercise. Mullins et al. [39] measured CFR and peak

flow responses to papaverine using an intracoronary Doppler flow probe in the proximal left anterior descending coronary artery in 61 transplant patients studied between 3 months and 10 years after transplantation. Twenty-one patients had angiographic evidence of minor coronary occlusive disease, whereas the remaining forty patients had normal coronary angiograms. CFR measured with papaverine was maintained in transplant patients with normal coronary angiograms, as compared to nontransplant controls, whereas it was impaired in transplant patients with minor occlusive disease. Mean resting flow velocity was similar in the three groups. Thus, endothelium-independent microvascular dilation was preserved in transplant recipients in the absence of minor occlusive lesions. Fearon et al. [40] measured fractional flow reserve (FFR) with a coronary wire in 53 asymptomatic transplant patients without angiographically significant coronary disease. FFR correlated with IVUS findings and was abnormal in approximately 15 % of patients. A prognostic significance of graft microvascular dysfunction was observed in several studies [41–43], but not in others [44].

Structural Microcirculatory Changes

The relationship between intramyocardial and epicardial vessel disease is complex. Clausell et al. [45] correlated abnormalities in small intramyocardial vessels detected on routine endomyocardial biopsy specimens with abnormal IVUS or endothelial dysfunction in large epicardial coronary arteries. Histological abnormalities including intimal thickening in small intramyocardial vessels were detected in 76 % of 39 patients. All patients had intimal thickening by IVUS; however, intimal index did not correlate significantly with histological evidence of small artery disease. Endothelium-dependent vasodilation of large epicardial vessels determined by quantitative coronary angiography after acetylcholine administration was abnormal in 43 % of patients and did not correlate with either abnormal IVUS abnormalities or small vessel disease. Thus, graft small vessel and epicardial vessel disease may represent distinct pathogenetic entities. Data by von Scheidt et al. [46] were consistent with this assumption. By contrast, Tona et al. [47] reported a correlation between CFR measured by transthoracic echocardiography and epicardial intimal thickening in patients after HTx. Left ventricular hypertrophy and the severity of graft vasculopathy were independent contributors to the decrease in CFR [48].

Recent evidence suggests that structural abnormalities of the coronary microvasculature may be of prognostic relevance after HTx. Hiemann et al. [49] showed a prognostic impact of histological evidence of microvasculopathy from 9,713 endomyocardial biopsies on survival after HTx. Stenotic microvasculopathy was present in 43 % of patients, mainly due to medial disease (91 %). In this study, stenotic microvasculopathy was associated with poor overall survival and reduced freedom from fatal cardiac events, independently of epicardial graft vasculopathy, whereas endothelial disease and nonstenotic medial disease were not.

Recently, Escaned et al. [50] correlated intracoronary flow velocity and pressure measurements with endomyocardial sampling in cardiac allografts. Intracoronary indices derived from pressure and flow, particularly the instantaneous hyperemic diastolic velocity-pressure slope, were superior to CFR for detection of structural microcirculatory changes. Both arteriolar obliteration and capillary rarefaction seemed to influence microcirculatory hemodynamics independently.

Clinical Manifestations

Classic angina is rarely perceived by patients with coronary graft vasculopathy because the transplanted heart is denervated. Conversely, symptoms often are atypical or completely absent. When present, angina may be related to partial reinnervation of the cardiac graft, which occurs in about 10–30 % of patients in the long term [51, 52]. Although sympathetic reinnervation of the transplanted heart may have beneficial effects on the regulation of myocardial perfusion and exercise performance, there is no evidence of a favorable impact on patient outcome [53]. Graft vasculopathy may be manifested by shortness of breath, decreased exercise capacity, syncope, arrhythmias, and congestive heart failure. Acute myocardial infarction in cardiac transplant recipients is characterized by lack of chest pain or typical electrocardiographic changes and high mortality rates. Multiple foci of nontransmural infarction are observed frequently [51]. However, a minority of patients present with chest pain, allowing early diagnosis and primary percutaneous coronary intervention (PCI), which has a positive prognostic impact [54]. Coronary spasm with ST-segment elevation has also been observed in cardiac transplant recipients [55]. Because many patients are asymptomatic or have atypical symptoms, in some cases the first manifestation of the disease is acute myocardial infarction or sudden death. It therefore is important to evaluate patients on an annual basis for the presence of coronary lesions. Serial echocardiography is valuable to detect progressive deterioration of cardiac function due to repeated ischemic events. Using serial IVUS and Doppler flow-wire measurements, Hollenberg et al. [43] reported significant associations between annual decrements in coronary endothelial function and progressive intimal thickening, as well as between acetylcholine-dependent vasomotor abnormalities and death.

Non-invasive Diagnostic Approaches

Non-invasive approaches are particularly attractive for serial assessment of graft rejection, coronary morphology, and coronary vasomotor function in transplant patients. Several noninvasive modalities including echocardiography, multidetector computed tomography (MDCT), myocardial perfusion imaging, and magnetic resonance imaging (MRI) have been evaluated in this regard [56, 57]. A good overall agreement of 64-slice MDCT and conventional coronary angiography was reported, with MDCT possibly being superior for identification of nonobstructive vessel wall thickening [58, 59]. A pilot study in 10 asymptomatic long-term survivors after HTx demonstrated the ability of a combined approach with MDCT and MRI to assess graft vasculopathy and rejection before applying more invasive methods [60]. Late contrast enchancement found by MRI correlated positively ($r=0.92$, $r^2=0.85$; $p<0.05$) with the histological diagnosis of transplant rejection evidenced by myocardial biopsy. A study with strain-encoded cardiac MRI in 69 consecutive patients undergoing cardiac catheterization revealed high accuracy of myocardial perfusion reserve (area under the curve, AUC=0.95; 95 %-confidence interval, CI=0.87–0.99) and mean diastolic strain rate (AUC=0.93; 95 %-CI=0.84–0.98) for detection of graft vasculopathy [61]. Echocardiography and MRI are particularly attractive for serial studies due to lack of ionizing radiations.

Therapeutic Advances

Recent therapeutic advances include the use of antiproliferative drugs such as sirolimus (rapamycin), 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins), calcium channel blockers, and angiotensin converting enzyme (ACE) inhibitors. Calcineurin inhibitors such as cyclosporine A and tacrolimus affect endothelial function in many ways including production of vasoconstrictory metabolites such as angiotensin II, increased endothelial oxidative stress, decreased secretion of proinflammatory cytokines, and decreased expression of adhesion molecules [62]. Renal transplant recipients treated with tacrolimus exhibited less impairment in brachial endothelial function than those treated with cyclosporine [63]. Meiser et al. [64] reported reduced intimal proliferation during the first year after HTx in patients treated with mycophenolate mofetil and tacrolimus, as compared with mycophenolate mofetil and cyclosporine A. Glucocorticoids act on endothelial and vascular smooth muscle cells in a dose-dependent manner. Proliferation inhibitors such as mycophenolate mofetil have less pronounced effects on endothelial function compared with calcineurin inhibitors and glucocorticoids [65]. The m-TOR inhibitor sirolimus (rapamycin) was associated with slower progression of graft coronary vasculopathy in patients with established angiographic disease. The related agent everolimus was associated with a lower incidence of acute rejection and graft vasculopathy. A study by Raichlin et al. [66] showed that sirolimus as primary immunosuppression was associated with improved coronary vasomotor function compared with calcineurin inhibitors in stable cardiac transplant recipients. Starting sirolimus treatment at transplantation reduced the incidence of acute rejection episodes by approximately 40 % at 6 months and preserved coronary artery luminal size 2 years after HTx. A double-blind trial by Eisen et al. [67] included 634 cardiac transplant recipients who were randomly assigned to receive either everolimus (2.5 or 3.0 mg/day) or azathioprine (1.0–3.0 mg/kg of body weight per day) in combination with cyclosporine, corticosteroids, and statins. At 6 months, the percentage of patients who had reached the primary end point (a composite of death, graft loss or retransplantation, loss to follow-up, biopsy-proved acute rejection of grade 3A, or rejection with hemodynamic compromise) was significantly smaller in the group given 3.0 mg of everolimus (27.0 %; $p<0.001$) and the group given 1.5 mg of everolimus (36.4 %, $p=0.03$) than in the azathioprine group (46.7 %). IVUS showed a smaller increase in maximal intimal thickness 12 months after HTx in the two everolimus groups compared with azathioprine. The prevalence of vasculopathy was significantly lower in the two everolimus groups than in the azathioprine group, as were serum creatinine levels. Wenke et al. [68] showed that statin therapy started early after HTx significantly improved 8-year survival rates and reduced the incidence of graft vasculopathy. Simvastatin treatment given to patients without accelerated coronary artery disease improved coronary endothelial function and increased coronary lumen area [69]. ACE inhibitors were associated with less graft microvascular endothelial dysfunction [70], plaque regression [71], and improved graft survival after HTx [72]. The calcium channel blocker diltiazem may slow down graft coronary lumen narrowing [73]. An IVUS study suggested a synergistic protective effect of ACE inhibition and calcium antagonism on graft vasculopathy [74].

Conclusions

Coronary allograft vasculopathy is a particularly vexing aspect of HTx. The disease frequently affects the microvasculature and can be detected as an abnormal CBF response to a vasodilator agent or structural changes of small vessels in endomyocardial biopsies. Most patients with graft vasculopathy after HTx have atypical symptoms or are asymptomatic, whereas patients suffering from typical angina are relatively rare. In many cases, the disease is manifested as silent ischemia with a progressive decline of ventricular function. Serial imaging studies are important to detect graft vasculopathy at early stages in order to make

therapeutic decisions. Recent advances in pharmacological treatments have moderately slowed down the progression of the disease, although they have failed to fully prevent it. A number of approaches including donor organ and recipient preconditioning protocols to reduce ischemia-reperfusion injury at the time of organ procurement and transplantation, novel immunosuppressive drugs, specific inhibitors of proinflammatory cytokines and chemokines, inhibitors of intracellular signaling cascades and adhesion molecules, and more aggressive therapies against classic cardiovascular risk factors, are being investigated.

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Immune Responses in Atherosclerosis and Microvascular Angina

15

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Abstract

Intense research into the mechanisms that trigger and drive atherosclerosis has dramatically challenged the view that this disease is merely caused by the accumulation of lipids (mainly low density lipoproteins, LDL) in the vessel wall and clearly demonstrated that chronic inflammation orchestrated by the immune system is crucial for atherogenesis. The innate as well as the adaptive arms of the immune system are actively involved in atherosclerosis. In support of this is the observation that immune cells like macrophages and T cells constitute a great part of the inflammatory infiltrate in atherosclerotic lesions. In addition, some patients with atherosclerosis develop T-cell-dependent and T-cell-independent antibodies that recognise modified lipids such as oxidised LDL (oxLDL). In this chapter, we provide a brief overview of the contribution of the immune system and in particular of T lymphocytes to atherosclerosis and discuss the importance of research in this area in patients with microvascular angina. A better understanding of the immune mechanisms that underlie atherogenesis both in patients with coronary artery disease and microvascular angina has important clinical implications as it may unravel novel targets for immunotherapy that may allow efficient control of these clinical entities.

Keywords

Atherosclerosis • Immune response • T lymphocytes

Abbreviations

ACS	Acute coronary syndrome
APC	Antigen presenting cell
CAD	Coronary artery disease
DC	Dendritic cell
HSP	Heat shock protein
IFN-γ	Interferon-γ
IL-12	Interleukin-12
LDL	Low density lipoprotein
MMP	Matrix metallo-proteinases
oxLDL	Oxidised low density lipoprotein
Th	T helper
TGF-β	Transforming growth factor-β
TNF-α	Tumour necrosis factor-α
VSMC	Vascular smooth muscle cell

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Introduction

The immune system is designed to recognise and eliminate infectious agents efficiently. However, in certain circumstances, altered or uncontrolled immune responses may have deleterious effects, as observed in hypersensitivity and autoimmune disorders. Recent findings from research into the mechanisms of atherosclerosis have highlighted central contributions for cells of the immune system to this disease [1]. Indeed, in addition to lipids, atherosclerotic plaques often contain infiltrates of immune cells belonging both to the innate (e.g. macrophages) and to the adaptive (e.g. T lymphocytes) immune system. Modulation of the immune response in atherosclerosis could be used to complement current therapies that target hyperlipidemia and the acute vessel obstruction caused by rupture of atherosclerotic plaques. However, this requires a clearer understanding of the precise immune changes that take place in patients suffering from atherosclerosis. The present chapter focuses on the role of T cell subsets in atherosclerosis, including the early phases of the disease that precede the formation of an obstructive plaque. As recent evidence suggests that endothelial dysfunction and subclinical atherosclerosis are present in patients with microvascular angina, it is likely that similar immune alterations can contribute to the pathogenesis of angina in this group of patients and their characterisation could unravel novel therapeutic targets.

Immune Response in Atherosclerosis: The Basic Principles

Atherosclerosis is a disease caused by the deposition of lipids in the intima of large and medium-sized arteries. Data from studies using animal models of atherosclerosis as well as findings from the human disease demonstrate that chronic activation of innate and adaptive immune mechanisms regulates the development and progression of atherosclerosis [1]. Indeed, one of the initial alterations that leads to the formation of atherosclerotic plaques is endothelial activation (or dysfunction) that is accompanied by an increase in permeability and upregulation of adhesion molecules [2]. This facilitates the entry of lipids (mainly low density lipoproteins, LDL) into the intima and the recruitment from circulation of immune cells like monocytes and T lymphocytes. The infiltrating monocytes differentiate into macrophages in the intima, which have increased ability to phagocytose lipids either in their native state or following alteration in situ (e.g. oxidised LDL, oxLDL). Phagocytosis of lipids triggers macrophage activation and production of inflammatory mediators, such as the cytokine interferon-γ (IFN-γ). In time, initial lesions develop into mature atherosclerotic plaques. Often, these are characterised by: a lipid core; infiltrates of immune cells such as lymphocytes, macrophages and foam cells (which differentiate from macrophages following lipid uptake); proliferation of vascular smooth muscle cells (VSMC) both in the media and, as a thin layer underneath the endothelium (forming the fibrous cap); apoptotic cell death; formation of neo-vessels and fibrosis (detailed in [3]). Two main types of atherosclerotic plaques have been described: stable plaques that are characterised by low level infiltration with immune cells, thick fibrous cap and a small necrotic core; and unstable (vulnerable) plaques that have significant numbers of inflammatory cells, thin cap and a large necrotic core [2]. The acute and most severe clinical manifestations of atherosclerosis (i.e. myocardial infarction, sudden death, and stroke) are often caused by rupture of vulnerable plaques with the formation of a thrombus and occlusion of the artery [2]. One of the mechanisms that underlies plaque rupture is the destruction of the fibrous cap by extracellular matrix degrading enzymes such as metallo-proteinases (MMPs), which are released from activated macrophages, a process mediated at least in part by IFN-γ [4]. In addition to monocytes/macrophages that belong to the innate immune system, adaptive immune cells like lymphocytes are also crucial in atherosclerosis. Indeed, T cells are consistently found in atherosclerotic lesions and can account for as much as 20 % of the cells in the shoulder region of the plaque [5].

Several subsets of T cells with various roles have been described in atherosclerosis. Helper T (Th) lymphocytes are characterised by the expression of the CD4 surface marker, which distinguishes them from cytotoxic T lymphocytes (CTL) which express CD8. The main function of $CD4^+$ Th cells is to provide signals required for the optimal function of other immune cells (e.g. macrophage activation; production of antibodies by B lymphocytes). In contrast, $CD8^+$ T cells are able to directly kill cells infected by intracellular pathogens like viruses. Most of the T cells in atherosclerotic lesions are $CD4^+$ T cells and they are regarded as the main perpetrators of the disease, while $CD8^+$ T lymphocytes have minor effects. Several subsets have been characterised since the original identification of $CD4^+$ Th cells such as: Th1, Th2, Th9, Th17, Th22, follicular helper T cells (Tfh) and regulatory T (Treg) cells. These Th subsets differentiate from naive $CD4^+$ T cells under the influence of various cytokines (Fig. 15.1) produced by cells of the innate immune system (e.g. DCs, macrophages) in response to pathogens or other triggers [6]. As Th cells do not express characteristic surface markers but just CD4, they are usually identified by the cytokines they secrete, the target cells on which they act and finally by their functional effects [7]. In the next sections we summarise the current knowledge on the role of the best characterised so far T cell subsets in atherosclerosis.

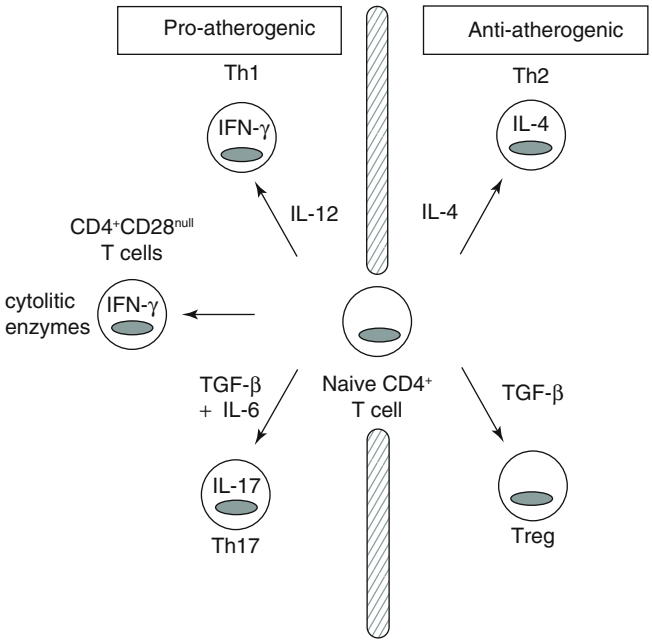

Fig. 15.1 Various subsets of T helper (Th) cells have been described with either pro-atherogenic or anti-atherogenic roles. Th1 cells differentiate from naive CD4⁺ T cells under the influence of interleukin-12 (IL-12), a cytokine produced by dendritic cells. Th1 cells secrete interferon-γ (IFN-γ) and have potent inflammatory functions. Data suggest that Th1 cells promote atherosclerosis. The differentiation of Th2 cells is mediated by IL-4, which is also the main cytokine that identifies this subset. Th2 cells antagonise the functions of Th1 lymphocytes and seem to have mainly protective roles in atherosclerosis (although some studies found that this is not always the case). $CD4^+CD28^{null}$ T cells are a particular subset of Th1 cells that are characterised by the lack of the receptor CD28. These cells have pro-inflammatory and cytotoxic properties and have been suggested to promote atherogenesis and plaque rupture. Th17 cells differentiate in the presence of transforming growth factor-β (TGF-β) and IL-6 and characteristically secrete IL-17, a cytokine which mediates inflammation. Although there is some controversy regarding the role of Th17 in atherosclerosis, they have the potential to augment this disease due to their pro-inflammatory effects. Another subset of CD4⁺ T cells that has been investigated in atherosclerosis is the regulatory T (Treg) cells. These cells are specialised in immune suppression and have been suggested to protect against atherosclerosis

Th1 Cells

Th1 cells have important roles in cell-mediated immunity as they provide signals for macrophage activation that enable efficient destruction of intra-cellular pathogens. Their signature cytokine is IFN-γ, a potent pro-inflammatory factor (Fig. 15.1). Th1 cells have also been implicated in diseases associated with chronic inflammation such as autoimmune disorders (i.e. rheumatoid arthritis, diabetes, inflammatory bowel disease) and graft-versus-host disease [8]. Th1 cells have been found to have mainly pro-atherogenic roles. Indeed, Th1 cells that produce IFN-γ constitute most of the CD4⁺ T cells in atherosclerotic lesions of both murine and human origin [5, 9]. Administration of the Th1 signature cytokine IFN-γ to *Apoe*$^{-/-}$ mice increased the size of atherosclerotic lesions [10], and promoted the development of atherosclerosis in human arterial segments transplanted in immunodeficient mice [11]. Deficiency in IFN-γ or its receptor attenuated atherosclerosis in *Apoe*$^{-/-}$ and *Ldlr*$^{-/-}$ mice [12–14]. However, reconstitution of *Ldlr*$^{-/-}$ mice with bone marrow from *Ifn-γ*$^{-/-}$ mice surprisingly enhanced atherosclerosis, suggesting that IFN-γ could also have some protective effects in atherosclerosis [15]. A recent study targeted the transcription factor T-bet that regulates the differentiation of Th1 cells from naive CD4⁺ T cells [16]. Induction of T-bet deficiency in atherosclerosis-prone *Ldlr*$^{-/-}$ mice significantly reduced the extent of atherosclerosis [16], which further supports a pro-atherogenic role for Th1 cells. The main cytokine produced by Th1 cells, IFN-γ, can enhance atherogenesis in various ways. IFN-γ triggers the expression of MHC II (major histocompatibility complex class II, which is involved in antigen presentation) on endothelial cells and VSMCs and therefore promotes presentation of antigens and T lymphocyte activation in the atherosclerotic plaque environment [17, 18]. In addition, IFN-γ enhances the recruitment of T cells and macrophages into atherosclerotic lesions and induces activation of APCs (e.g. macrophages and DCs), which increases their ability to present plaque-derived antigens to T-cells and amplifies the immune response. Another effect of IFN-γ is that it induces the secretion of MMPs from activated macrophages, which cause apoptosis of SMCs and promote thinning of the fibrous cap and plaque rupture. The ability of IFN-γ to inhibit the differentiation and proliferation of VSMCs and collagen synthesis further contributes to thinning of the fibrous cap [19].

$CD4^+CD28^{null}$ T Cells

A characteristic subset of CD4⁺ T lymphocytes was identified in patients with acute coronary syndrome (ACS), known as $CD4^+CD28^{null}$ T cells [20]. These cells are characterized by the lack of CD28, a receptor that delivers co-stimulatory signals crucial for optimal activation of T cells following antigen recognition on APCs [21]. CD28 is expressed constitutively on naive CD4⁺ T cells and its ligands B7.1 (CD80) and B7.2 (CD86) are present on APC such as dendritic cells. CD28 signals control the production of IL-2 and the expression of the IL-2 receptor by activated T cells, which promote cell proliferation and survival [21]. In the absence of co-stimulatory signals transduced by CD28, T cells enter a state of immune unresponsiveness called anergy.

Healthy individuals have very low frequencies of $CD4^+CD28^{null}$ T cells, while patients with rheumatoid arthritis (RA) and other inflammatory disorders show expansion of this cell subset [22]. The expansion of $CD4^+CD28^{null}$ T cells correlates with extra-articular involvement and the

severity of disease in RA [22]. Of note, the frequency of $CD4^+CD28^{null}$ T cells is significantly higher in patients with ACS when compared with stable angina (SA) and healthy controls [20]. These cells have been suggested to contribute to plaque instability as they have been identified preferentially in unstable coronary plaques [23]. Another feature that suggests that $CD4^+CD28^{null}$ T cells could trigger plaque rupture is their ability to produce IFN-γ, which induces the secretion of extracellular matrix degrading MMPs from activated macrophages [23, 24]. Recurrence of acute coronary events (i.e. myocardial infarction) has been found to correlate with the frequency of $CD4^+CD28^{null}$ T cells [25]. Recently, it was shown that $CD4^+CD28^{null}$ T cells are also expanded in patients with diabetes mellitus [26], a disease associated with an increased risk of ACS and that $CD4^+CD28^{null}$ T cell frequencies higher than 4 % correlate with the occurrence of the first cardiovascular event and poor outcome of ACS in diabetic patients [26].

$CD4^+CD28^{null}$ T cells differ from conventional $CD4^+CD28^+$ T cells by the expression of cytolytic enzymes (granzyme A and B) and perforin (a protein that forms pores in the membrane of target cells and enables the entry of granzymes) [27]. These molecules involved in cytolysis are usually found only in cytotoxic $CD8^+$ T lymphocytes and natural killer (NK) cells, and are not expressed by conventional $CD4^+CD28^{pos}$ T cells. In contrast, $CD4^+CD28^{null}$ T cells have been shown to lyse endothelial cells and SMCs in vitro by the release of perforin and granzymes from cytosolic granules [28], a mechanism that could explain their propensity towards plaque rupture. We have recently found that $CD4^+CD28^{null}$ T cells harbour significant differences in the levels of alternative co-stimulatory receptors OX40 and 4-1BB and that blockade of these receptors interferes with the production of pro-inflammatory cytokines and cytolytic function of $CD4^+CD28^{null}$ T cells [29]. As $CD4^+CD28^{null}$ T cells have potent pro-inflammatory and cytotoxic roles understading the precise mechanisms that regulate their accumulation in patients with severe atherosclerosis (ACS) may lead to identification of novel therapeutic targets to achieve plaque stability.

Th2 Cells

Th2 cells are instrumental in protection against extra-cellular pathogens and the production of antibodies. They are identified by the production of IL-4, IL-5 and IL-13 cytokines [7]. In disease, Th2 cells have mainly been implicated in allergies and asthma [30]. As Th1 and Th2 cells antagonise each other, it could be expected that Th2 cells have protective effects in atherosclerosis. Indeed, *Apoe*$^{-/-}$ mice on a BALB/c background, in which Th2 responses predominate, developed significantly less atherosclerosis than *Apoe*$^{-/-}$ mice on the C57BL/6 background in which the immune response is dominated by Th1 cells [31]. Similarly, T-bet deficient *Ldlr*$^{-/-}$ mice that have impaired differentiation of Th1 cells, showed attenuated atherosclerosis compared to wild type *Ldlr*$^{-/-}$ mice [16]. However, deficiency of IL-4 (the Th2 signature cytokine) in *Apoe*$^{-/-}$ mice (which impairs Th2 lineage differentiation) attenuated atherosclerosis [32]. On a similar line, reconstitution of *Ldlr*$^{-/-}$ mice with bone marrow from IL-4-deficient animals reduced the extent of atherosclerosis [33], suggesting that Th2 cells could promote atherosclerosis. In conclusion, the precise role of Th2 cells in atherosclerosis remains to be demonstrated.

Regulatory T Cells

A subset of T cells that has sparked a lot of interest in the research community is the regulatory T (Treg) cell subset. These cells are important in the maintenance of immune tolerance and homeostasis and prevent the development of deleterious immune responses. Treg cells are usually identified by the expression of CD4, high levels of CD25 (the α chain of IL-2 receptor) and of the transcription factor Foxp3 [34]. In autoimmunity, several changes in the number, phenotype and/or function of Treg cells have been described [35, 36]. Treg cells were found to inhibit both the initiation and progression of atherosclerosis in several animal models [37]. Lethaly irradiated *Ldlr*$^{-/-}$ mice reconstituted with bone marrow deficient in Treg cells developed markedly increased atherosclerotic lesions compared to mice that received wild type bone marrow [38]. Similarly, depletion of Treg cells with a monoclonal antibody specific for CD25 resulted in significantly larger atherosclerotic lesions in *Apoe*$^{-/-}$ mice in comparison to mice treated with control antibodies [38]. Furthermore, atherosclerotic lesions from Treg-depleted *Apoe*$^{-/-}$ mice resembled vulnerable plaques with increased infiltration of macrophages and T cells and decreased collagen [38].

The precise contribution of Treg cells to atherosclerosis in humans is still not completely understood. Initial studies have suggested, as expected, that patients with ACS have decreased frequencies of Treg cells in the peripheral blood when compared to patients with chronic stable angina and healthy subjects [39] and that the suppressive function of Treg cells from ACS patients was impaired compared to Treg cells from healthy controls [40]. Recently, these results were questioned by the finding that levels of circulating Treg cells do not correlate with the extent or severity of atherosclerosis [41]. Treg levels were not altered in patients with chronic stable angina, whilst ACS patients showed either a decrease (STEMI) or an increase (NSTEMI) in the frequency of this T cell subset [41]. However, the suppressive function of Treg cells was not investigated in this study. This needs to be

addressed in future studies as defects in the suppressor function of Treg cells could contribute to atherosclerosis even if their frequency was not decreased. Indeed, in systemic lupus erythematosus, Treg cells have impaired suppressive function although their frequency is not different from healthy subjects [42].

Therapeutic protocols that could augment the number or suppressive function of Treg cells in disorders associated with chronic inflammation such as autoimmunity and atherosclerosis are being currently investigated. In experimental models, induction of oral tolerance to antigens involved in atherogenesis such as oxLDL and HSP60 in *Ldlr*$^{-/-}$ mice resulted in a reduction of atherosclerotic lesion size, which was accompanied by increased numbers of $CD4^+CD25^+Foxp3^+$ Treg cells in the spleen and mesenteric lymph nodes [43, 44]. Furthermore, adoptive transfer of Tr1 cells (a subtype of inducible Treg cells which characteristically produces the immunosuppressive cytokine IL-10), limited the development of atherosclerosis in *Apoe*$^{-/-}$ mice by inhibiting Th1-mediated responses [45]. These results suggest that activation and expansion of Treg cells *in vivo* may provide targeted immuno-therapy to slow down the progression of atherosclerosis. However, a better understanding of the mechanisms that regulate the development and suppressive function of Treg cells, is required for the design of optimal therapeutic protocols.

Th17 Cells

Th17 cells are a relatively recently discovered subset of T cells that have been implicated in the pathogenesis of autoimmune disorders such as multiple sclerosis, rheumatoid arthritis and inflammatory bowel disease (reviewed in [46]). They also have important roles in the defence against various pathogens [47]. Th17 cells are characterised by the production of the pro-inflammatory cytokine IL-17 [48, 49]. Research on Th17 cells in atherosclerosis has generated conflicting results, with some authors suggesting pro-atherogenic roles, while others found Th17 to protect from atherosclerosis. T cells isolated from human coronary arteries were found to express IL-17 in addition to IFN-γ and have therefore been proposed to participate synergistically with Th1 cells in the inflammatory response that drives atherosclerosis [50]. IL-18 deficient *Apoe*$^{-/-}$ mice which have reduced numbers of Th1 cells developed increased atherosclerosis and, interestingly, they were found to have increased frequencies of Th17 cells [51]. However, in other circumstances Th17 cells were found to protect from atherogenesis. Analysis of IL-17 expression in plaques from patients with carotid or coronary atherosclerosis revealed a correlation between IL-17 levels and markers of plaque stability [52]. Similarly, attenuation of atherosclerosis in *Ldlr*$^{-/-}$ mice lethally irradiated and reconstituted with SOCS3-deficient T cells was associated with increased production of IL-17 [52]. The authors also found that IL-17 neutralisation abrogated the atheroprotective effect of T-cell-specific SOCS3 deletion. A recent study that investigated the effects of B cell depletion on atherogenesis in *Apoe*$^{-/-}$ or *Ldlr*$^{-/-}$ mice found that atherosclerosis reduction was accompanied by decreased IFN-γ levels, increased production of IL-17 from T cells and a skewing from a Th1-driven pro-atherogenic to a Th17-dominated atheroprotective immune response [53]. Further studies are thus required to clarify the contribution of Th17 cells to atherosclerosis and other chronic inflammatory disorders.

Inflammation and Immune Disregulation in Microvascular Angina

Microvascular angina refers to a group of patients without atherosclerosis of the epicardial coronary arteries that develop typical angina-like chest pain and a positive exercise stress test. Patients with microvascular angina are a heterogeneous group with some patients displaying no overt atherosclerotic lesions in epicardial vessels, others showing subclinical atherosclerosis and others dispaying minor non-obstructive atherosclerosis (i.e. irregularities or very mild stenosis <20 %) [54, 55]. Although the prognosis of these patients is relatively better regarding survival compared to patients with coronary artery disease, microvascular angina dramatically impairs the quality of life of these patients and may also affect long term prognosis. The mechanisms of microvascular dysfunction in patients with microvascular angina are still unclear. Endothelial dysfunction as evidenced by increased carotid artery intima-media thickness [56], has a pivotal role in causing abnormalities in the coronary microcirculation in these patients [57]. It has been suggested that traditional cardiovascular risk factors such as hypercholesterolemia, hypertension, obesity and smoking, contribute not only to coronary atherosclerosis but also to microvascular angina, as they impair endothelium-dependent vasodilatation of coronary microvessels [58]. An increase in the vasoconstrictor activity of the endothelium mediated by endothelin-1 has also been implicated in microvascular angina [59]. Other mechanisms for endothelial dysfunction in microvascular angina are oestrogen deficiency (which may explain the prevalence of microvascular angina in postmenopausal women), insulin resistance and inflammation [60–62]. Patients with microvascular angina have elevated levels of C-reactive protein (CRP) [61], soluble CD40L [63], IL-1 receptor antagonist [64], and circulating adhesion molecules such as vascular adhesion molecule-1 (VCAM) and intercellular adhesion molecule-1 (ICAM) [65], suggesting an important contribution of inflammation to microvascular angina and not only to coronary atherosclerosis. Moreover,

some data suggest that increased CRP levels correlate with the severity of symptoms in patients with microvascular angina [61]. Whether the presence of endothelial dysfunction influences the prognosis of microvascular angina is still debatable. Some authors found that endothelial dysfunction in patients with microvascular angina associated with an increased occurrence of coronary events in these patients [66], while others did not identify any spontaneous acute coronary events in patients followed up for more than 10 years [67]. These findings suggest that endothelial dysfunction and subclinical atherosclerosis are present in patients with microvascular angina and have a role in the pathogenesis of this entity. Although the contribution of immune cells in general, and of T cells in particular, in atherosclerosis is widely accepted, little information is available on the involvement of the immune system in microvascular angina. In a pilot study, we found that the frequency of $CD4^+CD28^{null}$ T cells was significantly higher in patients with microvascular angina compared to healthy controls. $CD4^+CD28^{null}$ T cells had a mean frequency of 4.17 (mean ± SEM, 4.17 ± 1.4) in the microvascular angina group compared to 0.52 (mean ± SEM, 0.52 ± 0.18, $p < 0.001$) in the healthy controls (Dumitriu et al., manuscript in preparation). As this subset of T cells produces high levels of inflammatory cytokines and is endowed with cytotoxic abilities, it could contribute to endothelial dysfunction and inflammation in patients with microvascular angina. Further characterisation in microvascular angina patients of various subsets of T cells with known deleterious or protective role in atherosclerosis would provide a better understanding of the pathogenesis of angina. As microvascular angina patients have significantly better prognosis than CAD patients, it is tempting to speculate that mechanisms are in place that actively protect them from developing atherosclerotic plaques (for example increased levels of regulatory T cells) and severe acute coronary events. This makes microvascular angina patients an interesting group for future research into the mechanisms that govern atherosclerotic plaque development.

Future Directions

Modulation of T cell responses in atherosclerosis could provide a useful addition to the therapeutic arsenal of cardiologists. However, a better understanding of the immune alterations present in patients with atherosclerosis is a prerequirement for achieving this goal. Another important consideration is that T cells have many 'flavours' and very diverse functions, and optimal modulation would require subset-specific targeting to facilitate elimination/inhibition of pathogenic T cells (i.e. Th1, $CD4^+CD28^{null}$ T cells) coupled with augmentation of subsets that protect against atherogenesis (i.e. Treg cells). Of note, some of the therapeutic agents that are being used in patients with CAD have important effects on T cells. For example, statins, which were designed to lower lipid levels, were found to have important immunomodulating activities. Interestingly, the frequency of circulating $CD4^+CD28^{null}$ T cells is significantly decreased in ACS patients that receive statins [68]. Moreover, statins were found to elevate Treg cell numbers in ACS [69]. Another study showed that treatment with neutralizing antibodies against tumour necrosis factor-α (TNF-α) improved endothelial function in RA patients [70]. Whether anti-TNF-α antibodies could have protective roles in atherosclerosis, remains to be investigated. Further research into the immune mechanisms of atherosclerosis in both animal models and the human disease holds great potential for unraveling novel strategies to tackle this disease.

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Microvascular Coronary Dysfunction Post–Myocardial Revascularization

16

Guarini Giacinta and Mario Marzilli

Abstract

Subcellular events that occur during the ischemic phase and after the restoration of coronary blood flow in patients with myocardial infarction are key factors responsible for the development of post revascularization microvascular coronary dysfunction. Indeed, ischemia-reperfusion injury has been recognized to attenuate the benefits of coronary revascularization in ACS. Clinically, ischemia-reperfusion injury can be manifested as the no-reflow phenomenon. In the following section ischemia-reperfusion injury and the no-reflow phenomenon are discussed with special attention to pathogenesis, prognostic information and diagnoses.

Keywords

Coronary microcirculation • Microvascular dysfunction • No-reflow phenomenon Ischemia-reperfusion injury

Pathophysiology

In the last 20 years, large efforts have been dedicated to the prevention and treatment of acute coronary syndromes (ACS). The introduction of reperfusion strategies (mechanical and pharmacological) have decreased the overall mortality for ACS, but have been less effective in reducing morbidity associated to acute myocardial infarction. As matter of fact, it is expected that in the next 20 years the prevalence of heart failure and coronary artery disease in the United States will approach 3.5 and 9.3 %, respectively [1]. Limitations of current reperfusion strategies can be largely explained by the processes that occur during the ischemic period and at the time of reperfusion – globally defined as ischemia-reperfusion injury (IRI). Noteworthy, several studies have clearly demonstrated that the salvage of jeopardized myocardium depend on (a) total ischemic time (b) microcirculatory Integrity, and (c) myocytes and non-myocytes (endothelial cells and fibroblasts predominantly) preservation after the ischemia–reperfusion sequence [2, 3]. Along with these conclusions are data deriving from animal studies in which it has been clearly demonstrated that restoring blood flow to ischemic myocardium can directly induce myocardial injury. This phenomenon, termed myocardial reperfusion injury, can substantially attenuate the benefits expected from myocardial reperfusion.

Myocardial reperfusion injury is defined as irreversible injury and death of cardiac myocytes that were viable before reperfusion. Ischemia-reperfusion injury decreases and negates the infarct-reducing effects of myocardial reperfusion by independently inducing cardiac myocytes death. Jennings was the first to introduce the concept of IRI [4]. This irreversible injury is characterized by morphological alterations that appear after the onset of reperfusion at the level of the coronary microvasculature. They include cardiomyocyte swelling, mitochondrial clarification, intracellular calcium phosphate deposition, hypercontracture, and loss of sarcomere organization. It is important to note that the ischemic damage appears and becomes irreversible after 30–40 min of ischemia, while the reperfusion injury occurs within minutes from coronary blood flow restoration.

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A number of pathophysiologic mechanisms have been postulated to explain the occurrence of ischemia-reperfusion injury (IRI) with the focus on the central role of the coronary microcirculation. However, it is generally accepted that IRI is the result of a cascade of events including the "endothelial trigger" and "the inflammatory amplification" steps [5]. Indeed, histological studies have documented plugging and activation of platelets and leukocytes in the coronary microcirculation. As a consequence, microvascular vasoconstriction and thrombosis is observed, facilitated by the release of free oxygen radicals, proteases, and pro-inflammatory mediators. Increased oxidative stress, reduced bioavailability of nitric oxide, elevated levels of endogenous endothelin, activation of the local renin-angiotensin system, intracellular calcium overload contribute to irreversible damage. Complement activation is another important factor because it favours the release of histamine and increases cell permeability. As a result, endothelial cell and myocyte swelling can be observed, along with endothelial protrusion in the vessel lumen (blebs) and interstitial oedema. All these modifications/changes in the structure and function of endothelial and surrounding cells condition the development of coronary microvascualr dysfunction following AMI.

One major determinant of endothelial dysfunction [6] is the loss of the endothelial cells capacity to release nitric oxide (NO) [7], which occurs early after reperfusion (within 2.5–5 min following re-establishment of flow). The reduced release of NO from the ischemic-reperfused endothelium occurs immediately after reperfusion, persists for hours, and appears to be related to superoxide radicals production by the abrupt reoxygenation [8]. A component of the reduced NO bioavailability is enhanced quenching of NO by superoxide radicals. Therefore, the final infarct area is the result of processes that are initiated during vessel occlusion and adjunctive damage at the onset of reperfusion. These observations have two major consequences. First, they impose to recanalize an occluded artery and re-oxygenize an ischemic tissue as soon as possible in order to reduce ischemic damage and second, they mandate the use of protective strategies at the time of reperfusion to limit further myocardial damage. The importance of lethal reperfusion injury is strongly supported by the reduction of infarct size with "protected" reperfusion [9–11]. The beneficial effect of cardioprotective strategies is higher when reperfusion is achieved early (less than 2 h), i.e. when viable myocardium is still present in the area at risk. Obviously, reperfusion damage contributes little to final infarct size when the myocardium is reperfused later, after ischemic cell death is completed.

Many strategies have been shown to be effective in preventing IRI. Ischemic preconditioning and postconditioning are cardioprotective in human as well as animal hearts. The mechanisms of cardioprotection from IRI appear to involve the RISK pathway and the inhibition of mitochondrial permeability transition pore (PTP) opening. The mitochondrial PTP is a nonselective channel of the inner mitochondrial membrane. Opening the channel collapses the mitochondrial membrane potential and uncouples oxidative phophorylation, resulting in ATP depletion and cell death [12]. During myocardial ischemia, the mitochondrial PTP remains closed, and it only opens within the first few minutes after myocardial reperfusion in response to mitochondrial Ca^{2+} overload, oxidative stress, restoration of physiologic PH and ATP depletion [13, 14]. The RISK pathway [15] refers to a group of protein kinases that when specifically activated during myocardial reperfusion, confer cardioprotection by preventing lethal reperfusion injury [16]; in a sense, the RISK pathway mediates a form of programmed cell survival. There is extensive preclinical evidence that activation of the RISK pathway by pharmacologic agents or by mechanical interventions such as ischemic preconditioning or post-conditioning may reduce myocardial infarct size by up to 50 % [17, 18].

Angiographycally, microscopic tissue changes associated with IRI can manifest as the no-reflow phenomenon. The no-reflow phenomenon implies lack of myocardial tissue reperfusion despite successful epicardial coronary recanalization [19–23]. This phenomenon occurs in a large portion of patients with ACS, ranging from about 40 to 20 % depending on diagnostic modalities [24, 25]. Ischemia and reperfusion are the major players involved in the pathogenesis of no-reflow. In addition, the no-reflow phenomenon has also been attributed to the embolization of thrombus and plaque debris from mechanical fragmentation of the vulnerable plaque by PCI [26, 27]. Distal embolization has been found in 9–15 % of patients undergoing primary percutaneous coronary intervention (PCI) for STEMI, and has been associated with an eightfold increase in 5-year mortality [28]. However, the inefficacy of distal protection devices and thrombus aspiration has seriously questioned the role of microvascular obstruction due to plaque debris in precipitating the no-reflow phenomenon. The incidence of coronary microvascular dysfunction and no-reflow is related to the ischemic time [29]. Factors that are more likely associated to endothelial dysfunction and the no-reflow phenomenon are the metabolic syndrome [30, 31] and hyperglycemia [32], while chronic statin therapy seems to protect from it [33, 34]. The observed benefit may be related to pleiotropic effect of statins (improving endothelial function) more than to a decrease in fat content of the coronary plaque. Patients with pre-infarction angina (ischemic preconditioning) appear to be protected from the development of the no-reflow phenomenon [35, 36].

Significance

The clinical relevance of coronary microvascular dysfunction is underscored by the negative prognostic impact of no-reflow [13]. Patients with the no-reflow phenomenon

Table 16.1 Invasive assessment of the no-reflow phenomenon

Invasive methods to detect no-reflow
1. TIMI flow grades (TFGs)
2. Corrected TIMI frame count (cTFC)
3. TIMI myocardial perfusion grade (TMPG)
4. Myocardial Blush Grade (MBG)
5. Coronary blood flow velocity
6. Intracoronary Doppler ultrasound
7. Microvascular Resistance Index (IMR)

Table 16.2 Non-invasive assessment of the no-reflow phenomenon

Non-invasive methods to detect no-reflow
1. ST segment-resolution (STR) on ECG
2. Persistent/recurrent chest pain
3. Perfusion arrhythmias
4. Myocardial contrast echocardiography
5. Cardiac magnetic resonance imaging

are at higher risk to develop congestive heart failure and death [20]. Hombach et al. have shown that persistent microvascular dysfunction is a stronger predictor than ejection fraction of late left ventricular remodelling and survival [37].

Diagnosis and Prognosis

The important role played by coronary microvascular dysfunction in predicting patients prognosis after acute coronary syndromes has drawn attention on how to properly assess myocardial reperfusion. Invasive methods during primary PCI and non-invasive techniques in addition to other clinical parameters like haemodynamic stability, resolution of chest pain and ST elevation, reperfusion arrhythmias are currently used to assess coronary microvascular status following myocardial revascularization. Invasive diagnostic techniques to evaluate no-reflow after primary angioplasty, including grading of flow in the infarct vessel, grading of myocardial blush by angiography and coronary flow velocity measurement with intracoronary Doppler wire are listed in Table 16.1, while non-invasive techniques are listed in Table 16.2.

Coronary Angiography

Of the many diagnostic modalities currently employed for the assessment of reperfusion, coronary angiography has been considered the "gold standard". Angiographic assessment is based on the Thrombolysis in Myocardial Infarction (TIMI) flow grade determination in the epicardial infarct related artery (IRA). Flow grade 0 or 1 represented failed reperfusion, whereas flow grade 2 or 3 represented epicardial patency and successful reperfusion. The incidence of no-reflow, judged on the basis of the initial TIMI classification, is around 10–15 %. Although restoration of TIMI flow grade 3 has been used as the gold standard for reperfusion success, distal coronary flow can vary considerably despite flow grade 3 in the epicardial vessel, with subsequent differences in prognosis [38, 39]. Indeed, among patients with TIMI grade 3 flow, those in which microvasculature fails to open (TMPG 0/1) have a sevenfold increase in mortality (from 0.7 to 5.4 %) compared to those with both TIMI grade 3 flow in the epicardial artery and at myocardial level. Achievement of TIMI grade 3 flow in both the artery and the myocardium is associated with a lower mortality rate (under 1 %) [40].

Electrocardiography

Evaluating ST segment resolution (STR) with serial electrocardiograms was first recommended as a useful bedside marker of reperfusion success by Braunwald and Maroko 25 years ago. This measurement can be very simply performed on a 12-lead electrocardiogram taken within few hours after primary PCI. Indeed, Brodie et al. have demonstrated that partial or poor STR was associated with higher rates of in-hospital mortality, re-infarction, urgent target vessel revascularization, higher values of peak creatine kinase and MB fraction, and a lower left ventricular ejection fraction at follow-up. STR was also strongly correlated with late cardiac survival (mean follow up of 11 years), with survival curves for complete, partial, and poor STR values that diverged over time. After adjusting for other variables (including TIMI flow after PCI), absolute ST-segment elevation after PCI was a significant independent predictor of late cardiac mortality (hazard ratio 1.63, 95 % confidence interval 1.06–2.50, $p = 0.028$). When only patients who had TIMI grade 3 flow after PCI were considered, STR, measured as absolute ST-segment elevation after PCI, remained a strong independent predictor of late cardiac mortality (hazard ratio 1.69, 95 % confidence interval 1.08–2.66, $p = 0.022$) [41].

One of the main limitations of invasive assessment of microvascular coronary dysfunction following myocardial revascularization is the temporal limitation. Indeed, an angiographic "snapshot" of coronary anatomy cannot describe the fluctuations in coronary flow over time that have been reported during the acute phase of myocardial infarction in 35–50 % of patients. In contrast, the ST-segment changes observed on the electrocardiogram (ECG) can provide a continuous, non-invasive, real time physiologic marker of cellular reperfusion. Continuous ST segment monitoring provides information regarding the speed and stability of reperfusion achieved and thus, may be more useful than evaluating ST segment resolution at fixed time points. Finally, restoration of normal myocardial perfusion is associated

with complete ST resolution and earlier STR on continuous ST-segment monitoring. Rapid ST-segment resolution within 30–60 min of successful primary angioplasty predicts greater improvement in ejection fraction, reduced infarct size and improved survival as compared with delayed ST segment resolution.

Noninvasive Imaging

To provide more information regarding the coronary microcirculation and the no-reflow, image modalities like myocardial contrast echocardiography (MCE) [42–44] and cardiac magnetic resonance imaging (cMRI) [45, 46] may be employed. Contrast-enhanced MRI can accurately characterize the presence and spatial extent of no-reflow regions, discriminate between areas of necrosis with and without no-reflow, and provide clinically meaningful predictive information regarding left ventricular remodelling and patient outcome [47–49]. cMRI perfusion measurements are mainly performed with T1-shortening contrast agents such as gadolinium-DTPA either by visual analysis or based on the analyses of signal intensity time curves. For the detection of myocardial ischemia the first pass kinetics of a gadolinium-DTPA bolus and for the detection of myocardial necrosis and the definition of viable myocardium steady state distribution kinetics are assessed. Quantitative analysis of myocardial perfusion can be performed but requires complex modelling due to the characteristics of gadolinium-DTPA. Thus, semi-quantitative parameters are preferred. Myocardial infarction and microvascular dysfunction can be reliably detected and the infarcted area determined. Non-reperfused infarcted myocardium can be differentiated from reperfused myocardium by different enhancement patterns that correlate to myocytes viability. Francone et al. using cMRI [50] observed that patients reperfused within <90 min had a smaller infarct size, showed less severe microvascular damage and greater myocardial salvage after reperfusion, whereas patients reperfused later (>6 h) presented with larger infarcts and greater microvascular obstruction and limited, if any, myocardial salvage. They also reported that the area at risk reduced over time only in patients reperfused within 90 min while it progressed to irreversible damage when reperfusion was achieved later. These data clearly confirms that the potential for myocardial salvage decrease dramatically with time and that after 90 min of ischemia there is limited benefit, if any, in term of infarct size reduction [3]. Cardiac magnetic resonance is a promising technique that can combine different functional studies during one examination, such as the assessment of wall motion and perfusion at rest and stress.

Myocardial contrast echocardiography (MCE) which utilizes microbubbles can assess myocardial perfusion in real time. These microbubbles remain exclusively within the intravascular space, and their presence within any myocardial territory denotes the status of microvascular perfusion within that region [51]. The volume of blood present in the entire coronary circulation (arteries, arterioles, capillaries, venules, and veins) is roughly 12 mL/100 g of cardiac muscle, and approximately one-third of this is present within the myocardium itself and is termed myocardial blood volume (MBV) [52]. The predominant (90 %) component of MBV resides within the capillaries. Myocardial contrast intensity reflects the concentration of microbubbles within the myocardium. When a steady state of microbubble concentration has been achieved in the myocardium, during a continuous infusion of contrast, the observed signal intensity denotes the capillary blood volume. Thus, any alteration in signal intensity in this situation occurs principally because of a change in capillary blood volume. Furthermore, it has been shown that following destruction of microbubbles in the myocardium with high-energy ultrasound, myocardial contrast replenishment, both during low and high power, reflects myocardial blood velocity. The product of these two components denotes myocardial blood flow at the tissue level. Thus, MCE can detect capillary blood volume and, by virtue of its temporal resolution, can also assess myocardial blood flow [44]. Its ability to assess myocardial perfusion and function in one examination allows it to ascertain the extent of myocardial reperfusion achieved in the risk area. Furthermore, in stable patients after AMI, MCE allows assessment of coronary no-reflow, LV function, residual myocardial viability, and ischemia which are all powerful prognostic markers of outcome [36]. Its portability, rapid acquisition and interpretation of data, and the absence of radiation exposure make it an feasible bedside technique to assess coronary mycrovascular function early after ACS [53].

Conclusions and Future Directions

At the time of AMI, the angiographic display of an occluded epicardial artery with intra-luminal thrombus and slow or even absent anterograde flow that persists after recanalization led to the widely accepted opinion that the coronary microcirculation is an innocent bystander in the initial phase of the acute coronary event but becomes dysfunctional in its aftermath. In support to this hypothesis, the results of several studies that were able to confirm myocardial microcirculatory dysfunction after AMI but they were not designed to answer the question as to whether this predated the initial acute coronary event. The presence of myocardial microcirculatory dysfunction is in fact a strong predictor of clinical outcome, including future acute coronary events, even in the absence of haemodynamically significant epicardial disease [54]. These data are consistent with the findings of Britten et al., who followed patients with angiographically normal or

minimally diseased coronary arteries over an average of 6.5 years and noted a more than threefold higher cardiovascular event rate in patients in the lowest compared with the highest tertile of coronary flow reserve (CFR) (18 vs. 5 %, P = 0.019) with 36 % of all events related to ACS [55]. Taken together, there is a growing body of multi-layered evidence to suggest that the integrity of the coronary microcirculation plays an integral role in the evolution of STEMI. In line with the concept of the primary significance of the myocardial microcirculation, pre-existing transient or permanent microcirculation coronary dysfunction may contribute to the development and prognosis of ACS via reduction of coronary blood flow, leading to an alteration of shear stress and thereby aggravation of endothelial function on epicardial level as well as aggravation of thrombus formation. If indeed microcirculatory dysfunction is considered as it is one of the major contributors to the evolution and not just the consequence of an AMI, this could substantially alter future research directions and approaches to therapy. Nonetheless, it could exert an influence upon the selection of adjuvant therapy prior and/or following the revascularization procedure. Identifying the coronary microvasculature as an important determinant of myocardial perfusion both in normal and in the presence of atherosclerotic coronary disease, will perhaps in the near future direct scientific research towards the development of new therapeutic and preventive strategies, this time aimed at the world be discovered, that of the coronary microcirculation, whose role in ischemic heart disease is still poorly recognized.

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The Role of Microvascular Coronary Dysfunction in Acute Myocardial Infarction

17

Andreas J. Flammer, Bernard J. Gersh, and Amir Lerman

Abstract

The role of the coronary microcirculation in acute myocardial infarction is not yet completely understood. Microcirculatory coronary dysfunction can be a consequence of the primary event secondary to a severe flow-limiting lesion or occlusion in an epicardial infarct-related artery – or alternatively microcirculatory coronary dysfunction may be a contributor to the clinical course of the coronary event.

The aim of this chapter is (1) to provide the reader with essential information about the physiology of microvascular coronary dysfunction in the context of acute myocardial infarction, (2) to describe the different viewpoints concerning causality in addition to the consequences of microvascular coronary dysfunction in myocardial infarction and to (3) discuss the impact of microvascular coronary dysfunction on patient' management and therapy.

Keywords

Microcirculation • Acute myocardial infarction • Microvascular coronary dysfunction

Abbreviations

ACE	Angiotensin Converting Enzyme
ACh	Acetylcholine
ACS	Acute coronary syndrome
AMI	Acute myocardial infarction
CBF	Coronary Blood Flow
CFR	Coronary Flow Reserve
ECG	Electro Cardiogram
ET	Endothelin
MRI	Magnetic Resonance Imaging
MVO	Microvascular obstruction
NO	Nitric Oxide
NOS	Nitric Oxide Synthase
NTG	Nitroglycerin
PCI	Percutaneous Coronary Intervention
PET	Positron Emission Tomography
SPECT	Single Photon Emission tomography
STEMI	ST-elevation myocardial infarction
TIMI	Thrombolysis in Myocardial Infarction

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Introduction: Microvascular Coronary Dysfunction in the Context of Myocardial Infarction

Blood flow to the different regions of the heart is constantly adapted to different needs and changing physical and hemodynamic conditions, primarily achieved by changes in vascular resistance within the microcirculation to match blood flow with myocardial oxygen consumption. During exercise,

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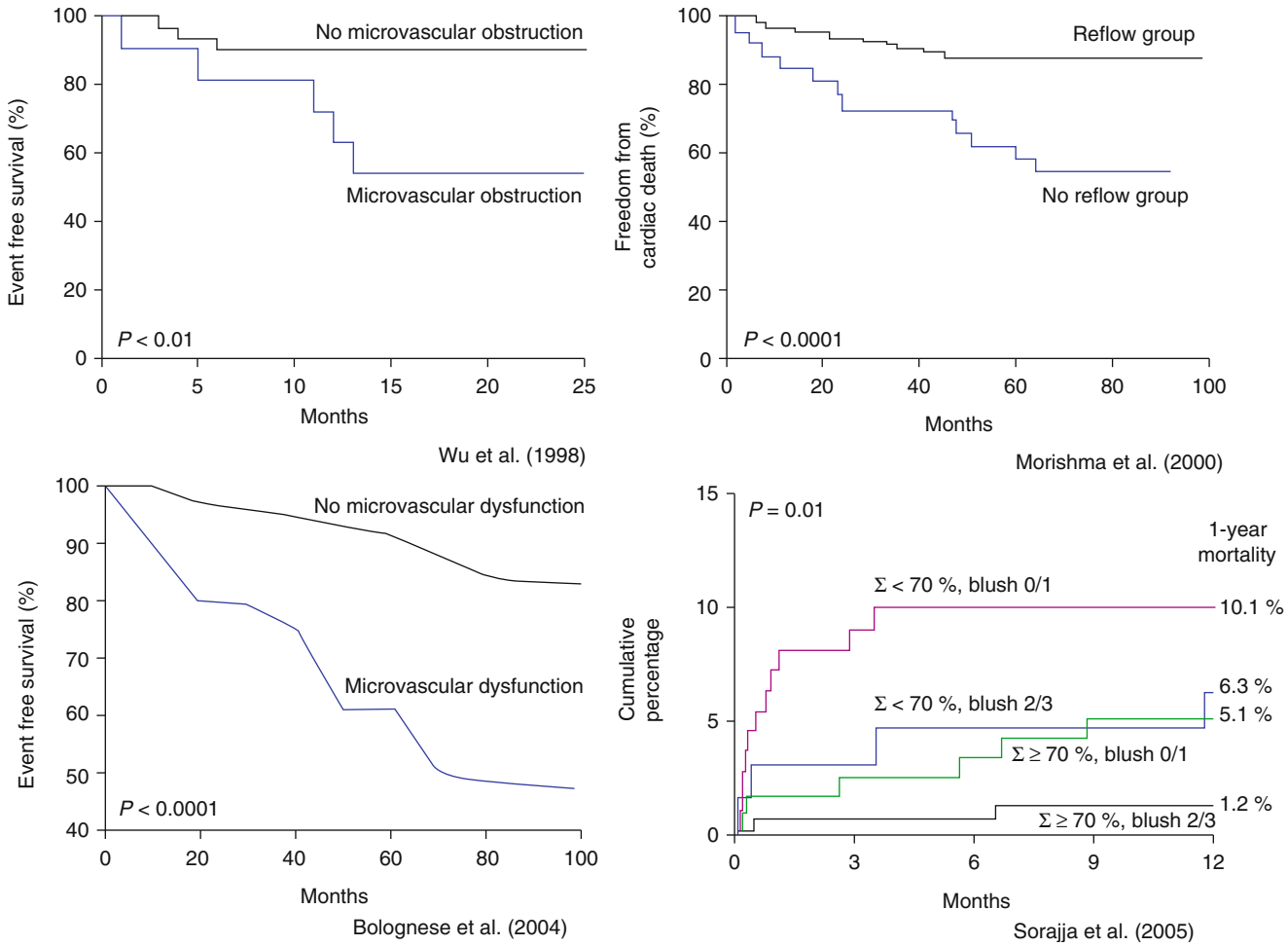

Fig. 17.1 Impact of microvascular coronary dysfunction on prognosis after myocardial infarction. Figure depicts four important prognostic studies assessing the risk of microvascular coronary dysfunction in myocardial infarction. All studies show significant reduction in event free survival in patients with microvascular impairment as demonstrated by magnetic resonance imaging (*upper left*), angiographically by TIMI flow (*upper right*), intracoronary myocardial contrast echocardiography (*lower left*) as well as a combination of ST segment recovery and myocardial blush (*lower right*). Σ = ST segment recovery (Adapted from [5, 7, 8, 153])

mental stress or other stimuli, the coronary vasculature increases blood flow to a maximum level to match myocardial oxygen demand. This maximal increase is referred to as coronary flow reserve (CFR) and is mainly a measurement of the ability of the microvasculature to respond to a stimulus and therefore to adapt to the metabolic requirements of the myocardium [1]. In obstructive coronary artery disease and in acute myocardial infarction, microvascular coronary function will thus be significantly impaired.

Myocardial infarction, ST-elevation myocardial infarction (STEMI) in particular, is a devastating condition with a high mortality if not treated rapidly. Reperfusion of the (partly-) closed vessel is the mainstay of therapy. In recent decades, intense research and the introduction of reperfusion techniques like thrombolysis and percutaneous coronary interventions like balloon angioplasty and stenting have resulted in major improvements in outcomes [2]. Although time to treatment is critical and the objective of many research protocols, early successful reopening of the infarct related artery is still often accompanied with suboptimal myocardial perfusion, with all its negative prognostic implications [3–5].

The mechanisms underlying myocardial malperfusion are complex and not fully understood. One proposed and logical explanation is that it is a consequence of the initial event or the result of reperfusion injury, which refers to the phenomenon of slow or no-reflow, inadequate myocardial perfusion without evident mechanical vessel obstruction [6], an angiographic expression of microvascular coronary dysfunction [7]. Indeed, microvascular coronary dysfunction has been documented in most studies after an acute event and is indicative of an impaired prognosis (Fig. 17.1) [5, 7–9, 153]. No-reflow on angiography strongly predicts 5-year mortality, independent of infarct size, in patients with STEMI and was significantly more common in patients with clinical factors associated with worse prognosis after infarction, as age, or previous cardiovascular disease [10]. Interestingly, no-reflow might be reversible in some cases, which is associated with a better prognosis [11].

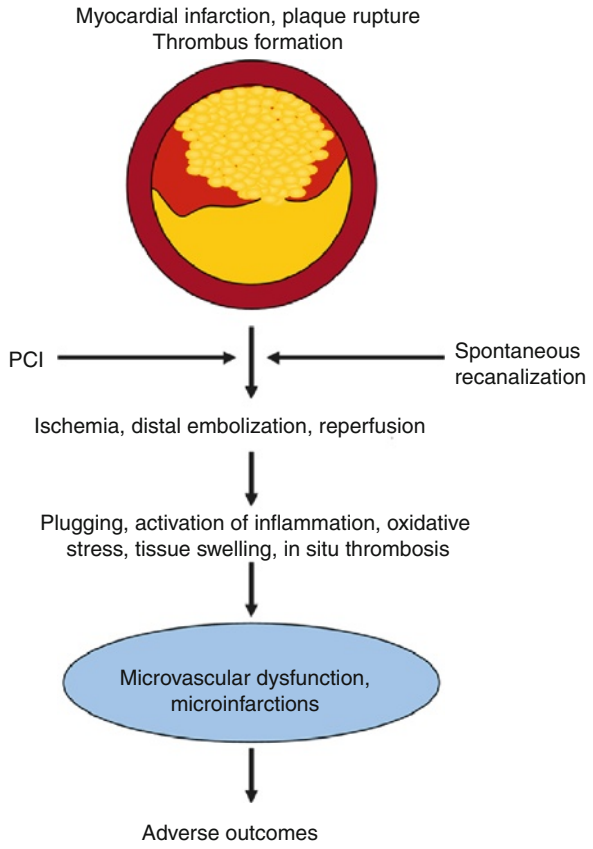

Fig. 17.2 Classical pathway of events. The schematic figure depicts the classical sequence of events from myocardial infarction to spontaneous or iatrogenic distal embolization to microvascular coronary dysfunction with its adverse outcomes

The role of the coronary microcirculation in the setting of ACS is further underscored by the observation that coronary blood flow (CBF) is significantly reduced not only in the culprit but also in the non-culprit coronary arteries, both before and after an acute coronary intervention [12]. However, whether microcirculatory dysfunction is a mediator or a simply a consequence of the initial event, secondary to edema or elevated left ventricular filling pressures is still a matter of debate.

Microvascular Coronary Dysfunction as a Consequence of Myocardial Infarction

Microvascular coronary function can be acutely impaired mechanically as a consequence of myocardial infarction by plugging of small vessels with thromboembolic debris (Fig. 17.2). In this context, the term microvascular obstruction (MVO) was generated [13]. By injecting microspheres into coronary vessels, it has been shown experimentally in dogs, that CBF, as a function of microvascular function, can be severely impaired depending on the size and volume of microspheres [14]. In another study in dogs, microembolization induced a progressive reduction in regional function without a measurable decrease in regional flow but in association with an intense inflammatory response [15]. This suggests that not only might 'mechanical' emboli be released into the microcirculation, but in addition a series of 'chemical' processes could result in an impairment of microcirculatory perfusion of the myocardium. There is abundant evidence to support mechanical obstruction as a cause of myocardial malperfusion. A pathology study in patients dying of an ACS revealed spontaneous, thrombotic distal embolization leading to occlusion of the small intramyocardial arteries thus causing microinfarctions [16]. A subsequent autopsy study confirmed distal microembolization of atherothrombotic debris after myocardial infarction in most patients who died after angioplasty or thrombolysis [17]. With the introduction of balloon angioplasty, concerns about distal embolization of atherothrombotic material due to intervention surfaced and, were supported by multiple studies which showed a correlation between the severity of microvascular impairment with the magnitude of reduction in plaque volume after PCI [18, 19]. Distal protection devices finally provided definitive morphological proof by retrieving atherothrombotic debris, which would have presumably otherwise embolized into the myocardial microcirculation [20]. Therefore there has been a large interest in mechanically preventing thrombotic material into the periphery, but - except for interventions in saphenous venous grafts [21] – trials with different devices have provided mostly negative results, presumably because they might have caused further physical damage to the endothelium and did not prevent atherothrombotic embolization or microvascular coronary dysfunction due to biochemical processes [22–24].

However, in the setting of acute myocardial infarction, manual thrombus aspiration by nontraumatic aspirations catheters have provided significant improvements in myocardial perfusion which was translated into a reduction in mortality in these patients [25, 26]. This highlights the possibility that distal embolization may actually precede the intervention and is also consistent with the possibility that the process of coronary thrombosis is dynamic with thrombosis and also spontaneous lysis. The totality of evidence from multiple sources strongly supports the clinical significance of distal coronary embolization.

In acute myocardial infarction, myocardial and endothelial injury can also be induced by direct ischemic damage (Fig. 17.2). Ischemia- related injury is characterized by endothelial protrusions and membrane-bound bodies leading to luminal obliteration. Furthermore these findings are accompanied by reduction of regional blood flow and myocardial cell swelling is associated with interstitial edema [27–29]. In addition to the damage induced by the limitation of blood flow, indirect biochemical mechanisms may result in incremental damage. Debris material analyzed from embolization protection devices revealed a high concentration of biologically active inflammatory mediators at the site of infarction, which might be released into the coronary

microcirculation [30]. In addition, microparticles further impair microvascular endothelial function as a consequence of pro-inflammatory and procoagulant activity [31]. Furthermore vasoactive factors, most notably vasoconstrictive endothelin-1 and tissue factor are likely to be involved, as they are expressed in active plaques and in the plasma of these patients [32, 33]. Moreover, slow-flow during PCI is associated with higher fibrofatty plaque volume over the entire lesion length, suggesting that in myocardial infarction, slow flow may be dependent on the tissue characterization of the culprit lesion [34].

In order to restore blood flow, reperfusion technologies are applied as fast as possible. It is well recognized that the successful achievement of flow in the epicardial infarct-related artery might not necessarily be accompanied by myocardial perfusion or infarct size [27]. In the experimental setting the term reperfusion injury was introduced as a description of the aggravation of ischemia-related myocardial injury by the restoration of CBF. Reperfusion injury refers to myocardial stunning, infarction extension, reperfusion arrhythmias and vascular stunning and endothelial function, respectively [35]. The literature about reperfusion injury is abundant but the vast bulk of the data emanate experimental animal studies [36] and a majority of human studies modifying reperfusion injury were not able to show cardioprotective benefit [37]. It is not clear to what extent reperfusion injury is relevant in the clinical setting and whether the process is one of accelerating necrosis in cells already destined to die as opposed to increasing the extent of infarction [38], a long-standing debate which continues.

In the experimental model of ischemia/perfusion, the series of pathophysiologic processes that characterize reperfusion injury have been quite well characterized. As a consequence of the restoration of blood flow to ischemic tissue, oxygen and other reactive molecules interact with hypoxic, abnormal cellular environments, which might produce further damage [29]. At the time of reperfusion of the microcirculation, activation of neutrophils and platelets, representing mainly plaque debris, takes place, thus leading to cell adhesion and migration. These cells then release oxygen free radicals and pro-inflammatory mediators. Moreover neutrophils may aggregate with platelets further plugging the microvasculature. Damaged cells again mediate vasoconstriction [39–41] and increase oxidative stress, further leading to a reduction in nitric oxide (NO) bioavailability and activation of the local endothelin and renin-angiotensin system with an increase in intracellular calcium. In addition, histamine is released as a consequence of complement activation and increases cell permeability [42].

Reperfusion of severely ischemic myocardium can also lead to intramyocardial hemorrhage by leakage of red blood cells through damaged endothelial vessels and reduce the change of recovery [43]. It occurs in about 25 % of patients with acute myocardial infarction after reperfusion and is associated with larger infarct size [44].

Taken together, a decrease in microvascular function after myocardial infarction is the rule and not the exception. The longer the duration of ischemia prior to reperfusion, the greater is the degree of microvascular coronary dysfunction, implying a cause and effect relationship. Distal embolization, in situ thrombosis, activation of inflammation, edematous swelling of tissue due to ischemia, vasoconstriction and reperfusion injury might play an important role in this multifactorial process, further increasing the damage of myocardial infarction [45].

Preexisting Microvascular Coronary Dysfunction and Its Impact on Myocardial Infarction

As pointed out earlier [46], there is a growing body of evidence to suggest that the integrity of the coronary (micro-)circulation plays a crucial role in the evolution of an acute myocardial infarction. From a mechanistic or pathophysiological standpoint, it is certainly feasible and there is evidence to support the concept that preexisting transient or persistent microcirculatory dysfunction might well contribute to the development and prognosis of myocardial infarction via a reduction in CBF, as opposed to it's role as a consequence of MI. Preexisting microvascular coronary dysfunction could result in alterations in shear stress on the epicardial level and lowering endothelial function and aggravate thrombus formation.

In this context, it is important to keep in mind that the presence of microvascular coronary dysfunction is an independent and strong predictor for clinical outcome, even in the absence of significant epicardial disease [47]. In one study of patients with only mild coronary artery disease, future cardiovascular events are limited to those with a reduction of CBF response to acetylcholine [48] and a more than three-fold higher cardiovascular event rate has been observed in patients in the lowest compared with the highest tertile of CFR in similar patients [49]. Even in patients with apparently normal coronary angiograms but chest pain, an almost three-fold higher mortality for the patients with microvascular coronary dysfunction (abnormal CFR) after an average of 8.5 years was found [50].

Importantly, patients characterized by myocardial microcirculatory dysfunction in association with the presence of cardiovascular risk factors have in general a higher risk of acute coronary events as well as worse consequences following ischemia and reperfusion than patients without these characteristics. Clinically, a significant microvascular coronary dysfunction can be found in asymptomatic early stages of atherosclerosis in patients with cardiovascular risk factors [51], hypercholesterolemia, hypertension, diabetes, in patients

with family history of premature atherosclerosis in particular [52–54]. Diabetes, as well as the accumulation of risk factors in the metabolic syndrome, have significant deleterious effects on myocardial perfusion and infarction size in patients with an acute infarction [55–58]

Moreover, patients with pre-procedural impairment of microvascular function are more likely to have post-procedural microvascular impairment as well as procedure-related injury and a worse outcome [59]. Thus, pre-existing microvascular dysfunction leads to a greater vulnerability to myocardial injury, highlighting the potentially clinically relevant role of a dysfunctional microcirculation and PCI- related damage.

A common denominator to account the adverse effects of microvascular coronary dysfunction, plaque rupture, and cardiovascular risk factors on prognosis could be the finding that inflammatory mechanisms are involved in all of these pathophysiological processes. Indeed in patients with normal coronary angiograms an inverse correlation between CRP serum concentrations and myocardial blood flow to cold pressor test was observed [60] and activation of neutrophils across the coronary circulation has been noted in patients with unstable angina, irrespective of the location of the culprit lesion [61]. Furthermore, the amount of locally produced lipoprotein-associated phospholipase A2, is correlated with the atheroma volume [62] and there is production of oxidative stress and inflammatory markers in the presence of coronary endothelial dysfunction without significant epicardial disease.

In this regard, the finding that the incidence and extent of myocardial injury with PCI, can be lowered by pretreatment with statins is intriguing. The incidence of no-reflow with primary PCI was reduced by 74 % [63] and periprocedural myocardial infarction by 81 % [64] in patients receiving statins before admission for an anterior myocardial infarction. Even short term pretreatment (12 h) with 80 mg atorvastatin in non-ST-segment elevation acute coronary syndromes improved outcomes significantly [65].

Is Microvascular Coronary Dysfunction a Requirement for Myocardial Infarction? – The Vulnerable Microcirculation Hypothesis

Taken into account the importance of preexisting microvascular coronary dysfunction as outlined before one could argue that such a dysfunctional, vulnerable vasculature is indeed a requirement for infarction and not just a mediator. One problem in assessing such a relationship in acute myocardial infarction is the conceptual design of studies so far. If microcirculatory dysfunction can be demonstrated after or during an acute myocardial event it does not automatically imply that this condition has not preceded the event [46]. A major problem herein lies in the diagnostic tools that have been used in most studies to date. With newer techniques, as in MRI first-pass perfusion, the presence of microvascular impairment in patients is indeed as high as 84 % in patients with acute myocardial infarction [66]. One can hypothesize that myocardial damage occurs mainly in patients with a susceptible, vulnerable microvasculature which is prone to react adversely to vasoactive mediators and microparticles as a consequence of regional dissemination of proinflammatory activity [31, 33, 67] with vasoconstriction rather than vasodilatation. The fact that during percutaneous coronary interventions, debris including atherothrombotic material can be demonstrated by the use of distal protection devices argues in favor of embolic microcirculatory obstruction as a consequence of either the initial event or the intervention thus plugging the vasculature. However, coronary microcirculatory vasoconstriction has not only been seen after ST-elevation myocardial infarction and primary PCI with the consequence of atherothrombotic embolization but also during ischemia in patients with unstable angina [68]. Furthermore, in an experimental model in rabbits, it has been shown that plaque rupture lead to a rapid and marked increase in vascular vasoconstriction as opposed to distal embolization [69]. Thus the presence of debris may serve as marker for biochemical processes resulting in microvascular constriction in addition to other potential sequelae, rather than mechanical obstruction. Therefore we can assume that a "vulnerable" microcirculation is likely an integral component rather than an innocent bystander of impaired CFR in ACS (Fig. 17.3).

This might possibly explain, at least in part, the observation that at the same time a plaque rupture can remain clinically silent and (normal microvascular coronary function), on the other hand, have devastating consequences (impaired microvascular coronary function). Interestingly, autopsy studies in sudden cardiac death patients demonstrate healed older plaque ruptures [70, 71], an intravascular ultrasound-based study demonstrated that many ruptured plaques were encountered in patients with stable angina or no symptoms at all [72] and one study suggested a delay of at least 3 days from plaque rupture to the classical presentation of an acute myocardial infarction [73]. Moreover, although many plaques do progress over time, others can stabilize or even heal, as shown in a virtual histology study in patients [74]. The fact that the damage might be dependent on other factors rather than plaque rupture alone is also highlighted in patients with ACS where an intravascular ultrasound study observed multiple and not just one plaque rupture [75] and angioscopic as well as IVUS images suggest thrombosis in the absence of ruptured plaque [76].

When studying microvascular coronary function in patients with stable single vessel disease, it is remarkable that microvascular coronary function is impaired even in

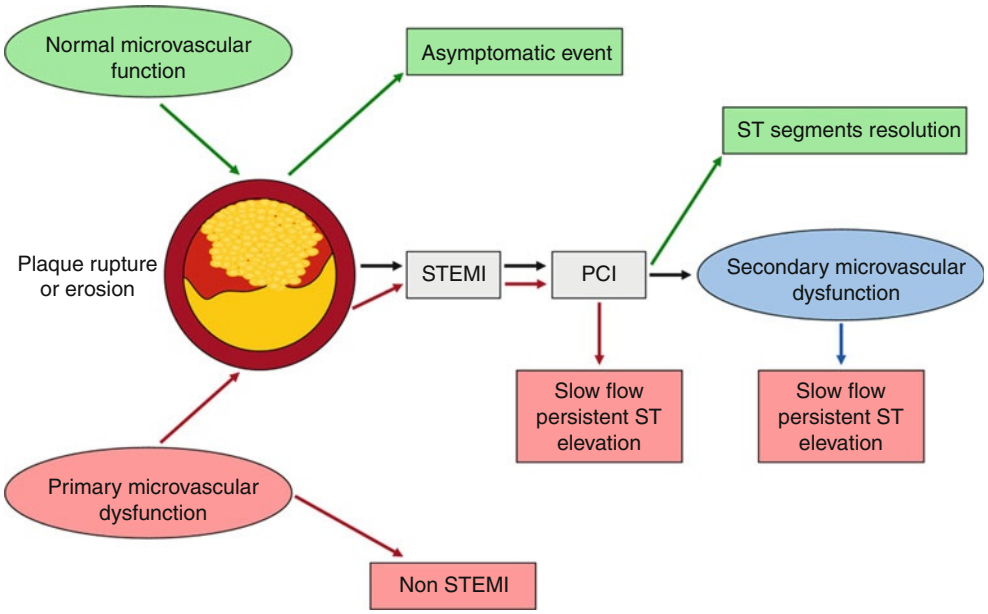

Fig. 17.3 The role of microvascular coronary dysfunction in acute myocardial infarction. Normal microvascular function (*green boxes* and *arrows*) might lead to an asymptomatic event despite plaque rupture and/or prompt recovery of ST-segment resolution (and thus secondary microvascular coronary dysfunction). Preexisting (primary) microvascular coronary dysfunction (*red boxes* and *arrows*) might lead to non ST-segment myocardial infarctions per se and might be the prerequisite for an acute ST-elevation myocardial infarction. Slow flow and persistent ST-elevation after *PCI* might be due to primary microvascular coronary dysfunction and/or secondary microvascular coronary dysfunction due to mechanical or chemical embolization (see text)

those myocardial territories supplied by angiographically normal coronary arteries [77]. Thus, these regions are involved in the pathophysiology of the disease or are at least also affected by acute events. This might explain why in patients with stable angina, persistent symptoms may be present even after successful intervention of the diseased vascular segment. Furthermore, the observations that impaired CFR before coronary intervention predicts post-procedural CFR and procedure-related myocardial injury can also be explained on the basis of pre-existing microvascular coronary dysfunction which renders the heart prone to injury [18, 59].

An argument against the vulnerable microcirculation hypothesis could be that in experimental models, structural evidence of myocardial injury precedes evidence of microvascular injury [78]. However, dysfunction of the microvascular endothelium develops independently form myocardial stunning after ischemia and reperfusion [79], and ST-segment recovery in the ECG relates to infarct zone wall motion and late survival in the presence TIMI II or III flow but persistent ST segment elevation in this context might represent persistent microvascular coronary dysfunction, thus pointing towards a potential dissociation between cardiomyocyte function and coronary blood flow [80–82] Importantly, in early stages of reperfusion, apoptosis occurs first in microcirculatory endothelial cells with a subsequent spread to the surrounding myocytes, thus highlighting the significance of the microcirculation for myocyte viability [83].

Can Microvascular Coronary Dysfunction Trigger a Myocardial Infarction?

Although disputed years ago [84], with the beginning of the reperfusion area and the demonstration that the earlier the angiography is performed the greater the likelihood of complete occlusion [85], coronary thrombus formation is believed to be a primary event in acute myocardial infarction, due to plaque rupture in most cases. However, despite novel plaque imaging tools as intravascular ultrasound, angioscopic or optical coherence tomography, a culprit plaque rupture cannot be demonstrated in up to an intriguing 40 % [86–88].

Nonetheless, whether preexisting microvascular coronary dysfunction could be sufficiently severe in some cases to trigger a thrombotic event or even plaque rupture and subsequent thrombus formation, respectively, due to slow flow is intriguing. In this context, it is questionable if microvascular coronary function and CBF, respectively, can deteriorate so acutely and extensively as to contribute to thrombosis due to slow flow. However, acute impairment in microvascular function has been shown postprandial in patients with diabetes.

In addition a dysfunctional endothelium is more sensitive to catecholamines, which may explain the increase in cardiac events with stressful live events [89]. Research in this field is hampered by the fact that there is only scarce data on microvascular coronary function prior to the acute coronary event.

Interestingly, in up to 12 % of patients with an acute MI, normal coronary arteries are documented during prior coronary angiography, another indirect hint that the vulnerable myocardial microcirculation is crucial in triggering ACS [90]. A similar phenomenon can be seen in infiltrative heart disease like in Fabry disease or amyloidosis, where the high frequency of angina is presumably due to impaired microvascular function [91].

Recently tako-tsubo cardiomyopathy (apical ballooning), a particular variant of the presentation of MI in the presence of non-obstructive epicardial coronary arteries has been recognized [92], and was first reported with a reference to multivessel coronary artery spasm [93]. Later on, studies confirmed that provocation with intracoronary injection of acetylcholine lead to coronary vasoconstriction in most of these patients and microvascular spasm has been demonstrated by angiogram, nuclear studies and invasive microvascular testing [92–98]. Because of the common presence of reduced TIMI flow [99] and a spontaneous improvement in CFR in most patients [100], the microvasculature has been proposed to play a crucial role in the disease.

In a recent contrast-echocardiography study by Crea et al., the contribution of the microcirculation has been convincingly demonstrated. They showed that irrespectively of the etiology, a common pathogenetic mechanism is reversible coronary microvascular vasoconstriction with subsequent regional myocardial dysfunction [101].

This condition highlights the possibility of acute myocardial infarction due to myocardial microvascular coronary dysfunction, although other explanation for tako-tsubo must be taken into account.

The Impact of Microvascular Coronary Dysfunction on Diagnosis, Management and Therapy in Patients with Acute Myocardial Infarction

There are several diagnostic modalities that play a role in the evaluation of microvascular perfusion and microvascular function, respectively, in the setting of myocardial infarction: electrocardiographic ST-segment changes, angiographic measures of flow, magnetic resonance imaging, intracoronary measurement of flow velocity by Doppler, and contrast echocardiography.

Angiographic methods during catheterization, for example the assessment of TIMI flow and myocardial blush, have been used routinely. This techniques uses the kinetics of dye penetration, and has been reviewed in detail [102].

Even if angiographically a TIMI 3 flow is documented after reperfusion of myocardial infarction, a high incidence of sub-optimal microvascular reperfusion persist as assessed by the index of microcirculatory resistance (measurement by pressure wire: mean distal coronary pressure times hyperemic transit time) [103]. Using this method, still 30 % exhibit microvascular coronary dysfunction despite revascularization. Additionally the index of microcirculatory resistance measured in patients with acute myocardial infarction provides important prognostic information [104, 105].

After myocardial infarction, although direct imaging of the coronary microvasculature is difficult, patients with residual ST segment elevation after reperfusion could point towards high risk patients, which might warrant more intensive treatment to reduce afterload and attenuate infarct expansion [106]. A <70 % reduction in the amount of ST-segment elevations indicates successful reperfusion, however, there is no consensus about the timing of the ECG and which exact measure is to analyze [107]. Incomplete ST segment resolution is associated with microcirculatory function in Doppler flow wire measurement and myocardial contrast echocardiography [82, 108]. Persistence of microvascular coronary dysfunction, 7 days after infarction seems to be the most important predictor for adverse remodeling [109] and intracoronary Doppler flow measurements confirmed a close relationship between microvascular coronary dysfunction and microvascular obstruction as assessed by magnetic resonance imaging after 4–8 day [110].

Variation in ST segment resolution within the first 72 h after a PCI treated STEMI has been shown to depend upon the status of the microvasculature as defined my MRI [111]. In this study an ECG done at 48–72 h after ST elevation PCI is an accurate predictor of microvascular coronary obstruction, intramyocardial hemorrhage, infarct size and area at risk. [111]

Recently, imaging techniques are becoming more and more reliable and available to measure microvascular function after myocardial infarction, single photon emission computed tomography (SPECT), for example. With this technique there was an 80 % concordance with angiographic methods [112], however, angiographic evaluation did not correlate with SPECT defined infarct size at 3 month [113]. An important limitation of this technique is its poor spatial resolution. Promising studies arise using intracoronary myocardial contrast echocardiography and significant correlations to angiographic methods have been demonstrated. With this method, CFR can be quantified noninvasively and compares well to SEPCT and MRI [114–116]. Microvascular coronary damage as assessed by myocardial contrast echocardiography can help to predict further outcome in patients with STEMI [117]. Its advantage is also the high spatial and temporal resolution. Cardiovascular magnetic resonance is able to detect microvascular perfusion and to identify no-reflow very accurately [118] but is limited by its cost and availability as well as its difficult use in the acute setting. Interestingly, whereas angiographically assessed low myocardial blush was a good predictor for microvascular coronary dysfunction in cardiovascular MR, normal myocardial blush did not exclude microvascular obstruction. Therefore angiographic quantification might be indeed specific, but not sensitive for microvascular damage after myocardial infarction [119].

For the acute management of no-reflow, potentially the direct administration of the NO-releasing drug nitroglycerin is able to dilate large conduit coronary artery. Interestingly, vasodilatory therapy with nitroglycerin was not able to improve clinical outcome in myocardial infarction, a fact supporting the concept of microvascular coronary function as a main contributor to myocardial infarction as nitroglycerin, in contrast to nitroprusside, has no impact on the coronary microcirculation and thus is unable to increase coronary blood flow [120]. This is due to the lack of enzymatic conversion of nitroglycerin to nitric oxide in the resistance-regulating arteries. Indeed, a study showed that infusing nitroprusside instead of nitroglycerin shows a significant higher rate of TIMI 3 flow and TIMI frame count in patients with STEMI undergoing PCI with distal protection device (Table 17.1) [146]. However, another study was associated with a statistically borderline improvement of clinical outcome after 6 months but no improvement in coronary flow [136]. Studies with Ca-Channel blockers demonstrate the potential to attenuate microvascular coronary spasm and to reduce myocardial ischemia and infarct size [121, 124, 147]. Similar results were achieved by infusion of the endogenous purine nucleoside analogue adenosine, however, the data is not conclusive [125, 128, 129]. In one large study, adjunctive, acute-phase treatment with atrial natriuretic peptide after reperfusion therapy in patients with acute myocardial infarction reduced infarct size by 14.7 %, increased the left ventricular ejection fraction during the chronic phase, and decreased the incidence of cardiac death and readmission to hospital because of heart failure, effects attributed to an increase in nitric oxide and activation of G kinase [143].

A high burden of thrombus could more likely result in distal physical and chemical embolization and thrombus aspiration has been shown to beneficially affect outcome [25]. Potentially there is a benefit for antithrombotic therapy like glycoprotein IIb/IIIa inhibitors in this situation [148–150].

Applying the concept of intracoronary hyperoxemic reperfusion for the prevention of reperfusion injury, improved microvascular blood flow and decreased infarct size has indeed been seen experimentally [151]. Hoverer, although in humans this approach did reduce infarct size, there was no improvement in tissue perfusion [152]. Recently cytoprotective strategies by pharmacological

Table 17.1 Vasodilatory and cardioprotective drugs on microvascular coronary function in human myocardial infarction studies

Author (year) [Ref.]	Study description	No. of patients	Effect
Ca-antagonists			
Taniyama et al. (1997) [121]	IC verapamil vs. placebo	40	Improved microvascular function (myocardial contrast echocardiography)
Werner et al. (2002) [122]	IC verapamil Nonrandomized study in consecutive patients with no reflow after PCI	23	Reversal of no-flow in 65 % (angiography)
Hang et al. (2005) [123]	IC verapamil Nonrandomized, prospective study with a retrospective control group	50	Improved TIMI flow
Vijayalakshmi et al. (2006) [124]	IC verapamil vs IC adenosine vs. placebo	150	Verapamil and adenosine improved TIMI flow
Adenosine			
Marzilli et al. (2000) [125]	IC adenosine vs placebo	54	Improved angiographic no-reflow, clinical outcome
Barcin et al. (2004) [126]	Adenosine vs adenosine and nitroprusside	41	Improved TIMI flow in the combination group
Claeys et al. (2004) [127]	Ic adenosine vs historical cohort	79 (vs. 200)	Improved myocardial reperfusion as assessed by ST-segment elevation
Micari et al. (2005) [128]	IV Adenosine vs. placebo	30	Improved microvascular function (myocardial contrast echocardiography) and infarct size
Ross et al. (2005) [129]	IV adenosine vs placebo Multicenter study Multicenter study	2,118	High dose adenosine reduced infarct size but not outcome. No effect with low dose adenosine
Stoel et al. (2008) [130]	IC Adenosine vs. placebo Randomized, placebo-controlled study in patients with <70 % ST-segment resolution after PCI	51	Improved ST-segment resolution and TIMI flow
Fokkema et al. (2009) [131]	IC Adenosine vs. placebo after thrombus aspiration and stenting	448	No difference in residual ST-segment elevation. No difference in outcome
Desmet et al. (2011) [132]	IC adenosine vs. placebo Double-blind randomized	112	No effect on myocardial salvage or microvascular obstruction (MRI) and on TIMI flow

(continued)

Table 17.1 (continued)

Author (year) [Ref.]	Study description	No. of patients	Effect
Nitroprusside			
Hillegass et al. (2001) [133]	Iv Nitroprusside Retrospective study in patients who developed no-reflow	19	75 % of patients showed improved TIMI flow
Wang et al. (2004) [134]	Ic Nitroprusside	11	Improvement in TIMI flow in 9 out of 11
Pasceri et al. (2005) [135]	Ic Nitroprusside	23	Improvement in TIMI flow
Amit et al. (2006) [136]	Iv Nitroprusside vs. placebo	98	No improvement in microvascular function and tissue reperfusion (TIMI) but improved outcome
Shinozaki et al. (2007) [137]	Ic Nitroprusside vs control Nonrandomized, prospective study with a retrospective control group	120	60 % reduction in slow reflow (TIMI)
Nicorandil			
Sakata et al. (1997) [138]	Ic Nicorandil	1	Disappearance of no-reflow
Ito et al. (1999) [139]	Iv bolus followed by 24 infusion of Nicorandil then oral, vs. placebo	81	50 % reduction in incidence of no reflow (myocardial contrast echo)
Ikeda et al. (2004) [140]	Iv bolus followed by 72 infusion of Nicorandil vs. Nitroglycerin	60	Improved ST-segment resolution and improved LV function
Ishii et al. (2005) [141]	Single IV nicorandil administration before reperfusion. Randomized double-blind	368	Reduced angiographic no-reflow, improved ST segment resolution and clinical outcomes after mean 2.4 years
Kawai et al. (2009) [142]	IV bolus of nicorandil before PCI vs. placebo	408	Decreased incidence of slow-reflow
Atrial Natriuretic Peptide (ANP)			
Kitakaze et al. (2007) [143]	IV ANP, IV Nicorandil, IV placebo	1,216	Lower infarct size and better outcome in patients with ANP, however no effect of Nicorandil
Cyclosporine			
Piot et al. (2008) [144]	IV Cyclosporine vs placebo	58	Smaller infarct size (MRI)
Morphine			
Rentoukas et al. (2010) [145]	Morphine, Remote ischemic periconditioning	96	Improved ST Segment resolution

conditioning and administration of cyclosporine or morphine have been evaluated with mixed success [144, 145]. However, more specific therapies for microvascular function on the time of acute coronary syndrome presentation are desperately wanted.

Dozens of agents that have worked experimentally have failed in the clinical setting, likely because by the time they are given the impact might be too late, whereas in animal models many of these drugs were given as pre-treatment. If microcirculatory coronary dysfunction is demonstrated to be one of the major contributors to the evolution and not just the consequence of myocardial infarction, future therapies, even though they will not change clinical practice to restore coronary blood flow and myocardial perfusion, should be designed to improve microvascular coronary function before or during an acute event. Because abnormalities of endothelial function in the coronary microcirculation occur before structural changes are noted, early identification of asymptomatic individuals with intermediate or low cardiovascular risk is important. This would allow implementing adequate preventive treatment strategies in early stages of the disease process. In theory, lifestyle factors and medications that increase the release or prevents the degradation of endothelial derived relaxing factors, NO in particular, and those which decrease production of endothelial-derived constricting factors such as endothelin among others, should improve endothelial function. Therefore, measures to maintain endothelial functional integrity make sense from a primary prevention standpoint and conceivably could reduce microvascular coronary dysfunction before, during and after a myocardial infarction.

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Part IV

Diagnosis

Diagnostic Algorithms

18

Filippo Crea and Gaetano Antonio Lanza

Abstract

Microvascular angina (MVA) is the likely diagnosis in most patients with chest pain typical enough to suggest obstructive coronary artery disease, but who show normal coronary arteries at angiography. A definitive diagnosis, however, requires documentation of coronary microvascular dysfunction (CMVD). To this aim, invasive methods, in particular, intracoronary Doppler wire recording of coronary blood flow is the reference method, but they can not be applied widely in routine clinical practice. Transthoracic Doppler echocardiography is a suitable non invasive method for the routine assessment of CMVD in patients with normal coronary arteries. Alternative methods include cardiovascular magnetic resonance, myocardial contrast echocardiography and positron emission tomography. These methods, however, are excellent research tools but have limitations for worldwide application in clinical routine. In patients with suspected MVA, CMVD should be assessed with endothelium-independent dilator stimuli, i.e. adenosine or dipyridamole and with the cold pressor test to assess endothelium-dependent vasodilation. The response to intracoronary administration of vasoconstrictor stimuli (like ergonovine or acetylcholine) is useful in patients with suspected coronary artery spasm

Keywords

Microvascular angina, diagnosis • Transthoracic echo-Doppler • Contrast echocardiography Cardiac magnetic resonance • Positron emission tomography • Intracoronary Doppler

Introduction

A large body of clinical studies has demonstrated that cardiac syndrome X (CSX), which is constituted by the triad of stable effort angina, ischemia-like ST-segment depression during exercise stress test and normal coronary arteries at angiography, is usually related to myocardial ischaemia caused by coronary microvascular dysfunction (CMVD), a condition that is better defined as microvascular angina (MVA) [1, 2].

In clinical practice, the diagnosis of MVA is usually achieved by exclusion, i.e., based on the absence of obstructive coronary artery disease (CAD), and after excluding other cardiac diseases (e.g., cardiomyopathy, valve heart disease and pericardial disease, vasospastic angina).

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Although the exclusion of other diseases remains crucial for a correct diagnosis, we have recently proposed that efforts should be done to prove the diagnosis of MVA by showing the presence of CMVD [3].

It would be highly desirable to distinguish patients with MVA from those with obstructive CAD on the basis of a careful assessment of clinical findings and non invasive investigation only, which would avoid to the patient the small but definite risk associated with coronary angiography and would also have favourable effects on costs and use of medical resources. Unfortunately, although some clinical characteristics of chest pain, clinical history and non invasive tests may suggest the diagnosis of MVA, the angiographic documentation of normal coronary arteries is usually needed.

In this chapter we review the main clinical diagnostic features of MVA and the methods that can be applied to achieve the diagnosis of MVA.

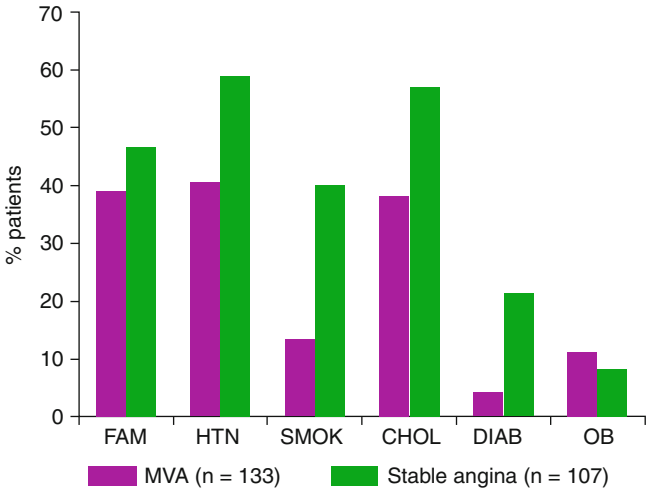

Fig. 18.1 Prevalence of cardiovascular risk factors in a series of consecutive patients with stable effort angina and a diagnosis of obstructive coronary artery disease or of microvascular angina (MVA). *CHOL* hypercholesterolemia, *DIAB* diabetes, *FAM* familiar history of coronary artery disease, *HTN* hypertension, *OB* obesity, *SMOK* active smoking

Clinical Clues to Diagnosis of MVA

Chest Pain

In most cases chest pain in MVA patients is indistinguishable from that occurring in patients with obstructive CAD. The patients present indeed typical constrictive retrosternal pain, induced by efforts and relieved in a few minutes by rest. In some patients, however, some characteristics of chest pain may suggest a relation with CMVD rather than with obstructive CAD.

These include, in particular, (1) the persistence for several minutes of a dull chest discomfort, after the resolution of a typical acute chest pain, following the interruption of an effort, and (2) a similar persistence of a chest discomfort after pain relief by nitroglycerin (NTG) assumption, or even a poor or inconstant response of chest pain to short-acting nitrates [4, 5]. In a comparison between 133 patients with the clinical features of MVA and 107 patients with stable angina and obstructive CAD at angiography, a persistence of chest discomfort after pain resolution was reported by 48 and 13 % of patients, respectively, whereas NTG relieved angina pain within 5 min in 53 and 89 % of patients, respectively (unpublished data).

Clinical History

The general clinical characteristics of patients are also often unhelpful to identify patients with MVA. Classical cardiovascular risk factors, including hypertension, diabetes, hypercholesterolemia, obesity and smoking, are often present in MVA patients as in CAD [6–9] (Fig. 18.1), as also are some recently recognized new risk factors for atherosclerosis, such as an increased status of inflammation and of insulin resistance [10, 11].

In contrast with CAD patients, however, MVA patients are predominantly women [4, 12]. This gender difference does not help significantly when angina appears in postmenopausal women, as CAD incidence also significantly increases in women after menopause. Instead, the appearance of anginal pain in regularly menstruated women or in the peri-menopausal period should always raise the possibility of MVA.

Non Invasive Testing

Usually, the characteristics of ST-segment depression induced by exercise stress test (severity, extension, recovery) do not allow distinguish between CAD and MVA patients [13, 14] (Fig. 18.2).

Similarly, the analysis of the episodes of ST-segment depression detected during daily life on Holter recordings has revealed comparable characteristics in these two populations of patients, including a high prevalence of silent ischaemic episodes and a bimodal circadian distribution, with prevalence in the morning and mid-late afternoon [14–16]. Analogous considerations apply to the detection of reversible perfusion defects on stress (exercise or pharmacological) myocardial scintigraphy (Fig. 18.2) [17, 18].

In contrast, the absence of left ventricular regional wall motion abnormalities on echocardiography during typical chest pain and ischaemic ST-segment changes, induced by pharmacological (dipyridamole, adenosine, dobutamine) or exercise stress test, strongly supports CMVD as the cause of angina pain [19–21], in accordance with the notion that the

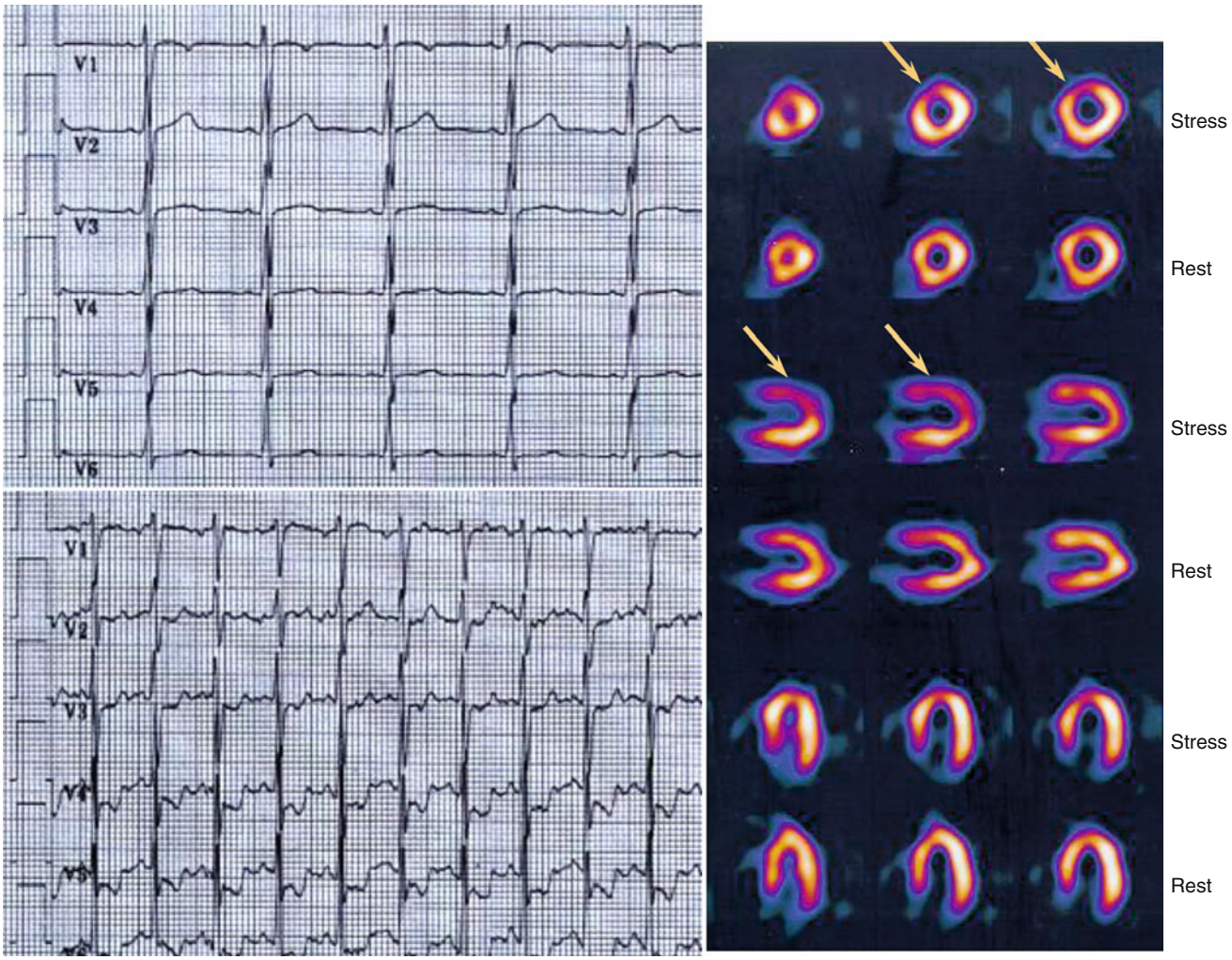

Fig. 18.2 ST-segment depression on the electrocardiogram and reversible perfusion defects at myocardial scintigraphy (*arrows*) during exercise stress test in a patient with typical cardiac syndrome X (effort angina with normal coronary arteries)

patchy distribution of CMVD does not cause detectable regional wall motion abnormalities [22]. It should be taken into account, however, that regional left ventricular dysfunction on echocardiography may also be undetectable in some patients with minor degree of obstructive CAD, despite significant ST-segment changes [23].

Finally, two studies have suggested that valid information to distinguish MVA patients from those with obstructive CAD can derive from the comparison of the results of a baseline exercise stress test (EST) with those obtained when EST is performed after administration of short-acting nitrates [24, 25]. Both studies have indeed shown that nitrates typically delay exercise-induced ischaemic ST-segment changes and angina in obstructive CAD patients, whereas they do not improve ischaemic changes and angina in MVA patients; furthermore, a paradoxical earlier appearance of ST-segment changes can be considered specific for MVA, although this may only be observed in a few patients.

In summary, a careful clinical and non invasive diagnostic assessment of patients with effort angina can provide strong clues to the diagnosis of MVA, in particular when they concur together in individual patients.

Coronary Angiography

In patients with effort angina and signs of myocardial ischaemia at non invasive testing, coronary angiography is usually believed necessary to either confirm or exclude obstructive CAD. This approach is mandatory in patients in whom full clinical assessment and non invasive tests do not provide sufficient clues to the diagnosis of MVA.

In patients, instead, in whom clinical findings and non invasive test results strongly suggest MVA, the exclusion of a significant CAD might be obtained by multislice spiral computed tomography (CT) coronary angiography, which has a high negative predictive value and can avoid the small, but

definite, risk of invasive coronary angiography in most cases [26]. The choice between the two angiographic approaches, however, is difficult and is still a matter of debate.

Diagnosis of CMVD

As said above, a direct documentation of CMVD should be obtained in all patients to confirm the diagnosis of MVA. The functional status of coronary microcirculation in such patients can be assessed by measuring the changes in coronary blood flow (CBF) and/or of coronary vascular resistance in response to vasodilator stimuli known to induce dilatation of coronary microcirculation.

Typically, the stimulus is administered at doses presumed to achieve maximal vasodilation and the vasodilator capacity of coronary microcirculation is measured as the ratio between CBF during maximal vasodilation and basal CBF, which corresponds to the coronary flow reserve (CFR).

The vasodilator stimuli that have more frequently been used in clinical research to this scope are dipyridamole and adenosine. Adenosine induces direct arteriolar dilatation by stimulating A_2 receptors on smooth muscle cells (SMCs), and is known to play a major role in the metabolic regulation of CBF, in particular during ischaemia [27]. The usual dose of adenosine to assess CFR is 0.14 mg/kg/min intravenously, which has been shown to achieve maximal vasodilation in experimental studies [28]. Possible side effects include sinoatrial and atrio-ventricular node conduction blockade and bronchoconstriction, both mediated by A_1 receptors. A relevant advantage of adenosine is its very short half life (10 s), which allows rapid regression of side effects.

Dipyridamole is usually administered at intravenous doses of 0.56–0.84 mg/kg and results in similar effects of adenosine, as it increases the interstitial levels of endogenous adenosine by inhibiting its cell uptake and its consequent degradation [29].

In most patients, particularly in those with normal or borderline response to adenosine/dipyridamole, it would be mandatory to investigate the endothelium-dependent coronary microvascular dilator function. The agent most widely used to this scope is *acetylcholine* [30]. This drug, however, can only be used during invasive procedures as it requires intracoronary infusion. Furthermore, acetylcholine is not the ideal drug to assess endothelium-mediated vasodilation, as it might also have direct constrictor effects on SMCs of predisposed vessels.

An alternative stimulus to assess endothelium-dependent vasodilation is *cold pressor test* (CPT) [31]. CPT is a simple non invasive test which consists in putting a hand in ice water for 90–120 s. Cold and peripheral pain induce sympathetic stimulation that slightly increases heart rate and blood pressure; the consequent enhancement of myocardial oxygen demand increases arteriolar CBF and flow-mediated dilation of prearteriolar vessels. Stimulation of α-adrenergic endothelial receptors also leads to NO release. CPT, however, may also induce α-adrenergic-mediated constriction of SMCs in susceptible vessels, thus complicating the interpretation of its vascular effects. Similar considerations apply to some other stress stimuli, such as handgrip [32].

Finally, in patients with normal or borderline responses to vasodilator stimuli and in those with a significant variability of ischaemic threshold or chest pain at rest, the assessment of the coronary microvascular response to more specific vasoconstrictor stimuli, including hyperventilation, ergonovine and increasing doses of acetylcholine [1, 33–35], can be helpful for documentation of CMVD. Coronary microvascular constriction, however, might be appropriately assessed only during invasive investigation, as possible epicardial constriction cannot be excluded without angiography.

Methods to Assess CMVD

Transthoracic Doppler Echocardiography

Transthoracic colour-Doppler echocardiography (TTDE) is a non invasive method that allows measurement of CBF velocity, taken as a measure of CBF, mainly in the left anterior descending (LAD) coronary artery, which is sufficiently easy to visualize and interrogate by the method [36]. In several patients, however, CBF in the left circumflex and in the posterior interventricular descending coronary artery can also be assessed [36].

Diastolic CBF velocity is measured at baseline and during vasodilator stimuli, and coronary flow reserve is measured as the ratio of hyperaemic peak flow velocity during maximal vasodilator stimuli (usually adenosine) over basal flow velocity (Fig. 18.3). Reproducibility of results is high, with intra-observer and inter-observer variability not exceeding 5–10 % [36].

Several studies have shown that TTDE is reliable in assessing coronary flow reserve, showing good correlation with values obtained with intracoronary Doppler flow wire (ICDW) recording [37, 38] or positron emission tomography (PET) [39], with correlation coefficients ranging from 85 to 97 %.

A significant reduction of coronary flow reserve has been documented with TTDE in patients with CSX [40, 41]. In a recent study, we have assessed CBF response to both adenosine (as an endothelium-independent vasodilator stimulus) and to CPT (as an endothelium-dependent vasodilator stimulus) in 71 CSX patients and in 20 age- and sex-matched healthy controls. Both responses were significantly lower in patients compared to controls (Fig. 18.4) [40]. The correlation between results of the two tests was only moderate. An impaired coronary microvascular dilator response to

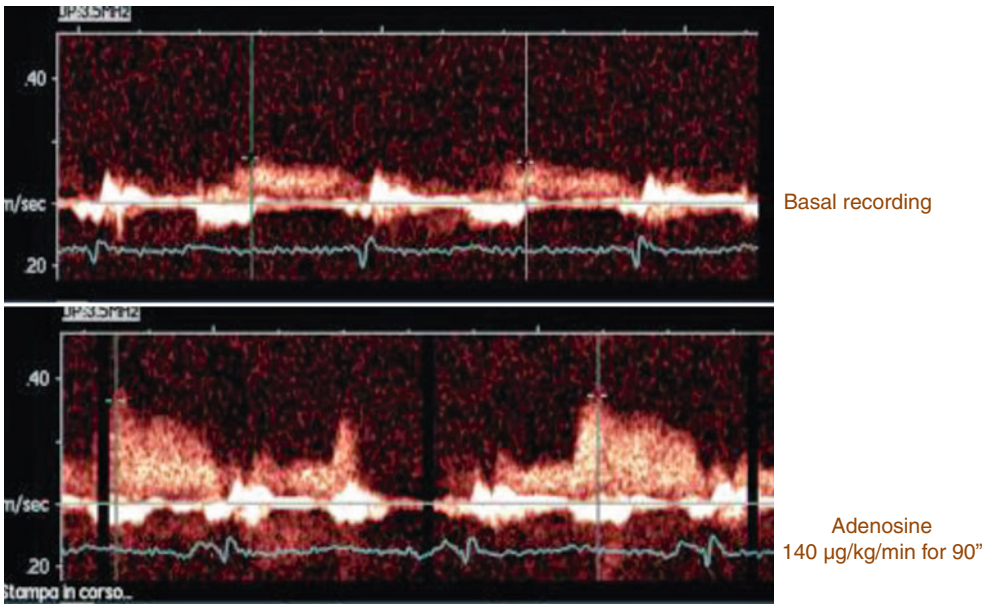

Fig. 18.3 Recording of coronary blood flow velocity by transthoracic Doppler echocardiography at baseline (*top panels*) and at peak adenosine (*bottom panels*) in a healthy control subject

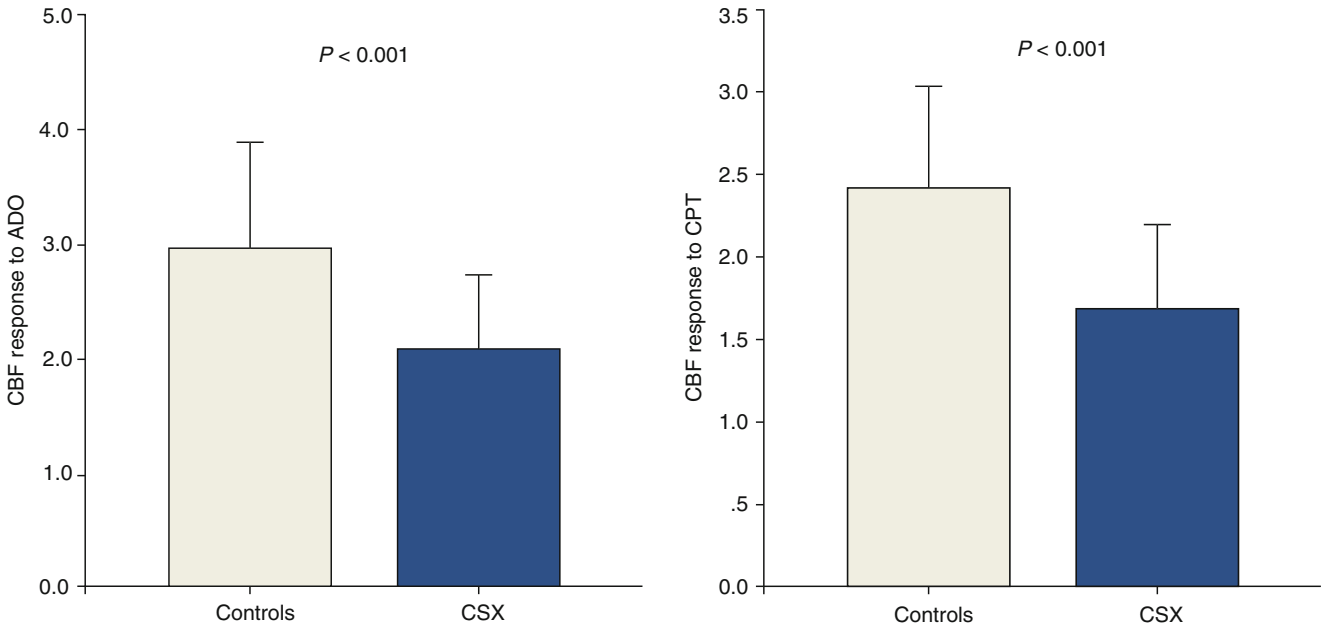

Fig. 18.4 Coronary blood flow response to adenosine and to cold pressor test in 71 patients with cardiac syndrome X and in 20 controls (Modified from Sestito et al. [40]. With permission from Wolters Kluwer Health)

adenosine (CBF increase <2.5) was observed more frequently in CSX patients than an impaired response to CPT (CBF increase <1.6), but only the latter was impaired in a few patients. Importantly, an impairment of coronary microvascular dilator response to both stimuli was not detectable in any healthy control subject, and only 1 out of 20 controls (5 %) showed an impairment of one of the two tests when a restrictive value of CBF response of <2.0 for adenosine and <1.6 for CPT were taken as "abnormal".

In another study we have shown that CFR to adenosine in the LAD artery was significantly lower in CSX patients in whom reversible perfusion defects were detectable on dobutamine stress cardiovascular magnetic resonance (CMR) [42]. Finally, we have also found a significant correlation of CFR to adenosine measured by TTDE and by contrast echocardiography (Fig. 18.5) [43]. These data confirm that TTDE can be considered a reliable method to identify a reduced CFR in most patients, and might constitute a

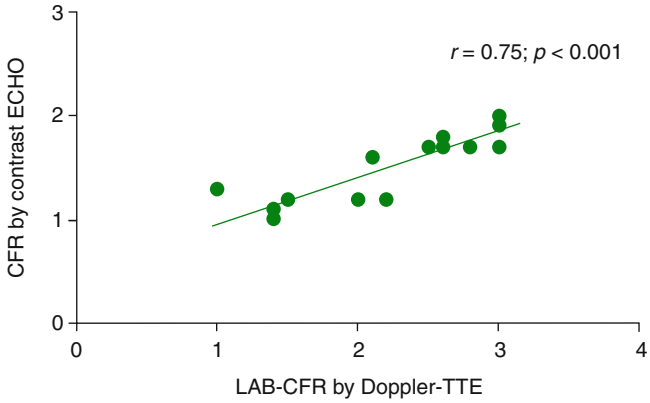

Fig. 18.5 Correlation between coronary blood flow response to adenosine as assessed by transthoracic Doppler echocardiography and by myocardial contrast echocardiography in 17 patients with cardiac syndrome X (Modified from Galiuto et al. [43]. With permission from Elsevier)

reference test to this scope in clinical routine. Compared to other methods, indeed, TTDE presents several advantages; it is non-invasive, easily available at bedside, quick, cheap and suitable for serial measurements to follow coronary microvascular function over time.

Doubtless, however, the method also presents some important limitations. First, at present there is sufficient evidence of its reliability only when coronary microvascular function is assessed in the LAD coronary artery. Second, a good echocardiographic window cannot always be obtained in all patients. Finally, the test requires appropriate experience by the operator.

Myocardial Contrast Echocardiography

Myocardial contrast echocardiography (MCE) is another non invasive imaging to assess myocardial blood flow (MBF) by echocardiography. Microbubbles are injected intravenously, thus acting as a "contrast" agent. The signal derived from microbubbles is proportional to their concentration in the blood and therefore they can be related to myocardial blood volume and MBF. Accordingly, perfusion defects compatible with myocardial ischaemia, appear as completely or partially non opacified areas [44]. Furthermore, by depicting the curve of microbubble intensity over time, a quantitative measure of MBF can be obtained, with values that have been found to correlate well with those obtained with PET [45].

MCE has been found to be helpful in assessing CMVD in acute conditions such as myocardial infarction [46] and takotsubo disease [47]. We have shown lower CFR to adenosine in CSX patients using MCE as compared to controls, with excellent correlation with TTDE results (Fig. 18.5) [43]. It remains to be established whether this method may offer any advantage over TTDE in assessing coronary microvascular function in patients with suspect of MVA.

MCE is easy to perform and has a good cost-effectiveness ratio. However, a wider application in clinical practice has been hampered by safety issues following the report of major adverse events in critically ill patients after contrast administration [48]. However, the available data overall indicate that MCE can be considered a reasonably safe method.

Cardiovascular Magnetic Resonance

Contrast CMR, using gadolinium as a paramagnetic contrast agent, allows a reliable assessment of myocardial perfusion [49].

CMR has helped confirming the presence of CMVD in patients with CSX. Panting et al. first showed an impairment of subendocardial CBF in response to adenosine in these patients [50], and, as mentioned above, we [42] have shown significant perfusion defects to occur during dobutamine stress testing in 56 % of 18 CSX patients (Fig. 18.6), which correlated with a reduction of CFR assessed by adenosine using TTDE.

CMR offers several advantages over other methods in the assessment of microvascular dysfunction, and is becoming the reference method to this aim. It is characterized by a high spatial resolution and is radiation free. Furthermore, it allows the accurate assessment of subendocardial and subepicardial perfusion, together with measurements of regional coronary resistance [51, 52]. Finally, the addition of techniques and tracers that allow assessment of myocardial metabolism may further improve the reliability of this method in detecting ischaemic cardiomycyte abnormalities [32].

CMR cannot be utilized, however, in patients with claustrophobia, arrhythmias and implanted devices. Furthermore, gadolinium has to be used with caution in patients with impaired renal function, in particular if high doses are needed, as it is the case in the measurements of MBF [53].

Positron Emission Tomography

PET allows quantitative measurements of MBF by quantifying the cardiac concentrations over time of specific tracers (usually oxygen-15 labelled water [$H_2{}^{15}O$] or nitrogen-13 labelled ammonia [$^{13}NH_3$] [54]. The most important advantage of PET in assessing coronary microvascular function is that it allows an accurate measure of MBF both at rest and during hyperaemia, which allows to establish whether a reduction of CFR is caused by an impaired increase of MBF (i.e., by a true CMVD) or, rather, by an increase of basal MBF, as observed in hyperadrenergic states. A further

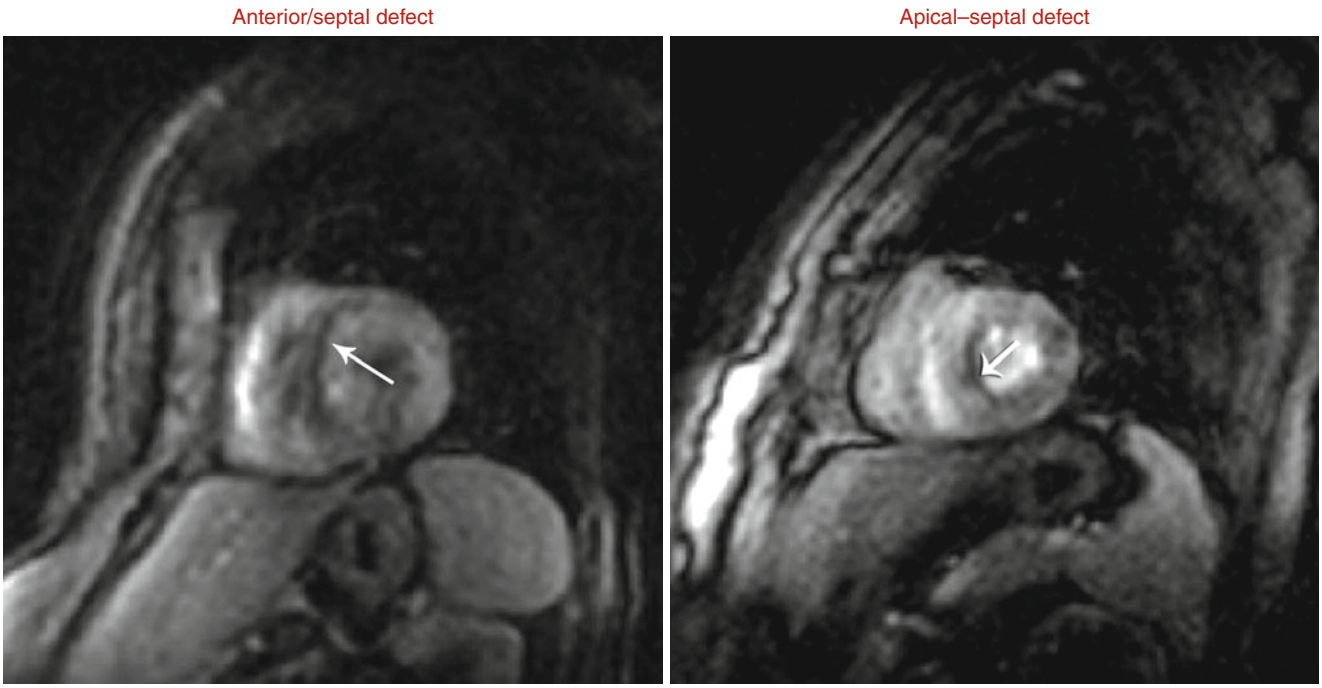

Fig. 18.6 Perfusion defects in the antero-septal (*left*) and in apico-septal (*right*) myocardial regions (*arrows*) detected on cardiovascular magnetic resonance imaging during dobutamine stress test in two patients with cardiac syndrome X (Modified from Lanza et al. [42]. With permission from Elsevier)

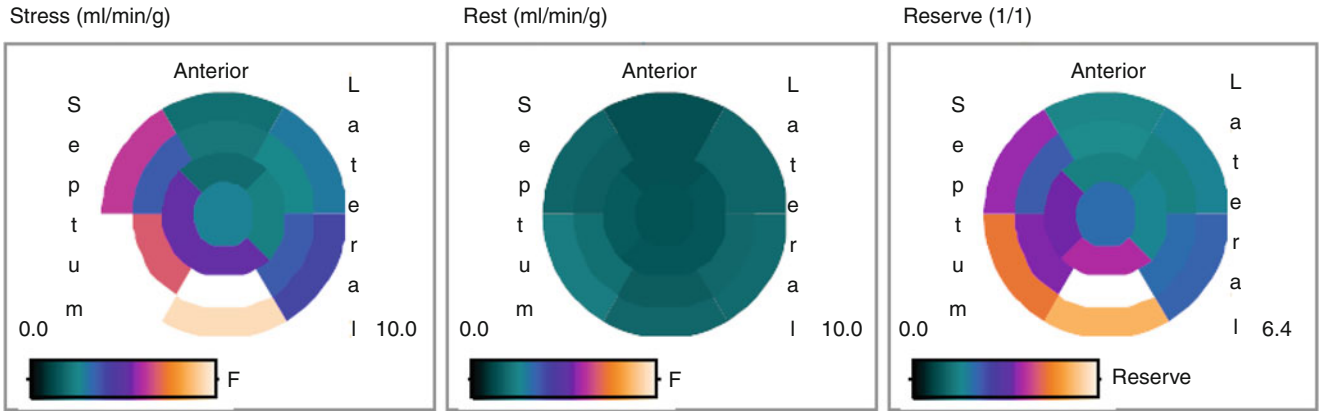

Fig. 18.7 Quantitative analysis of positron emission tomography (PET) with NH^{4+} during (stress) and after (rest) adenosine in a patient with cardiac syndrome X, showing significant reduction of coronary flow reserve (<2.0) in the anterior and antero-lateral regions of the left ventricle (*right panel, green segments*)

advantage of PET is the possibility to assess both global and regional CMVD by a non invasive method (Fig. 18.7).

PET has significantly contributed to characterize CMVD in MVA. Although data have not always been concordant [55], several studies have shown a reduction of coronary microvascular dilation in response to both endothelium-independent, and also endothelium dependent, stimuli [56–59].

Importantly, two studies have shown the presence of heterogeneous MBF after stress testing in MVA patients, supporting the notion that a patchy distribution of CMVD may explain the lack of detectable left ventricular dysfunction during angina and ST-segment depression [58, 59]. The use of tracers that allow assessment of myocardial metabolism, as for CMVR, may improve the detection of myocardial ischaemic abnormalities [60].

Unfortunately, PET has several shortcomings for a wide utilization in clinical practice. The technique is expensive, time-consuming and requires to be performed in specialized centres. Accordingly, the technique is not widely available and has limitations for use in the serial assessment of CMV function. Finally, its resolution (5 mm) is less than optimal, making impossible to detect small areas of MBF abnormalities.

Invasive Methods

Early studies in patients with MVA utilized *thermodilution* or the *gas wash-out method*, both based on the indicator-dilution (Fick's) principle [34, 61]. Quantification of CBF by these methods, however, requires accurate measurement of temperature or of gas concentration in the coronary sinus. The reproducibility of the results is limited and they have now been practically abandoned in clinical practice.

ICDW recording is at present the invasive method of choice to assess CMVD in the absence of obstructive atherosclerosis. ICDW recording allows direct measurement of CBF velocity in single epicardial arteries [62]. Measurement of CBF velocity by ICDW is reliable. Measurement of the cross-sectional area of the vessel is needed to calculate volumetric CBF, but this does not apply in case of normal coronary arteries as variations of epicardial vessel diameter during administration of vasodilator stimuli for assessment of CFR are negligible. An advantage of ICDW recording is that it allows measurement of CBF in the different coronary artery territories.

Several studies have contributed to identifying and characterizing CMVD dysfunction in patients with CSX (Fig. 18.8) [63, 64]. Of note, intracoronary thermodilution can now be performed using intracoronary catheters that incorporate thermal sensors. Intracoronary thermodilution methods are reliable and measurements of CFR correlate well with those obtained by ICDW recording [65].

Invasive methods have inevitable limitations, however. They are more expensive compared to most non invasive methods, have to be done at the time of diagnostic coronary angiography, can be time consuming and may be associated with adverse events.

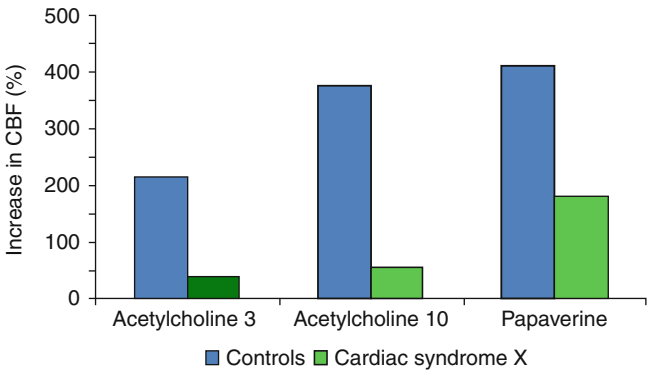

Fig. 18.8 Coronary blood flow increase in response to papaverine and acetylcholine in a group of cardiac syndrome X patients and in a group of controls as assessed by intracoronary Doppler wire recording (Based on data from Chauhan et al. [64])

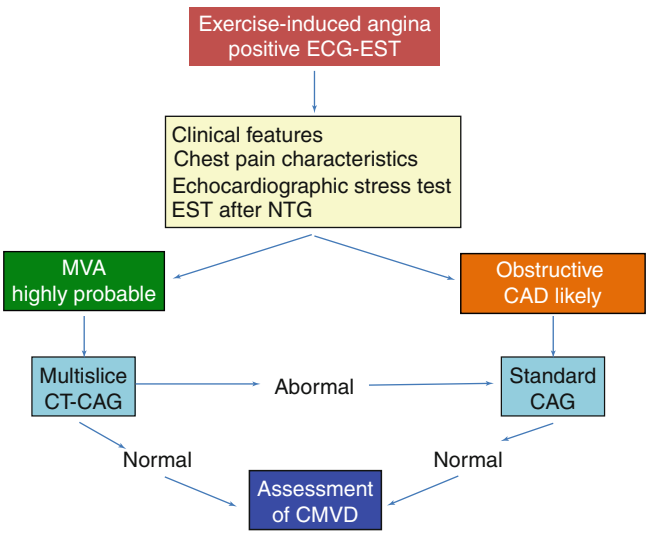

Fig. 18.9 Flow chart for a rational approach to diagnosis of microvascular angina in patients with angina pain. *CAD* coronary artery disease, *CAG* coronary angiography, *MVA* microvascular angina, *EST* exercise stress test, *ECG* electrocardiogram, *NTG* nitroglycerin, *CT* computed tomography

Structural Assessment of CMVD

The presence of relevant structural alterations of small coronary artery vessels in patients with MVA is controversial. Heterogeneous abnormalities of myocardial and/or microvascular tissue have been reported in the few studies carried out in these patients on endomyocardial biopsy samples [60, 66, 67]. Importantly, due to the benign outcome of the disease this invasive procedure does not appear ethically and clinically justified at present in these patients.

Diagnostic Algorithm

A diagnostic algorithm for the characterization of patients with suspect MVA is shown in Fig. 18.9. Documentation of normal (or almost normal) coronary arteries remains fundamental for a definitive diagnosis. In patients with effort/stress angina in whom strong clues to MVA are present according to clinical features, the documentation of normal coronary arteries might be obtained by non invasive multislice computed tomography angiography, whereas in patients in whom the clinical picture suggests the possibility of obstructive coronary artery disease, standard invasive coronary angiography remains the reference test.

Documentation of CMVD can be obtained by several methods. In patients who undergo coronary angiography, the assessment of CMV function might be obtained invasively by ICDW recording. However, in clinical practice this is unlikely to be achieved routinely. The simple and cheap TTDE might instead be the first method to investigate CMV function in these patients.

More sophisticated tests should be performed when a definitive diagnosis cannot be achieved with the more basic investigations.

Adenosine testing, for example, provides useful information on coronary microvascular vasodilation, and the assessment of microvascular constrictor activity can be explored with intracoronary acetylcholine.

Beyond CSX

As recently highlighted [6], CMVD can be responsible for angina symptoms not only in patients presenting with the classical clinical features of CSX, but also in other groups of patients with different clinical presentations. Although classically CMVD is associated with chronic symptoms of angina, CMVD can be also documented in non ST-elevation acute coronary syndrome (NSTE-ACS) patients. Angiographically normal coronary arteries are found in 5–10 % of NSTE-ACS patients [68]. This clinical presentation can be triggered by diffuse or focal epicardial coronary spasm, microvascular spasm, transient thrombosis and myocarditis; recent studies have shown that CMVD can play an important role [69, 70]. Accordingly, we have suggested the term "unstable primary MVA" for this clinical syndrome [6].

The coronary microvascular origin of symptoms should be proven by the documentation of CMVD, which, in these patients, is expected to mainly consist in enhanced coronary microvascular constriction. In some patients this is suggested by the presence of slow coronary flow at angiography, as assessed, for example, by TIMI frame count. However, a more objective demonstration of CMVD requires the documentation of abnormalities in CBF or myocardial perfusion, as induced by vasoconstrictor agents.

Provocative tests of vasoconstriction (e.g., acetylcholine and ergonovine) should be carried out in these patients to establish a firm diagnosis. These tests are performed invasively in the catheter lab, and allow the assessment of epicardial spasm as a cause of the symptoms. The induction of typical angina and ECG changes, in the absence of significant epicardial constriction, should strongly suggest CMVD, which can be confirmed by the documentation of a reduction of CBF by ICDW recording. Coronary microvascular dilation should be assessed either invasively or non invasively also in these patients, for a complete investigation of coronary microvascular function.

Conclusions

MVA is the likely diagnosis in most patients with chest pain typical enough to suggest obstructive CAD, but who are found to have normal coronary arteries at angiography.

A definitive diagnosis requires the documentation of CMVD. To this aim, ICDW or other more commonly available tests in clinical practice, such as TTDE should be used. In patients in whom TTDE is either unreliable or inconclusive, CMR might be the method of choice to demonstrate CMVD, whereas MCE might be a valid alternative method. PET, however, remains a research tool.

Importantly, the exclusion of obstructive CAD in patients with typical symptoms and ECG changes but a low likelihood of coronary obstructions can be carried out using non invasive multislice CT coronary angiography (Fig. 18.9).

In patients with suspected MVA, CMVD should be assessed using adenosine (or dipyridamole) as an endothelium-independent dilator stimulus. An increase in CBF <2.5 should be usually considered abnormal, although a CBF increase <2.0 seems more specific for the presence of CMVD. CPT can be added as a valid test to assess endothelium-dependent vasodilation in patients with normal on borderline (CFR between >2.0 and <2.5) CBF response to adenosine. Normal values of CBF response to CPT are controversial and need further assessment, although in our experience values <1.6 are not found in normal subjects [40].

The response to vasoconstrictor stimuli (like ergonovine or acetylcholine) is required in patients presenting with unstable angina but normal coronary arteriograms and might be also useful in patients with stable MVA who also have rest angina.

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Angina in Women: Epidemiology, Prognosis and Diagnosis

19

Karin Schenck-Gustafsson

Abstract

Angina with normal coronary arteries/no obstructive coronary artery disease is a debilitating condition that affects more women than men.

Overall, 50–80 % of women evaluated for chest pain have non-obstructive disease by cardiac catheterization and the total number of women impacted is unknown.

Contrary to prior beliefs about the benign nature of angina with normal coronary arteries/no obstructive coronary artery disease, the prognosis is not benign, and there is considerably morbidity.

The heterogeneous etiologies, gender differences in pain perception, concomitant pain and co-morbidities make this condition difficult to study and manage but recently new knowledge has emerged.

When treating this condition it is recommended that these patients should be handled with great concern. The responsible doctor must initiate optimal diagnostic investigations as well as intensive recommendations of lifestyle changes and aggressive treatment of risk factors including the ones related to sex hormones like premature menopause, polycystic ovarian syndrome, pre-eclampsia or eclampsia, gestational diabetes or gestational hypertension.

Keywords

Chest pain • Normal coronary arteries/no obstructive coronary artery disease • Women Epidemiology • Prognosis • Diagnosis

Introduction

Angina with normal coronary arteries/no obstructive coronary artery disease (CAD) is a debilitating condition that affects more women than men. Overall, 50–80 % of women evaluated for chest pain have non-obstructive disease by cardiac catheterization, although the total number of women affected are unknown. Varying clinical definitions and the lack of large scale epidemiologic studies focusing on this illness have resulted in limited knowledge about its risk factors, diagnostics and prognosis. However, recent mechanistic and epidemiologic studies have given us considerably new information about the this condition. Contrary to prior beliefs about the benign nature of this entity, these women suffer considerable morbidity and the prognosis is not benign as

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earlier described and communicated with the patients. The heterogeneous etiologies, gender differences in pain perception, concomitant pain and comorbidities make this condition difficult to study and manage.

Epidemiology

There is a growing realization that ischemic heart disease (IHD) is an equal burden for both men and women. Cardiovascular disease is now recognized as the leading cause of death for women worldwide except in Africa, and it is more common than death from cancer, HIV/AIDS, malaria and tuberculosis combined [1]. Statistics from the AHA indicate that more women have died annually from IHD than men since 1984 [2]. However, only 50 years ago, IHD was considered to be the man's disease and the American Heart Association (AHA) sponsored a conference about women and cardiovascular disease entitled "How I Can Help My Husband Cope With Heart Disease" [3]. Not until 2006 cardiovascular disease in women was underlined by the European Society of Cardiology [4] and the European Heart Surveys were initiated.

As confirmed by two recent meta-analyses from Europe and the USA [5, 6] the knowledge about and the evidence to support the treatment of heart disease in women remain incomplete and is an area that requires further work. Especially, IHD still is an underreported area in women.

Prevalence

Chest pain is one of the most common symptoms causing men and women to seek healthcare.

It is estimated that about half of the cases can be caused by obstructive CAD, such as myocardial infarction, angina pectoris or acute coronary syndromes. Despite the declining incidence of myocardial infarction, the prevalence of angina remains high. The American Heart Association has estimated that over nine million people in the United States suffer from angina pectoris, which significantly impacts quality of life, ability to work, and costs to society [7]. Stable angina is the most common initial symptomatic presentation among women according to the Framingham study [8]. Angina pectoris has always been considered *not* to be as frequent in women as in men but over time and at different ages, independent of diagnostic and treatment practices, women have a similar or slightly higher prevalence of angina than men across countries with widely differing myocardial infarction mortality rates.

In an international comparison of 31 countries using the Rose Angina Questionnaire, the researchers uncovered a fairly consistent higher female prevalence of angina across countries with pooled estimates of 6.7 % in women versus 5.6 % in men [9]. These studies also included the frequency of angina and normal angiograms in women. Using the Rose Angina Questionnaire to diagnose angina pectoris in women has been criticized, among other thing because of being based upon self reports without clinical confirmation. Nitroglycerine response is another tool to diagnose angina. In an epidemiological study from a huge Finnish population the diagnosis of angina pectoris was based on supposed nitroglycerine intake calculated from the amount of dispensed nitroglycerine from pharmacies. In the Finnish cohort, 56,441 women and 34,885 men were included and the prevalence of angina pectoris was quite similar in men and women: the age-standardized annual incidence per 100 population of all cases of angina was 2.03 in men and 1.89 in women, with a sex ratio of 1.07 (95 % CI 1.06–1.09). Furthermore, stable angina in women was associated with increased coronary mortality relative to women in the general population and had similarly high absolute outcome rates to those of men. In this study, it is not known how many of the patients that had angina with normal angiographies [10].

It is well know that the *prevalence* of angina pectoris with no obstructive CAD is higher in women compared to men. The Coronary Artery Surgery Study (CASS) registry, one of the earliest large registry databases, described findings in approximately 25,000 patients undergoing coronary angiography for angina, of which 39 % of women compared with 11 % of men had normal coronary arteries [11]. Data from 375,886 patients referred for angiography due to stable angina in the American College of Cardiology-National Cardiovascular Data Registry (NCDR) showed that the prevalence of angina with no obstructive CAD was significantly higher in women (51 %) than in men (32 %) [12]. This high prevalence in women was again confirmed by the Women's Ischemic Syndrome Evaluation (WISE) study, where 62 % of women referred for angiography had no obstructive CAD [13] Chest pain with normal coronary arteries/no obstructive CAD is also a more common finding among blacks compared with whites. From the NCDR registry [12] it was reported that the highest rates of no obstructive CAD in those undergoing coronary angiography were found in black women compared with other ethnicities (59 % black, 53 % Hispanic, 50 % white, 47 % Asian, and 45 % Native American).

A Swedish report [14] using the Swedish Coronary Angiography and Angioplasty Register (SCAAR), evaluated the contemporary practice of an entire country (Sweden) in the use of first-time diagnostic coronary angiography for chest pain evaluation in women and men. All Swedish patients between 2006–2008 (n = 12,200) referred for a first-time elective diagnostic coronary angiography were included. Significant (obstructive) CAD was defined as ≥50 % luminal narrowing in any epicardial coronary artery. In the youngest age group (≤59 years), more women than men (78.8 % vs.

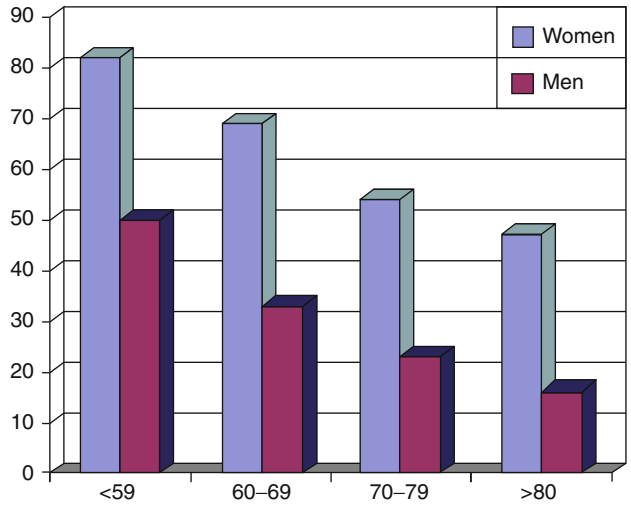

Fig. 19.1 Proportion of patients (%) with normal findings at coronary angiography according to sex and age group (Adapted from Johnston et al. [14]. With permission from Oxford University Press)

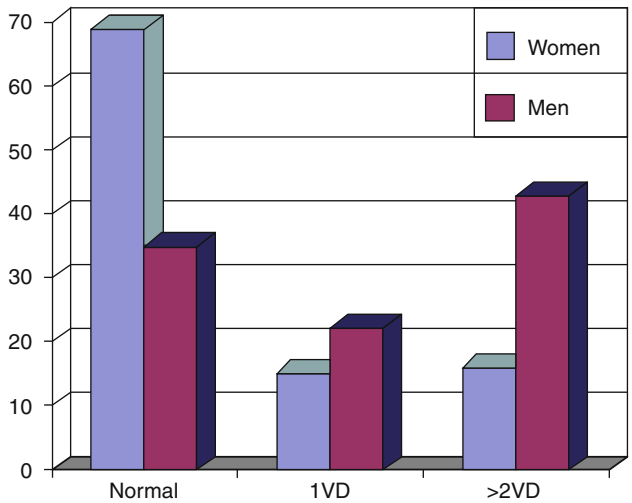

Fig. 19.2 Distribution of vessel disease (%) according to sex. *VD* vessel disease (Adapted from Johnston et al. [14]. With permission from Oxford University Press)

42.3 %, P < 0.001) had normal/no obstructive CAD (Fig. 19.1). More men had either left-main or three-vessel disease (18.2 % vs. 4.2 %, P < 0.001) (Fig. 19.2). The degree of chest pain according to Canadian Class rating system was the same for men and women in all age groups. The authors suggested that almost 80 % of women below the age of 60 years may have had an unnecessary diagnostic coronary angiography, a not complete risk-free investigation. Event rates were similarly low for men and women with normal/no obstructive CAD, except for a higher procedural complication rate in women. The observed sex differences suggest that we have poor diagnostic instruments in women with chest pain, and therefore need improved identification of women appropriate for investigation with coronary angiography.

Major population studies of ischemic heart disease in women have focused on patients hospitalized for acute coronary syndromes or fatal obstructive CAD, very seldom on chronic stable angina. However, similar to stable angina, women presenting with acute coronary syndromes including myocardial infarction are more likely to have no obstructive CAD compared with men, with prevalence rates of approximately 20 and 10 %, respectively [15]. The Swedish NIH-funded Stockholm Female Coronary Risk Study of female patients with acute coronary syndrome has demonstrated comparable proportions, where approximately 20 % had normal angiographies [16, 17].

Prognosis

Population estimates of angina in women have often been considered as "soft" outcomes, which do not reflect coronary artery pathologic findings. Population studies that might elucidate this paradox have traditionally been lacking but during the last years the situation has become slightly better with some new studies appearing [9]. In women all studies have been limited by the small number of cases of angina and subsequent coronary events, as well as by exclusion of older patients. Sex disparities in access to specialist referral and investigation of angina have been widely demonstrated, yet no study has determined sex differences in the incidence and prognostic effect of angina patients with and without potential bias in the referral and investigational system. Nor has any study investigated how the severity of incident angina or the presence of coexisting conditions might influence sex differences in prognosis.

The *prognosis* for angina pectoris without proven obstructive CAD has historically been believed to be very good. This misconception was mostly based on small studies initiated in the 1980 [18–23]. Additionally, the heterogeneous grouping of non-obstructive disease with completely normal coronary arteries, makes the generalizability of these results to the more general population that includes no obstructive CAD very difficult. A Canadian report from a registry cohort of 32,000 patients undergoing coronary angiography also confirmed the relatively good prognosis in terms of hard cardiovascular outcomes in such patients. Of all patients with normal coronary angiograms, death rate and stroke rate at one year were only 1 and 0.6 % respectively. However, a portion of these patients underwent coronary angiography due to acute coronary syndromes, which measurably increases subsequent vascular risk [24].

Nevertheless, these studies had an important impact for many years, whereby female patients with angina pectoris without obstructive CAD were reassured by the doctor that they were perfectly healthy and that the prognosis was good independent of potential risk factors. More contemporary work

including the National Heart, Lung and Blood Institute (NHLBI)-sponsored Women's Ischemia Syndrome Evaluation (WISE) studies report a considerable morbidity encountered by women with type of angina pectoris and without obstructive CAD. In an early substudy of 74 women with 3-years of follow up, there were no deaths or myocardial infarctions in women with angina and non-obstructive CAD, but they still had considerable cardiovascular event rates (19 %), consisting of hospitalizations for angina (16 %) and repeat angiography (7 %). Women with persistent chest pain were three times more likely to have cardiac events compared with those without such symptoms. In a more recent report, WISE participants with angina and normal coronary arteries (n=318) or non-obstructive CAD (n=222) were compared with 1,000 age and race matched controls from a community based sample of women free of heart disease. WISE women with normal coronary arteries had a more than threefold increase in composite cardiovascular events (7.9 % vs. 2.4 %, adjusted p=0.002) over 5 years, including higher rates of stroke and heart failure hospitalizations. However, there was no statistical difference in rates of myocardial infarction (0.9 % vs. 0.7 %, respectively) or cardiac death (1.5 % vs. 0.6 %, respectively) despite numerical trends. Of note, the WISE women with no obstructive CAD had significantly higher all cause mortality rates than the asymptomatic control group (3.0 % vs. 2.1 %, respectively, p=0.04) [25, 26]. Additional non-WISE work supports these findings, and demonstrates that the presence and severity of coronary atheromatosis among female patients with non-obstructive CAD relates to outcomes. The mentioned trials differed in criteria as to whether patients had normal angiograms with or without atheromatosis but both demonstrated a relatively high rate of recurrent cardiovascular events [24–26].

The prognosis of women with chest pain without obstructive CAD may be adversely impacted by the presence of concomitant coronary microvascular coronary dysfunction (MCD) [27–30]. Studies have suggested that patients with MCD are more likely to develop obstructive CAD in the future and have higher cardiovascular event rates [31, 32]. In fact, the WISE investigators stratified patients without obstructive CAD into those with and without myocardial ischemia on magnetic resonance spectroscopy. Those with evidence of myocardial ischemia, presumably from microvascular dysfunction, had significantly greater frequency of adverse cardiovascular events, even after accounting for accompanying risk factors [26].

From the Swedish Registry study [14] event rates for death, rehospitalization for any ischemic event, including myocardial infarction and repeat coronary angiography, were similarly low for men and women with normal/non-obstructive CAD. All event rates were higher in patients with significant CAD, where MI and repeat coronary angiography were more frequent in women and all-cause death more common in men. In both groups, more women than men suffered procedural complications.

Diagnosis

Angina Pectoris

The typical angina pectoris attack is characterized by the Diamond criteria of substernal chest pain induced by physical or mental effort and relieved with rest or nitroglycerine [33]. The chest pain in women might appear differently, for example as in stable angina pectoris, being more induced by mental stress than physical stress and more at rest than at physical effort compared to men [34, 35]. The typical features of unstable angina are stable angina pectoris accelerating for the last 3 or 4 weeks or newly debuted angina pectoris for 3–4 weeks with increasing symptoms every day. Atypical pain is more common in women than in men, because of the higher prevalence among women of less common causes of ischemia, such as vasospastic and microvascular angina.

Gender differences in pain pathways and vascular pathophysiology have been found. Pain researchers claim that there are gender differences in the experience of pain by humans and animals. Pain sensitivity is mediated by multiple factors including biological, psychological and socio-cultural. Men are reported to experience somatic pain (traumatic injury) more frequently than women, while women to experience more visceral pain than males. The two sexes have different pain-modulatory circuits to suit these needs. Cerebral blood flow measured with positron emission tomography shows gender differences of activation by pain and pain killers [36]. Anaesthetists have noted that redhaired women are more sensitive to temperature and less sensitive to the analgesic effect of lidocaine than men [37, 38].

In 1973, Kemp introduced the term cardiac syndrome X to describe patients with exercise-induced angina and normal coronary angiograms [39]. However, the use of this term has not always been limited to this specific meaning. The classic definition involves effort induced angina-like chest pain, ST segment depressions on stress testing, and normal epicardial coronary arteries. A broader definition found in the literature simply includes angina-like chest pain with normal epicardial arteries. Others have advocated a more stringent definition of effort induced angina attributed to coronary microvascular dysfunction [40]. Patients with other cardiac pathology, such as cardiomyopathy, left ventricular hypertrophy or valvular heart disease, are often excluded from these definitions [41]. The varying definitions of this entity contribute to the conflicting reports in the literature regarding its frequency, risk factors, and treatment.

Diagnostic Tools for Angina Evaluation

Risk Factors

Besides the typical angina chest pain and the physical examination including blood pressure and blood samples,

a proper risk factor analysis should be performed. This analysis should include the traditional risk factors such as dyslipidemia, hypertension, smoking, diabetes mellitus, stress, obesity, physical inactivity, unhealthy diet and alcohol drinking. Hormone related risk factors must be taken into account including premature menopause, polycystic ovarian syndrome, gestational diabetes and/or hypertension, preeclampsia and eclampsia. For women with angina and normal coronaries it especially appears to be an association with black race, estrogen deficiency, and insulin resistance**.**

Exercise Stress Testing

Exercise stress testing on a bicycle or treadmill is not as predictive of obstructive CAD in women as in men, especially when it comes to the ST depression indicating ischemia. Women more often have "pathological" ST depressions at exercise but a "normal" coronary angiography and even normal scintigraphy or other diagnostic test for ischemia. It has been discussed if this might be due to more frequent repolarisation abnormalities on baseline ECG or even (in premenopausal women) estrogen having a digitalis-like effect. Digitalis is a steroid like estrogen is known to induce ST depression on ECG. The products of pulse and blood pressure at baseline and exercise maximum might be better predictors of ischemia than the degree of ST depression, especially in younger women [42–44]. In the Stockholm Female Coronary Risk Study, typical angina symptoms during exercise test were induced in women to the same degree whether they had 3-vessel disease or almost normal coronary angiography [43]. The exercise test is a relatively economical and easy test, so it should be used also in women but with awareness of its drawbacks. It is always useful to know the objective maximal exercise capacity and also how pulse and blood pressure react during exercise.

Nuclear Stress Testing

Both sensitivity and specificity for single photon emission computed tomography (SPECT) have been hypothesized as better for exercise testing in women. Caveats include that the investigating laboratory has a good quality and is aware of artifacts caused by women's smaller left ventricular chamber sizes and soft tissue attenuation from breast tissue [45, 46]. In a meta-analysis used in the recommendations from the American Heart Association, it is concluded that the diagnostics of obstructive CAD appears to be rather gender neutral however women with diabetes, metabolic syndrome and polycystic ovary syndrome need special attention and should be investigated extra carefully [47]. The recent WOMENS trial suggests that nuclear stress testing does not provide additional benefit in low risk women able to perform standard exercise testing [48].

Coronary Angiography

As mentioned above, numerous prior reports have documented a lower prevalence of obstructive CAD in women undergoing coronary angiography for stable angina symptoms. In a recent report [14] using the Swedish Coronary Angiography and Angioplasty Register (SCAAR), demonstrated that non-obstructive CAD was more prevalent (78.8 % vs. 42.3 %, respectively, P 0.001) in the youngest age group (≤59 years) (Fig. 19.1), while men more frequently had either left-main or three-vessel disease (18.2 % vs. 4.2 %, P 0.001) (Fig. 19.2). These results demonstrate that female-pattern ischemic heart disease if not accurately recognized, leading to potentially unnecessary coronary angiography in women [49].

Coronary angiography complication rates are higher in women. Women compared to men have smaller dimensions of the coronary vessels despite correction for body surface area, [50] and this might induce more spasm causing complications during the investigational procedure. It is also well documented that women have more complications than men include procedure-related bleeding, and AV-fistulas following the procedure [14]. In chronic coronary artery disease, there is a referral bias for women who are less likely to be investigated by coronary angiography as documented in many studies like the European Heart Survey of Stable Angina [51].

Diagnostic Considerations

A factor that complicates the clinical assessment of patients with chest pain (cardiac or noncardiac in origin, with or without obstructive CAD) is the relatively common presence of psychological and psychiatric conditions such as depression or panic disorder. These factors have been found to cause or worsen chest pain especially in women but unfortunately they may not be easily detected [34].

Angina pectoris with "normal" coronaries is often a diagnosis of exclusion. First, non-cardiac etiologies of chest pain, including musculoskeletal, psychiatric, gastrointestinal, and pulmonary disorders, must be excluded. Noncardiac chest pain represents half of all cases of chest pain. Although there are a number of causes, gastro-esophageal disorders are by far the most prevalent, especially gastro-esophageal reflux disease. Patients with angina-like chest pain, and even some with atypical features, including more frequent or persistent pain [52] and inconsistent response to sublingual nitrates, should undergo stress testing. Down-sloping ST-segment depression remains a diagnostic criterion for classical angina with non obstructive coronary arteries. Most stress testing characteristics in angina with normal angiographies are indistinguishable from changes seen in patients with obstructive CAD,

although ST-segment depression at a higher rate pressure product might help [53].

Myocardial ischemia on noninvasive testing is used clinically. After demonstrating evidence of myocardial ischemia, patients should undergo cardiac catheterization or other direct imaging of the coronary arteries to confirm the presence or absence of obstructive CAD. The use of controlled vasoconstrictor stimulation with ergonovine has been proposed to rule out coronary artery spasm as a cause of chest discomfort [40]. However, the procedure is not without risks and is often not done. Newer provocative testing using graded doses of acetylcholine appears relatively safe, while intracoronary adenosine and measurement of coronary flow reserve (CFR) has an acceptable safety record similar to measurement of fractional flow reserve (FFR) for estimation of obstructive CAD [54]. Some recommend that all such patients should undergo testing to detect microvascular coronary dysfunction for a more definitive diagnosis [55]; testing is more widespread in Japan, Germany and the United Kingdom. Currently, research is ongoing to develop the optimal method for such testing with translation to practice. Due to the lack of a uniform diagnostic criterion and a reliable diagnostic test, diagnosing patients with angina pectoris and normal angiograms remains difficult.

Summary

- Angina with normal coronary arteries/no obstructive coronary artery disease, is a debilitating condition that affects more women than men.
- Overall, 50–80 % of women evaluated for chest pain have non-obstructive disease by cardiac catheterization (the total number of women affected are unknown).
- Contrary to prior beliefs about the benign nature of angina with normal coronary arteries/no obstructive coronary artery disease there is a considerable morbidity and the prognosis is not as good as believed earlier.
- The heterogeneous etiologies, gender differences in pain perception, concomitant pain and comorbidities make this condition difficult to study and manage but recently new knowledge has emerged.
- When treating these patients one option is to take this condition seriously and initiate optimal diagnostic investigations as well as recommendations about change of lifestyle changes and aggressive treatment of risk factors including the ones related to sex hormones, pregnancy and delivery.

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The Role of Positron Emission Tomography

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Abstract

The link between myocardial ischemia and obstructive atherosclerosis of the epicardial coronary arteries is well established, and coronary angiography has demonstrated a relationship between the severity and extent of coronary artery disease (CAD) and survival. In the past 20 years technological advances in positron emission tomography (PET) have enabled the noninvasive measurement of absolute (ml/min/g) myocardial blood flow (MBF) and flow reserve. In the absence of detectable CAD, a reduced maximum MBF and CFR can be ascribed to coronary microvascular dysfunction.

PET MBF studies have contributed significantly to the understanding of the pathophysiology of chest pain in patients with angiographically normal coronary arteries. These studies have highlighted the role of coronary microvascular dysfunction as a potential mechanism of myocardial ischemia in many conditions, from patients with risk factors for CAD to those with myocardial diseases. Quantification of absolute MBF with PET can be used clinically to demonstrate coronary microvascular dysfunction and how treatment can improve the function of the small coronary vessels. Therefore, the use of the term cardiac syndrome X to describe patients with chest pain and normal coronary angiograms is probably inappropriate in most cases and should be confined to those cases where no obvious risk factors for coronary microvascular dysfunction can be demonstrated.

Keywords

Coronary circulation • Coronary microcirculation • Coronary angiography • Myocardial blood flow • Coronary flow reserve • Cardiac imaging • Positron emission tomography

Measurement of Myocardial Perfusion with Positron Emission Tomography

The physical blood flow (Φ) is expressed in terms of volume of blood that flows past a point over a defined time (in milliliters per minute). The term *perfusion* (from Latin *per-fundere* [pour through]) implies the concept of volume of blood per unit of mass of tissue within an organ. What is of interest in the physiologic and clinical setting is the adequacy of delivery of nutritious substrates and removal of metabolites from the tissue of interest. The amount of substrate (e.g., oxygen) with a concentration in arterial blood (C_a) that is supplied to the tissue sample per unit of time is as follows: C_{a*} Φ [1]. However, the substrate requirements of the tissue

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sample depend on its volume, that is, a sample with a larger volume will require more mass of oxygen per unit of time. Thus, to assess the adequacy of the supply of nutrients, the concept of perfusion (Φ /Tissue volume) is used in positron emission tomography (PET) studies, although it is often mentioned as myocardial blood flow (MBF) in the current literature.

To achieve the accurate quantification of tracer uptake, which is a characteristic of PET, correction for photon attenuation is crucial. A rotating ^{68}Ge (half-life = 287 day) source has been used for photon attenuation correction in cardiac viability and perfusion scanning [2, 3]. Introduction of combined PET/CT systems, where the CT scan can be used for attenuation correction, allows image acquisition with far higher spatial resolution in a much shorter time (<4 s). The feasibility of adequate photon attenuation correction with the CT scan of a hybrid PET/CT scanner has been demonstrated for dynamic scanning with ^{13}N-labeled ammonia ($^{13}NH_3$) [4, 5].

Perfusion Tracers and Cameras

Various tracers have been used for measuring MBF by PET, including ^{15}O-labeled water ($H_2{}^{15}O$) [6–9], $^{13}NH_3$ [10–12], the cationic potassium analog ^{82}Rb [13, 14], ^{62}Cu-pyruvaldehyde bis(N4-methylthio-semicarbazone) (^{62}Cu-PTSM) and ^{11}C as well as ^{68}Ga-labeled albumin microspheres, ^{94m}Tc-teboroxime, and ^{38}K. Currently, $^{13}NH_3$, $H_2{}^{15}O$, and ^{82}Rb are the most widely used PET perfusion tracers. $^{13}NH_3$ and ^{82}Rb are given intravenously as boluses. In the case of $H_2{}^{15}O$, the tracer can be administered as an intravenous bolus injection [2], an intravenous slow infusion [15], or by inhalation of ^{15}O-labeled carbon dioxide ($C^{15}O_2$), which is then converted to $H_2{}^{15}O$ by carbonic anhydrase in the lungs [7]. Generator-produced ^{82}Rb is a very appealing MBF tracer because it does not require a cyclotron on site and has a very short half-life (78 s). Several models have been proposed for quantification of regional MBF using ^{82}Rb [16], they are limited by the heavy dependence of the myocardial extraction of this tracer on the prevailing flow rate and myocardial metabolic state [14]. Therefore, quantification of regional MBF with ^{82}Rb may be inaccurate, particularly during hyperemia or in metabolically impaired myocardium. In addition, the high positron energy (3.15 MeV) of this radionuclide results in relatively poor image quality and in a reduced spatial resolution due to its relatively long positron track.

Several tracer kinetic models for quantification of MBF have been successfully validated in animals against the radiolabeled microsphere gold standard over a wide flow range for both $H_2{}^{15}O$ and $^{13}NH_3$. Single-compartment models, based on Kety's model for an inert freely diffusible tracer [17], are used for estimation of MBF using $H_2{}^{15}O$ [7–9, 18]. A 3-compartment model describing the kinetics of the myocardial metabolic trapping and whole-body metabolism of $^{13}NH_3$ has been used for calculation of MBF using this tracer [11, 12, 19–21]. The models have to include corrections for underestimation of radiotracer concentration due to the partial-volume effect and spillover from the left chamber onto the ventricular myocardium [20, 22], which result from the limited spatial resolution of the PET camera and the motion of the heart. Additional corrections have been developed to account for the impact of flow [23] on myocardial extraction of $^{13}NH_3$ and for the radiolabeled metabolites [24] of $^{13}NH_3$, which accumulate in blood.

The equivalence of $H_2{}^{15}O$ and $^{13}NH_3$ as perfusion tracers has been demonstrated in experimental animals [25] and in humans [26], but the proof of congruence of the tracers in ischemic and infarcted segments requires further clarification. The use of $H_2{}^{15}O$ as a perfusion tracer is potentially superior to $^{13}NH_3$ because $H_2{}^{15}O$ is metabolically inert and freely diffusible across capillary and sarcolemmal membranes [27, 28]. Thus, it equilibrates rapidly between the vascular and extravascular spaces and its uptake by the heart does not vary despite wide variations in flow rate. The short half-life (123 s) of ^{15}O allows repetitive MBF measurements at short intervals (10 min, equivalent to 5 half lives of ^{15}O) and with excellent repeatability [29]. The differences between $H_2{}^{15}O$ and $^{13}NH_3$ are of little relevance when the measurements of MBF are performed in normal myocardium as proven by the comparable flow estimates obtained with the two tracers in healthy human subjects. However, in a highly heterogeneous tissue (e.g., jeopardized myocardium in patients with previous infarction), the diffusion/extraction and final uptake of $H_2{}^{15}O$ and $^{13}NH_3$ are determined by the flow rates in each tissue compartment—that is, higher in viable tissue and lower in scar tissue. $^{13}NH_3$ uptake (on which the model for the computation of MBF is based) in a given region of interest will reflect the average uptake and, hence, average flow in this mixture of viable and fibrotic tissue. On the other hand, since the uptake of $H_2{}^{15}O$ in scar tissue is negligible, washout of $H_2{}^{15}O$ (on which the model for the computation of MBF is based) will mainly reflect activity in better-perfused segments and the resulting flow can therefore be higher than that obtained with $^{13}NH_3$ in the same region [30].

The PET cameras used for the quantification of MBF, as well as for other cardiac PET applications, nowadays work in three-dimensional mode. Three D-only tomograms show a particularly high efficiency [9, 31].

Physiology of Myocardial Perfusion Investigated by PET

Information on myocardial perfusion in human beings and its regulation can be obtained indirectly with studies at the microcirculatory level by measuring parameters such as the

ratio of the maximal increase in blood flow above its resting value, known as coronary flow reserve (CFR) [32]. With the quantitative assessment of myocardial perfusion by use of PET, it is possible to challenge the function of the coronary microvascular bed by measuring CFR, thus gaining insight into the integrated circulatory function. In keeping with studies in animals [33], as well as with the fractal characteristics of the coronary vascular network [34], blood flow measurements with PET have highlighted the heterogeneity of both resting and hyperemic MBF in normal human beings [35, 36]. Baseline and hyperemic MBF values exhibit a similar degree of spatial heterogeneity, which appears to be temporally stable [35]. CFR is dependent on the coronary perfusion pressure and also assumes that maximal vasodilatation has been achieved [32]. PET studies in a large cohort of healthy human volunteers have established that the normal CFR in response to a standard intravenous dose of dipyridamole (0.56 mg/kg for 4 min) or adenosine (140 $g \cdot kg^{-1} \cdot min^{-1}$) is approximately 3.5–4.0 [35]. The use of PET has highlighted the effects of age [11, 35–37], sex [35, 38], and alteration in sympathetic tone [39] on MBF and CFR.

In normal subjects, resting MBF is higher in female subjects and older subjects whereas hyperemic MBF starts to decline over age 55 years. In older subjects there is a significant increase in resting flow associated with an increase in systolic blood pressure, which, combined with the reduction in hyperemic MBF, leads to a reduction in CFR [11, 35–37]. The effect of α1-receptor blockade on MBF at baseline is negligible, after α 1-receptor blockade, hyperemic MBF can increase by 39 % and coronary resistance decrease by 24 % in comparison with control conditions [39, 40]. The undue stimulation of α 1-receptors has been shown to limit the recovery of CFR after coronary angioplasty in patients with coronary artery disease [41]. The increase in MBF ensuing after the sympathetic activation induced by cold pressure test has similarly been used to compare the response of large conduit vessels assessed by angiography with perfusion measured by use of N-13–labeled ammonia [42]. The disturbance of the flow-dependent (and possibly endothelium-dependent) vasomotion in conduit arteries was paralleled by a homogeneous impairment of myocardial perfusion in the group of patients with atypical chest pain, normal angiograms, and coronary risk factors (hypertension, hypercholesterolemia, long term smoking). The diagnostic accuracy of PET has been exploited to detect impairments of myocardial perfusion in asymptomatic subjects with cardiovascular risk factors [43–47] and even in the relatives of patients with coronary artery disease, in whom coronary arteriography is not justifiable on the basis of family history alone [48]; and in diabetic patients without symptoms of cardiac disease [49].

Subendocardial and Subepicardial Perfusion

Reduced subendocardial CFR in response to exercise or pharmacologically induced vasodilatation is a hallmark of flow limiting stenoses. In the absence of coronary disease, this phenomenon has been demonstrated in patients with LV hypertrophy secondary to aortic stenosis [50]. Recent developments in hard- and software, have enabled the measurement of transmural MBF distribution during pharmacological stress in LV of normal thickness in a porcine model of ischemic heart disease [51] and in normal volunteers [52]. The use of a fully quantitative perfusion assessment is of clinical relevance as it circumvents the necessity of establishing a normal reference region of interest, which is particularly demanding in patients with multivessel disease and in all those conditions where there is an increased heterogeneity in myocardial perfusion due to the presence of fibrosis or scar. Differences in the composition of the different tissues surrounding the subendocardium and the subepicardium (blood versus chest wall and lung tissue) can account for the small systematic difference in the agreement with microspheres between subendocardial and subepicardial flow. The kinetic model used to quantify MBF contains an intrinsic correction for spill-over from arterial blood activity, but not for that from adjacent tissue activity as a result there is a slight overestimation in subepicardial MBF relative to that in the subendocardium.

Differences Among Stressors

Mechanistic differences between pharmacologic stressors may offer different clinical benefits. The effects of dobutamine and adenosine on absolute myocardial blood flow and coronary flow reserve have been compared between patients with coronary artery disease and healthy volunteers [53]. In normal volunteers myocardial blood flow and flow reserve during adenosine were higher than during dobutamine. In patients adenosine produced a more significant flow difference between ischemic and remote myocardium compared to dobutamine which achieved flow heterogeneity to a lesser extent and only in patients with severe coronary artery stenosis (75 %). However, in myocardial segments subtended by a significant coronary stenosis, dobutamine achieved greater hyperemia than adenosine stress and coronary flow reserve similar to adenosine stress. This greater hyperemia with dobutamine may indicate greater collateral recruitment or reflect the greater propensity for vasodilator agents to induce coronary steal. Therefore the higher diagnostic sensitivity quoted with vasodilator stress primarily reflects the greater hyperemia seen with these agents in remote myocardial segments. In summary, quantitative perfusion imaging demonstrated that adenosine stress has higher sensitivity whilst dobutamine has higher specificity.

Short and Long Term Reproducibility of Perfusion Measurement with PET

Different studies have tested the short term reproducibility of myocardial blood flow measurements using PET with nitrogen-13 labeled ammonia and oxygen-15 labeled water [29, 54]. Repeated measurements of resting and hyperemic myocardial blood flow using intravenous dipyridamole and adenosine during the same study session are highly reproducible, thus, demonstrating the robustness of the technique. The variability of hyperemic flow can be larger, as indicated by the larger repeatability coefficient, and it is paralleled by a greater variability of the rate pressure product. This could mean that the greater variability of myocardial blood flow during stress is more likely due to a variable response to vasodilators rather than to a larger measurement error. Serial myocardial blood flow measurements with PET can be used to quantify the effect of various interventions on myocardial blood flow and flow reserve [55–57].

Jagathesan et al. [56] have tested the long term reproducibility of myocardial blood flow measurement at rest and following dobutamine stress in patients with stable coronary artery disease using PET with oxygen-15 labeled water. Dobutamine induced reproducible changes in both global and regional myocardial blood flow and flow reserve over a time interval of 24 weeks. The reproducibility of myocardial blood flow and flow reserve with dobutamine was comparable with the short-term repeatability reported for adenosine and physical exercise in healthy subjects.

Perfusion and Microvascular Dysfunction

Assessment of microcirculation relies on the measurement of parameters that reflect its functional status, such as MBF and CFR. CFR is an integrated measure of flow through both the large epicardial coronary arteries and the microcirculation [58]. In the absence of obstructive stenoses on the epicardial arteries, a reduced CFR is a marker of coronary microvascular dysfunction. A single cutoff value of CFR (e.g., ≤2.0) below which microvascular function is deemed abnormal can be useful clinically. Nevertheless, it has to be born in mind that in healthy humans, CFR varies according to age and sex [35]. It is essential to compare CFR data in patients with those obtained in age- and sex-matched healthy subjects. In addition, resting MBF is linearly related to cardiac work. Therefore, when comparing different patients it is important to correct resting MBF for the main determinants of external cardiac workload (i.e., blood pressure and heart rate [RPP]). A corrected CFR can then be calculated by dividing hyperemic flow by RPP-corrected resting flow [59]. More complex is the assessment of coronary microvascular dysfunction in territories subtended by stenotic coronary arteries in which the evaluation of microvascular function depends on the clinical context.

As proposed by Camici and Crea [60], coronary microvascular dysfunction can be classified in the following four groups: coronary microvascular dysfunction occurring in the absence of obstructive epicardial CAD and myocardial diseases (type A), coronary microvascular dysfunction occurring in the context of cardiomyopathies (type B), coronary microvascular dysfunction occurring in the presence of obstructive epicardial CAD (type C), and iatrogenic coronary microvascular dysfunction (type D) (see Table 20.1).

In the last decade, several studies have expanded our understanding of coronary microvascular dysfunction in different clinical settings. In moderately hypertensive patients with stable CAD, the effect of treatment with the angiotensin receptor blocker valsartan on MBF was measured with PET and $^{13}NH_3$ [61]. Significant improvements in MBF both after cold pressor test and in response to pharmacologic vasodilatation with adenosine could be demonstrated after 1 and 16 week of treatment. The improvement in MBF preceded the reduction of blood pressure, suggesting direct beneficial effects on microvascular function. In hypertensive patients with LV hypertrophy, 6 months of treatment with the angiotensin-converting enzyme inhibitor perindopril, in combination with the diuretic indapamide on resting and hyperemic (adenosine) significantly reduced systolic, diastolic blood pressures and LV mass increasing hyperemic MBF [62].

In a randomized, double-blind, placebo-controlled study in 26 nondiabetic patients with familial combined hyperlipidemia, Naoumova et al. [63] tested the effect of treatment with the insulin sensitizer thiazolidinedione pioglitazone added to conventional lipid-lowering therapy on myocardial glucose use and blood flow using PET with ^{18}F-FDG and $H_2{}^{15}O$, respectively. After 16 week of treatment, there was evidence of significant increases in myocardial glucose use and hyperemic blood flow with adenosine, again suggesting improved coronary microvascular function.

In a pilot double-blind, placebo-controlled pilot trials, 16 consecutive patients with idiopathic-dilated cardiomyopathy were randomized to treatment with either carvedilol or placebo [64]. Regional MBF was measured at rest and after intravenous injection of dipyridamole using PET with $^{13}NH_3$ at baseline and after 6 month of treatment. Absolute MBF did not change significantly after carvedilol or placebo treatment, although hyperemic blood flow showed a trend toward increase in patients receiving active treatment. CFR significantly increased after carvedilol treatment; it remained unchanged after placebo, and stress-induced regional perfusion defects decreased after active treatment [64].

Table 20.1 Clinical classification of coronary microvascular dysfunction (CMD)

(Type A) CMD in the absence of obstructive coronary artery disease (CAD) and myocardial diseases
In patients with risk factors for CAD
Smoking
Hypertension
Hyperlipidemia
Diabetes and insulin resistant states
CMD Type A represents the functional counterpart of traditional coronary risk factors. It can be demonstrated by noninvasive assessment of coronary flow reserve (CFR). This type of CMD is, at least in part reversible and CFR can also be used as a surrogate endpoint to assess efficacy of treatments aimed at reducing risk factor burden.
(Type B) CMD in the presence of myocardial diseases
Primary (genetic) cardiomyopathies (hypertrophic, dilated, etc.)
Secondary cardiomyopathies (hypertensive, valvular)
CMD type B is sustained in most instances by adverse remodelling of intramural coronary arterioles. It can be demonstrated by invasive or noninvasive assessment of CFR and maybe severe enough as to cause myocardial ischemia. It bears independent prognostic value. It remains unclear whether in some cases it may be reverted by medical treatment.
(Type C) CMD in the presence of obstructive CAD
Stable CAD
Non ST elevation acute coronary syndromes
ST elevation acute myocardial infarction
CMD type C may occur in the context of either stable CAD or acute coronary syndromes and can be sustained by a number of different factors. Its demonstration is more complex than that in type A and B and may be achieved through an integrated approach which takes into account the clinical context using a combination of invasive and non-invasive techniques. There is some early evidence that specific interventions might prevent CMD or limit CMD-dependent ischemia.
(Type D) Iatrogenic CMD
Following percutaneous coronary interventions
Following coronary bypass surgery
CMD type D, which occurs following coronary re-canalization, seems to be primarily caused by vasoconstriction or distal embolization. It can be demonstrated either invasively or noninvasively by a reduced CFR which seems to revert spontaneously in the weeks that follow revascularization. Although pharmacologic treatment has been shown to promptly restore CFR, it is not known whether it may also change the clinical outcome. Distal embolization can be reduced by utilization of appropriate devices during high risk procedures.

Is Chest Pain in Cardiac Syndrome X Truly Due to Myocardial Ischemia?

Clinically, in a significant proportion of patients with a history of chest pain, the coronary angiogram does not show significant narrowing of the vessel lumen. These patients usually have a poor response to conventional anti-ischemic therapy, which may lead to the unnecessary performance of repeated coronary angiograms over the years because of recurrence of chest pain. Nevertheless, these patients have a life expectancy similar to that of the general population [65], with the exception of those with conduction abnormalities such as left bundle branch block that may develop dilated cardiomyopathy during follow-up.

The studies in the late eighties and early nineties hypothesized that the chest pain was of ischaemic origin based on the presence of ST-segment depression during spontaneous or stress-induced chest pain [66, 67], as well as on the evidence of reversible stress-induced myocardial perfusion defects [68].

Furthermore, some studies have provided evidence of reduced endothelium-dependent and independent coronary vasodilatation as well as metabolic evidence of myocardial ischemia [60]. Other studies, however, failed to find evidence of abnormal MBF or CFR or metabolic or functional evidence of ischemia during stress [69–72].

It must be noted, however, that inclusion and exclusion criteria in the vast majority of these studies have been variable. In particular, the category of 'normal coronary arteriogram' has been a broad one, often including cases of CAD ranging from minimal disease to coronary stenoses up to 50 % of luminal diameter. The most frequently used exclusion criteria are valvular heart disease, diabetes mellitus, left ventricular hypertrophy, hypertension, and cardiomyopathy [73]. However further restriction is deemed necessary in order to obtain a more homogeneous set of true cardiac syndrome X patients: absence of left bundle branch block; absence of even minimal irregularities on the angiogram; no evidence of diabetes mellitus, arterial hypertension, hyperlipidaemia, valve disease, epicardial arterial spasm, and

cardiomyopathy. These exclusion criteria are essential because, more recently, it has become clear that abnormalities in the function and structure of the coronary microcirculation, which may be severe enough to contribute to myocardial ischemia, occur in many of the above conditions [43, 44, 49]. Most commonly, myocardial ischemia is demonstrated in patients with CAD in whom CFR is reduced in parallel with the severity of coronary stenoses [59]. However, a reduced CFR can also be demonstrated in patients with angiographically normal epicardial arteries and, in this circumstance, suggests coronary microvascular dysfunction (CMD) [74–78]. The latter has been demonstrated in patients who are at higher risk of developing CAD and is thought to represent the functional counterpart of traditional coronary risk factors. CMD can also occur in patients with primary (e.g. hypertrophic) or secondary (e.g. hypertensive) cardiomyopathies and is most commonly due to adverse remodelling of intramural arterioles (for a detailed review of CMD see Camici and Crea [60]). The term syndrome X (originally the Group x in the paper of Arbogast and Bourassa of 1973) [79] was coined to stress the uncertainty over the pathophysiology of chest pain. Therefore, this term should not be used in patients, such as those with risk factors for CAD or cardiomyopathies, in whom myocardial ischemia due to CMD is known to occur.

It is possible, however, that a subset of patients exists who have a reduced CFR and metabolic evidence of myocardial ischemia in whom none of the known causes of CMD can be demonstrated. Maseri et al. [80] have proposed that in these patients focal ischemia in small myocardial regions scattered throughout the myocardium and caused by pre-arteriolar dysfunction might explain the paradox of angina and ST-segment depression. One possibility supporting the ischemic origin of pain in syndrome X, is that ischemia could be confined to small areas of the heart particularly in the subendocardium and elicit a sympathetically mediated excitatory response [81, 82].

In an article published in 2002, Panting et al. [83] have addressed this problem using cardiovascular magnetic resonance (CMR) imaging with the paramagnetic contrast agent gadolinium to assess myocardial perfusion in patients with cardiac syndrome X. In line with previous reports where CFR was measured, there was no significant difference in the value of the myocardial perfusion index (MPI) for transmural (i.e. full thickness) perfusion between controls and patients with syndrome X both at rest or following intravenous adenosine. However, while in the controls, the MPI increased significantly after adenosine in both the subepicardium and subendocardium, in the patients with syndrome X the MPI did not increase significantly in the subendocardium, but it did increase in the subepicardium. In addition, in their paper, Panting et al. [83] showed pictures of subendocardial signal reduction on the first pass CMR images and speculated that chest pain in these patients might be explained by ischemia secondary to diminished (or absent) vasodilatation of the coronary microvasculature following infusion of adenosine, leading to relative underperfusion of the subendocardium.

One of the advantages of CMR is that perfusion measurements can be combined with the evaluation of global and regional left ventricular function. Unfortunately, Panting et al. [83] failed to assess left ventricular function during stress and therefore they cannot prove whether the perfusion images obtained following adenosine are accompanied by the development of myocardial dysfunction (usually an early phenomenon in the cascade of events that follow myocardial ischemia) and represent myocardial ischemia rather than heterogeneity in transmural perfusion. In this respect, several previous studies with stress echocardiography consistently demonstrated that, despite the provocation of chest pain, patients with syndrome X had no impairment in contractility [84]. More recently Vermeltfoort et al. [71] have published a study whose design was very similar to that of the study of Panting et al. [83]. CMR was used to assess both visually and semi-quantitatively subendocardial and subepicardial perfusion, at rest and during intravenous adenosine in 20 patients with angina pectoris and normal coronary angiograms. Similarly to the study of Panting et al. [83], Vermeltfoort et al. [71] calculated the MPI using the normalized upslope of myocardial signal enhancement. An index for myocardial perfusion reserve (MPRI) was calculated by dividing the MPI values at maximal vasodilatation by the values at rest.

In contrast to the finding of Panting et al. [83] however, in the study of Vermeltfoort et al. [71] MPI increased significantly and, by a comparable amount, during adenosine infusion both in the subendocardium and the subepicardium. The transmural MPRI was 1.83 ± 0.50. In addition, they found that all patients showed initial subendocardial signal reductions on the first pass CMR images, which, however, disappeared after approximately five heart beats. As demonstrated by previous studies [85, 86], these temporary signal losses are artifacts related to the first pass sequence and the dose of gadolinium contrast and are different from the defects due to myocardial ischemia which are characterized by a more sustained signal loss.

The results of the study of Vermeltfoort et al. [71] are consistent with other studies where myocardial blood flow and flow reserve were measured in patients with cardiac syndrome X and age and sex matched controls using PET. In these PET studies, no difference in average transmural myocardial blood flow and flow reserve was found between patients and controls [87]. Although the resolution of the PET scanner used in these studies did not allow selective measurement of subendocardial and subepicardial blood flow, a severe reduction in subendocardial flow, such as that suggested in the study of Panting et al. [83] would have

resulted in an appreciable reduction in average transmural flow and the CFR. In spite of the progress attained in non invasive measurement of myocardial perfusion after more than 30 years and a wealth of different studies, the veil that surrounds the mechanisms of chest pain in patients with cardiac syndrome X seems far from being lifted. PET has been instrumental in suggesting a different mechanism, at least in some of these patients, pointing at the brain as the origin the origin of chest is not in the heart, but in the mechanisms of perception and elaboration of visceral pain [72, 88].

Conclusions

In summary, PET MBF studies have contributed significantly to the understanding of the pathophysiology of chest pain in patients with angiographically normal coronary arteries. PET studies have highlighted the role of coronary microvascular dysfunction as a potential mechanism of myocardial ischemia in many conditions, from patients with risk factors for CAD to those with myocardial diseases. Quantification of absolute MBF with PET can be used clinically to demonstrate coronary microvascular dysfunction and how treatment can improve the function of the small coronary vessels [89]. Therefore, the use of the term cardiac syndrome X to describe patients with chest pain and normal coronary angiograms is probably inappropriate in most cases and should be confined to those cases where no obvious risk factors for coronary microvascular dysfunction can be demonstrated.

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The Role of MRI for Diagnosis in Women with Angina and Open Arteries

21

Louise E.J. Thomson

Abstract

Magnetic resonance imaging (MRI) may be used for evaluation of women with angina and open coronary arteries. Magnetic resonance spectroscopy (MRS) is a unique noninvasive molecular imaging tool for characterization of cellular metabolites such as adenosine triphosphate and phosphocreatine. Multiple studies spanning more than a decade have provided evidence of biochemical changes due to myocardial ischemia in women who have angina without epicardial stenosis. Advances in perfusion imaging allow visualization of the first pass of contrast in the myocardium for detection of perfusion defects provoked by stress testing within the magnet. Having been validated for detection of epicardial coronary artery disease, this technique has also been used in patients with microvascular disease. The combination of rest and stress first pass imaging permits measurement of the myocardial perfusion reserve, calculated from the ratio of the normalized upslope of the time intensity curves during first pass of gadolinium based contrast. Quantitative approaches are likely to be particularly important for non invasive detection of diffuse microvascular coronary dysfunction. This chapter describes these different MRI techniques with examples of studies that have used this imaging method for non invasive evaluation of women with angina and open arteries.

Keywords

Cardiac magnetic resonance imaging • Microvascular coronary dysfunction • Myocardial perfusion reserve • Magnetic resonance spectroscopy

There has been considerable interest in the potential role of MRI as a non invasive imaging modality for the detection of an abnormal coronary reserve in the setting of both epicardial coronary disease and microvascular dysfunction. MRI has certain advantages over other imaging modalities that are commonly used in the diagnosis of myocardial ischemia. Unlike CT and nuclear techniques, there is no ionizing radiation exposure with MRI. Unlike echo, there is no limitation in the imaging "window" and the entire chest cardiac and vascular anatomy can be demonstrated. Unlike any other modality, MRI can depict changes in the myocardial cellular composition with very high resolution.

The most commonly used cardiac magnetic resonance imaging techniques include anatomic and functional imaging, contrast enhanced imaging for detection of myocardial scar, and imaging performed during stress testing for evaluation of

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coronary flow reserve. Magnetic resonance spectroscopy (MRS) is an additional technique for evaluation of myocardium at the cellular level, and has played an important role in the evaluation of women with microvascular dysfunction.

This chapter will overview the role MRI has played in the evaluation of women with angina in the absence of epicardial stenosis and describe the different MR techniques currently available.

Magnetic Resonance Spectroscopy

MRS is the only noninvasive imaging technique that can characterize myocardial composition at the cellular level. Whilst termed an "imaging" modality, the data that is produced using this technique is not a depiction of anatomy, but is instead a spectrum of cellular composition.

This technique assesses components of myocytes such as phosphocreatine, sodium or potassium and can be used to non-invasively observe changes in the relative chemical compositions of myocardial tissue in the setting of either myocardial ischemia or infarction. The technique is not widely available or part of routine clinical care; however it has been a very important research tool for more than decade.

While conventional magnetic resonance images are created by receiving radiofrequency signals based on the magnetic moment of water protons (^{1}H) within the magnetic field, the magnetic moment of other nuclei such as sodium-23, potassium-39 and phosphorus-31 can also be measured by adjusting the transmit and receive frequencies for the magnet. MRS allows observation of the phosphate-31 concentrations, including important cellular metabolites such as adenosine triphosphate (ATP), phosphocreatine, phosphodiester, and inorganic phosphate. Further, one can attempt to observe differences in phosphate concentrations between viable, ischemic and infarcted myocardium.

In one of the first major studies of the efficacy of 31P MRS compared to exercise Thallium 201 scintigraphy and evaluated 27 patients with severe LAD stenosis (>75 %) and 11 control subjects. Hand grip exercise was associated with significant alteration in the PCr/ATP ratio in patients with ischemia demonstrated by Thallium 201 scintigraphy [1].

Subsequent work by Jung et al. demonstrated similar alterations in myocardial metabolism in the hypertrophied myocardium of asymptomatic subjects with advanced hypertrophic cardiomyopathy (HCM) [2]. This finding showed that MRS could detect metabolic alterations in myocardium in the absence of epicardial stenosis. Delayed enhancement MRI has subsequently been used to demonstrate mid myocardial enhancement in patients with HCM, confirmed by histology to be due to alterations in cellular composition including fibrosis [3].

The Women's Ischemia Syndrome Evaluation study (WISE) has utilized this technique to determine the prevalence of myocardial ischemia in the absence of angiographically significant coronary artery disease. The first publication of this data in 2000 in the *New England Journal of Medicine* described the findings in a group of 35 women aged 31–72 years who presented to a single center with anginal chest pain in the absence of epicardial stenosis at angiography [4]. This group were compared to an age and weight matched control population of 12 healthy women (control) and to a group of 7 men and 4 women with >70 % left anterior descending coronary artery stenosis (CAD). 31P MRS at 1.5 T was performed at baseline, during and after isometric hand grip exercise with sampling of the anterior wall and apex of the left ventricle. Additional data was reported regarding the reproducibility of this technique, and the threshold for a significant decrease in PCr/ATP ratio was conservatively set at −22 %.

In the control population the PCr/ATP decreased by 2.6 ± 10 %, in the CAD group the decrease was 19.6 ± 10.7 % and these data reproduced previously reported findings. In the WISE group there was a spectrum of response, with the mean decrease of 6.6 ± 15 % in the PCr/ATP ratio. However in seven women there was a mean decrease of 28 ± 5 %, a definitely abnormal response in these women who represented 20 % of the study population. This provided evidence of biochemical changes due to myocardial ischemia in a significant subset of women who had angina without epicardial stenosis.

Subsequent work published in 2002 found a similar difference between a control population and a group of patients with heart transplantation, in whom there was a significant difference in response to hand grip stress [5]. The percent change in the PCr/ATP ratio in the control group was 1.50 ± 10.6 % and the transplant population showed an overall change of −6.7 ± 18.5 %. The responders, those that were at or below the 2 SD line from control, had a −25.6 ± 3.6 % decrease in PCr/ATP. The findings suggested that MRS may be able to detect presence of cardiac allograft vasculopathy.

There are several limitations of this technique for demonstration of myocardial ischemia. Firstly above studies utilized isometric handgrip exercise for cardiac stress. The subject uses a handgrip connected to a force transducer and squeezes the grip at about 30 % of maximum force ~ calibrated in advance of the study. This level of exercise is maintained for a period of about 10 min while the scans are obtained and results in very little chest motion, which is critical for MRS. However, the level of stress it induces is lower than that of most physical exercise and this is likely to reduce sensitivity for detection of ischemia.

A second major limitation of this technique is that the region of the heart that is "sampled" is a single relatively large volume of the data that can be obtained from the anterior wall only. Posterior and lateral wall abnormalities cannot

be detected and therefore it is possible that regional variation in stress perfusion leads to under recognition of the presence and extent of ischemia. This limitation means the technique is not useful for screening for CAD because only the LAD territory can be evaluated. The crude volumetric sampling also means that it is possible to inadvertently include adjacent skeletal muscle in the imaging field of view, which is a potential source of error.

Reproducibility data from the WISE study in a single male patient determined a standard deviation of 11 % for the mean difference between repeated measurements. This implies that for an individual being tested there needs to be more than 22 % change in measurement for there to be confidence in this being a true difference. This variability in measurements limits the potential use of this technique for detection of small changes in the ratio of PCr/ATP. This is particularly important for this population of women with angina and open arteries, in whom the ratio observed most often falls between values seen in normal controls and epicardial coronary disease.

The use of a higher field strength (3 T MRI) for spectroscopy results in more than 200 % increase in signal to noise ratios for spectroscopic data [6]. More recently, a study at 3 T has confirmed abnormalities in PCr/ATP ratios in hypertrophic cardiomyopathy, confirming observations at 1.5 T [7]. However, caution remains regarding the variability of measurements obtained. Although field strength increase improves signal, there is still considerable variation in measurements. This has been reported as being approx 20 % for intra subject variability and 18 % for inter subject coefficient of variation [8].

In summary, MR spectroscopic measurements of cardiac metabolism demonstrate abnormalities in the ratio of PCr/ATP in patients with significant epicardial disease, but also show abnormalities in women with angina and open arteries, and in hypertrophic cardiomyopathy. This imaging technique has provided proof of the presence of an abnormality in a subset of women with angina and no angiographically significant CAD in the WISE study. Limitations of the technique include issues of limited sampling, reproducibility, and the submaximal stress of isometric hand grip exercise, potentially decreasing specificity and sensitivity for detection of abnormalities.

MRI for Evaluation of Myocardial Structure, Coronary Anatomy and Myocardial Viability

The primary focus of this chapter is the detection of myocardial ischemia using MRI techniques, however the role of structural and functional MRI also needs to be acknowledged.

Evaluation of cardiac anatomy and ventricular function as part of a routine cardiac MRI evaluation may detect presence of otherwise unsuspected structural and functional abnormalities in patients with chest pain. These include coronary anomalies and other congenital anomalies that may have been missed by echocardiography. A routine imaging protocol for cardiac MRI can include short axis imaging in the aortic root, long and short axis cine (functional) imaging of the heart and additional views of the right ventricle if indicated. If a shunt is suspected, velocity encoded imaging flow is performed to interrogate flow in the proximal aorta and proximal main pulmonary artery (for calculation of the shunt, as expressed by the ratio of pulmonic to systemic flow, Qp/Qs).

Figure 21.1 shows the normal four chamber image of the heart compared to examples of abnormalities seen on MRI in three women who initially presented with atypical anginal symptoms.

The addition of gadolinium during MRI results in shortening of the T1 recovery time for tissues that retain gadolinium, and alters the usual balance of signal intensities between different tissue structures dependent upon their gadolinium content and speed of gadolinium clearance. Image sequences that maximize signal from structures with a shortened T1 are then used to image the heart and vascular system, emphasizing signal from structures with higher gadolinium content. This contrast agent is required for evaluation of the first pass myocardial perfusion, and is additionally used to image chest vascular structures and examine enhancement patterns in cardiac tissues.

Delayed enhancement imaging of the myocardium has been validated in animals and a large number of patients for the detection of myocardial scar. Relative retention of gadolinium is observed in irreversibly damaged, non viable myocardium in the acute and chronic infarct setting, and is also seen in a wide range of different pathologies that cause patchy myocardial cell necrosis. These include amyloidosis, myocarditis, hypertrophic cardiomyopathy, chagas disease and sarcoidosis. Complete discussion is beyond the scope of this chapter, however in broad terms it has been observed that non ischemic cardiomyopathic patterns of delayed enhancement of the myocardium are usually different from the pattern observed in coronary artery disease (Fig. 21.2) [9].

MRI for Evaluation of Myocardial Perfusion

Myocardial stress perfusion scintigraphy is a well established technique for the detection of epicardial coronary artery disease. Gamma camera approaches (SPECT) rely upon the regional variation in myocardial perfusion that exists in the setting of epicardial stenosis. Small perfusion defects are not detectable with this technique [10] as a consequence of the limited spatial resolution and the relative intensity of adjacent activity in normal myocardium. Diffuse subendocardial

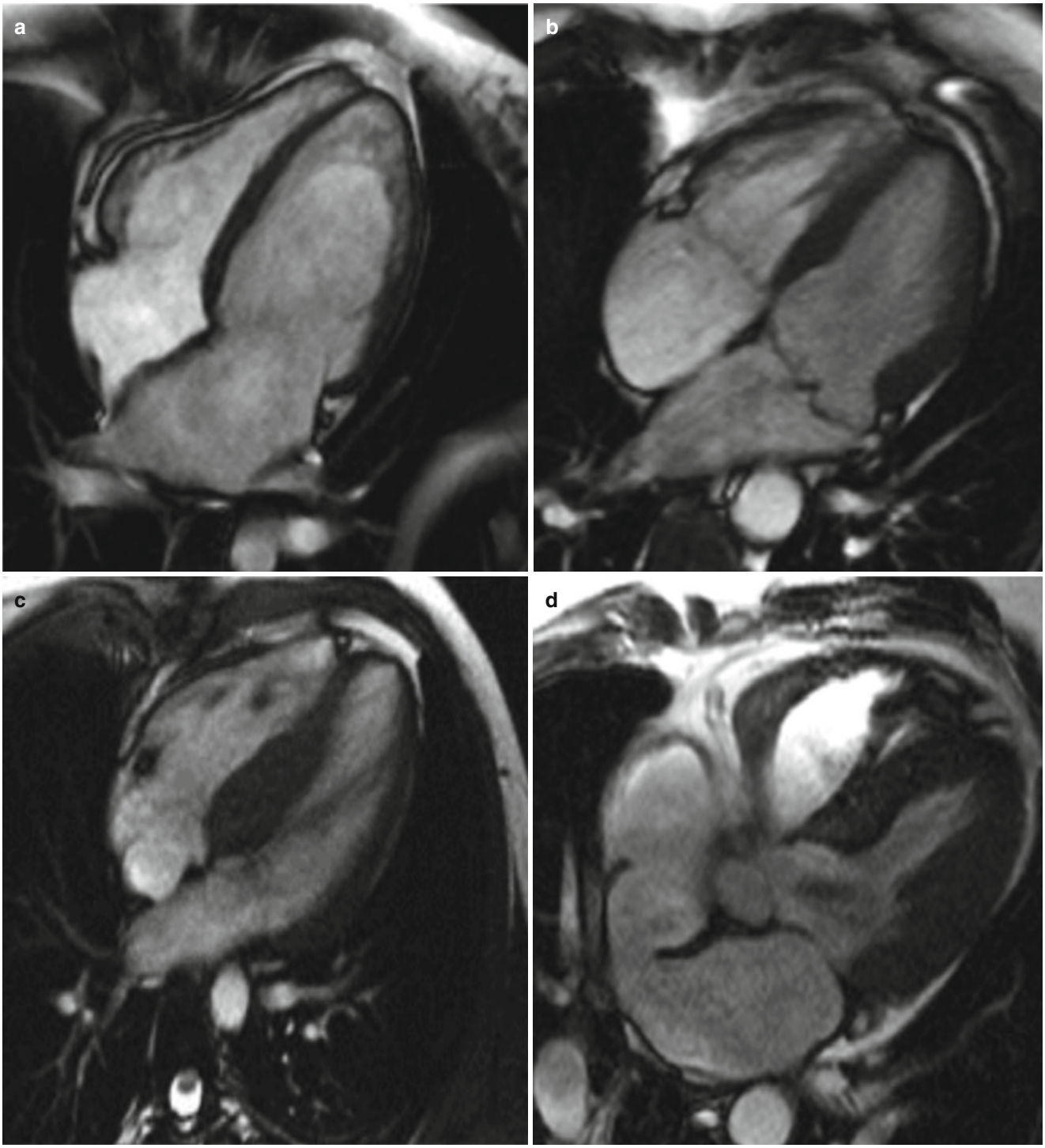


Fig. 21.1 Four chamber images (horizontal long axis of the left ventricle). (**a**) Normal (**b**) mitral valve prolapse (**c**) septal hypertrophy (**d**) venosus type atrial septal defect

ischemia is also potentially missed by SPECT unless the extent of ischemia is sufficient to cause transient global left ventricular dysfunction ("ancillary marker" of ischemia that is observed with severe triple vessel disease and a balanced reduction of flow on perfusion scintigraphy). Some of the limitations of SPECT techniques may be overcome by use of PET camera technology that permits absolute quantitation of flow, as detailed in the preceding chapter.

MRI myocardial perfusion imaging is a technique for evaluation of coronary flow reserve that utilizes gadolinium

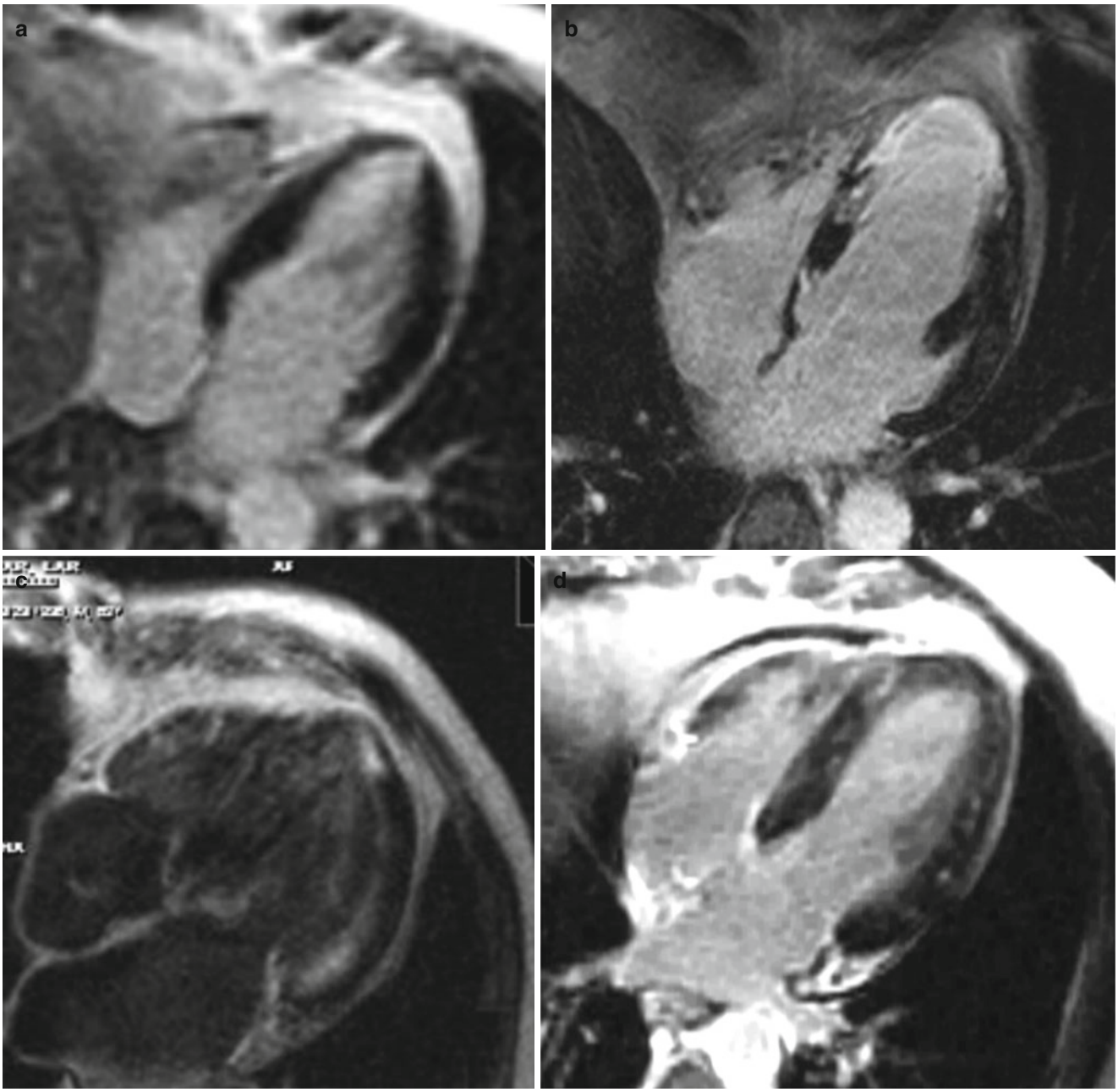


Fig. 21.2 Delayed Gadolinium contrast enhanced MRI of the heart shows different patterns of enhancement. The normal appearance is a null signal (*black*) left ventricular myocardium. Myocardial infarction is most often enhancement in a vascular territory, with subendocardial scar or transmural enhancement, dependent upon the extent of injury. (**a**) Normal (**b**) myocardial infarction (**c**) amyloidosis (**d**) myocarditis

based contrast to show first pass arrival of contrast labeled blood to the myocardium. This is unlike stress myocardial perfusion scintigraphy which images the steady state distribution of an injected radioisotope in the myocardium. It does have similarities to stress myocardial perfusion PET which can also be used to evaluate the first pass arrival of the injected radioisotope.

A variety of different protocols have been used for performance of myocardial stress perfusion MR imaging and these vary in terms of the gadolinium administration (dose, single vs. double bolus), stress agent (vasodilator, dobutamine), the use of stress alone or compared to rest perfusion and magnet strength (Table 21.1). Irrespective of these differences, MRI myocardial perfusion has been demonstrated to be an accurate method for detection of significant CAD, and compares favorably to echocardiographic and nuclear techniques in inter modality comparisons.

Two dimensional imaging of the myocardium in multiple slices (generally short axis of the left ventricle) is performed at maximal possible speed in order to see the first pass bolus

arrive and the myocardium blush. The evaluation of the myocardial perfusion requires that images are obtained at the same point in the cardiac cycle from one heart beat to the next, in order to evaluate the same segment of the heart. This is achieved by the use of cardiac gating of the MRI imaging, with images generally obtained as close to diastole as possible to minimize the effect of cardiac motion on image quality. Respiratory motion also impacts the location of the heart relative to the image, and so the data is obtained during breath holding.

Table 21.1 MRI myocardial perfusion

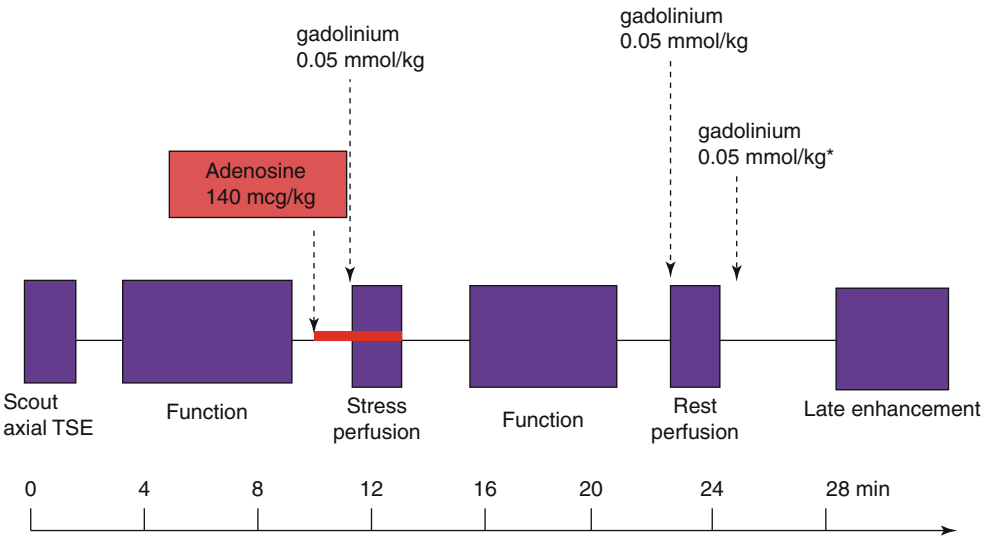
Gadolinium dose
0.05 mmol/kg for each perfusion series, total dose 0.1–0.2 mmol/kg
Gadolinium administration
MRI compatible power injector
Saline bolus immediately following Gadolinium
4 ml/s infusion rate
Double bolus protocol for absolute quantitation of flow
Stress testing method
Cold pressor
Vasodilator (Dipyridamole, Adenosine or Regadenoson)
Dobutamine (Stress wall motion with or without peak stress perfusion)
Exercise (limited availability, wall motion)
Testing protocols
Rest perfusion followed by stress perfusion[a]
Stress perfusion followed by rest perfusion[a]
Stress alone (visual analysis)
Combined stress protocols (Dobutamine + Adenosine, Adenosine + Cold pressor)
Magnetic resonance system
1.5 T or 3 T
Interpretation
Visual analysis
Semi quantitative analysis (ratio of time intensity curves for stress vs. rest)
Quantitative analysis with calculation of myocardial blood flow

[a]Minimum time between rest and stress perfusion is 10–15 min to allow Gadolinium washout

This requirement to obtain image data very rapidly (most often multiple images in each heart beat) compromises the ability for detail in terms of spatial resolution. The loss in spatial detail is offset by the use of sequences that maximize signal (T1 shortening) from the contrast and this signal is inherently greater at 3 T compared to 1.5 T. Newer image acquisition strategies such as k-space and time sensitivity encoding (k-t SENSE) combined with acquisition at higher field strength (3 T) allow improved in-plane spatial resolution with favorable signal to noise ratio.

The type of stress testing performed is limited by the size of the magnet bore and the need for the patient to be lying down, still and breath holding for the imaging. Although MR compatible equipment for exercise exists, the most frequent method of stress is pharmacologic stress using a vasodilator agent (dipyridamole, adenosine or regadenoson). Other stress types include dobutamine and cold pressor stress. Figure 21.3 outlines a typical protocol for performance of vasodilator stress testing in combination with a comprehensive evaluation of function and delayed enhancement.

The tolerance and safety of adenosine stress within the MRI scanner environment has been evaluated [11]. In a study of 351 patients (76 % having angiographically significant coronary artery disease) there were no deaths, myocardial infarctions, or episodes of bronchospasm. Transient 2nd (Mobitz II) or 3rd-degree atrioventricular (AV) block occurred



Function = Cine imaging left ventricular short axis, HLA and VLA, left ventricular outflow long axis and aortic valve short axis cine.

*Additional 0.05 mmol/kg dose administered immediately after rest imaging for optimization of delayed enchancement images. Total dose for protocol 0.15 mmol/kg of gadolinium based MR contrast.

Fig. 21.3 MRI protocol (vasodilator stress and rest)

Table 21.2 MRI myocardial perfusion contraindications

Gadolinium
GFR < 30 ml/min[a]
Previous allergic reaction to Gadolinium based contrast agent
Vasodilator stress
Asthmatic
High grade heart block
Previous sensitivity to vasodilator agent
Any stress testing
Unstable angina
Decompensated CHF
Critical aortic stenosis
General contraindications to MRI
Pacemaker or defibrillator[b]
Other implanted electronic device
Ferrous metal containing foreign body (shrapnel, some surgical devices)
Body size too great for the bore of the magnet
Relative contraindications
Implanted devices may be MR compatible but preclude chest imaging due to field distortion (e.g. spinal fusion rods)
Unmanageable claustrophobia

[a]FDA and ACR recommendation, due to increased risk of NSF in patients with significant acute or chronic renal dysfunction. This includes patients on dialysis

[b]Dependent upon local site experience and expertise, MRI may be safely performed in selected non pacing dependent patients with implanted pacemaker or defibrillator with support and device monitoring from cardiology

in 27 patients (8 %) and there were no sustained episodes of advanced AV block. Transient chest pain was the most common side effect (199 subjects-57 %). Contraindications to the use of this technique are detailed in Table 21.2 and include the contraindications to a patient being within the magnetic field, to stress testing generally, cautions regarding the use of the gadolinium contrast agents and contraindications to the use of the vasodilator stress agent.

Imaging laboratories commencing MRI stress testing must additionally have appropriate MRI compatible equipment for monitoring blood pressure and for infusion of the stress agent in addition to appropriate planned and rehearsed responses to emergency situations. Specialized cardiac imaging software is required for image acquisition, in addition to software for image processing and reading and appropriate training of technologist and physicians involved.

The Accuracy of MRI Myocardial Perfusion Imaging for Detection of Myocardial Ischemia

Validation of the Technique

Data in an animal model with direct comparison to myocardial perfusion scintigraphy has come from a study by Lee and colleagues who imaged 18 chronically instrumented dogs using first-pass MR perfusion and compared results to stress-rest SPECT for coronary stenoses of varying severity. The gold standard for assessment of myocardial perfusion in this study was obtained by post-mortem microsphere quantification of regional myocardial flow. Although limited to an animal model, this study found that perfusion across the transmural extent of the LV wall was visually and quantitatively apparent for reductions in coronary blood flow ≥50 %. Further, reductions in flow of ≥50 % that were not identified by dual isotope SPECT were apparent in first-pass MR perfusion. This early data suggested improved sensitivity over SPECT for detection of relatively mild reductions in coronary flow [12].

Two early studies in patients examined first-pass MR perfusion at rest and during pharmacological stress with comparison to the gold standard of cardiac catheterization. In 2000, Al-Saadi and colleagues studied 34 patients with CAD and compared signal time-intensity curves on first-pass MR perfusion images acquired before and after dipyridamole infusion [13]. Sensitivity and specificity in this population were 90 and 83 %, respectively, with low intraobserver variability. In 2003 Nagel and colleagues published data from 84 patients referred for primary diagnostic coronary angiography who had rest-adenosine first-pass MRI perfusion [14]. Sensitivity and specificity using a quantitative analysis of signal intensity curves for multiple slices were 88 and 90 %, respectively, while the corresponding values were 70 and 78 % for visual assessment.

Similar results have come from comparisons of MRI perfusion imaging to radionuclide methods and to invasive angiography. Ishida and colleagues studied 104 patients using first-pass MRI perfusion during dipyridamole and isometric handgrip exercise (published in 2003). Patients also had stress-rest ^{201}Tl SPECT (in a subset of 69/104) and invasive coronary angiography (104/104 patients) [15]. The sensitivity of first-pass MRI perfusion for detection of CAD was 90 %, with sensitivities for 1-, 2- and 3-vessel coronary disease of 85, 96, and 100 %, respectively. Receiver operator curve analysis suggested stress/rest first-pass MRI perfusion was more accurate than stress/rest thallium imaging for detection of a significant coronary lesion. Schwitter et al. studied 48 patients using a multislice first-pass MRI perfusion during dipyridamole compared to ^{13}N-ammonia PET and quantitative coronary angiography [16]. PET performed better than MRI, with sensitivity 91 % and specificity 94 % for detection of coronary artery disease, while the corresponding values for the MRI stress perfusion were 87 and 85 %.

In a recently published meta analysis of the diagnostic accuracy of MRI stress perfusion for the detection of coronary artery disease was evaluated. The authors identified 263 citations from which 55 relevant original articles were selected and 26 publications satisfied all of the inclusion criteria, and also presented data on patient-based analysis. Studies were included if they had at least 10 patients being

evaluated for the detection of obstructive coronary artery disease and used a reference standard of invasive coronary angiogram, defining significant stenosis as >50 % loss of luminal diameter. The overall patient-based analysis (pooled analysis of 2125 patients, 31 % female) demonstrated a sensitivity of 89 % (95 % CI: 88–91 %), and a specificity of 80 % (95 % CI: 78–83 %). Adenosine stress perfusion cardiac MRI had better sensitivity than with dipyridamole (90 % (range 88–92 %) versus 86 % (range 80–90 %), P = 0.022), and a tendency to a better specificity (81 % (78–84 %) versus 77 % (71–82 %), P = 0.065) [17].

The Use of Perfusion MR for Detection of Abnormal Coronary Flow Reserve in the Absence of Severe Epicardial Stenosis

Within the last decade there have been a series of studies reporting presence of coronary flow reserve abnormalities in the absence of significant epicardial stenosis. One of the initial observations of abnormal perfusion MRI in syndrome X came from Panting et al. who evaluated 20 patients (16 women) with syndrome X and published findings in 2002 [18]. The subjects had typical angina, positive stress ECG, normal angiograms and no evidence for coronary spasm at provocative testing. Adenosine stress MRI induced differences in the myocardial perfusion index were observed in the patient group, and were significantly different from age and sex matched controls. The observed pattern was a lack of increment in the perfusion in the subendocardium compared to the subepicardium. Additionally, the patient group were more likely to experience pain with adenosine infusion compared to the control group (95 % vs. 40 %). The findings of this study supported the hypothesis that subendocardial ischemia is the cause of chest pain in patients with syndrome X and additionally demonstrated utility of perfusion MRI for detection of coronary flow reserve abnormalities in the absence of significant epicardial stenosis.

Subclinical Abnormalities Detected by MRI

A subset of the MESA study had detailed wall motion analysis in addition to stress MR perfusion for detection of subclinical abnormalities in the absence of symptoms or known CAD [19]. Within this group of 73 patients (33 % female) wall motion abnormalities could be measured in the subjects who had the lowest hyperemic myocardial blood flow response to adenosine.

In another study of 110 predominantly asymptomatic patients (32 % female) who had stress perfusion MRI without evidence for regional myocardial ischemia, the relationship between the calculated myocardial perfusion reserve (MPR) and risk factors for coronary artery disease was examined [20]. After adjustment for baseline patient characteristics, the presence of hypertension showed the strongest correlation with MPR among other risk factors including diabetes and dyslipidemia.

These two studies support the theory that microvascular dysfunction occurs in patients with risk factors for coronary artery disease and may be subclinical. Additionally, it is possible that quantitative analysis of perfusion data is more sensitive than visual assessment for the detection of diffuse abnormalities in coronary flow reserve. Further work defining the "normal" range of myocardial perfusion reserve in a healthy population across a wide range of age groups would be invaluable in the interpretation of these data and for understanding the importance of various factors that influence vascular function.

Abnormalities in Symptomatic Women

Chest pain due to microvascular dysfunction in women is most commonly associated with presence of traditional risk factors for coronary artery disease. Chest pain is common in women with systemic lupus erythematosus (SLE) and these women have a significantly increased risk of atherosclerotic coronary events [21]. Traditional risk factors, such as hypertension and hypercholesterolemia, only partly account for the increased risk of coronary disease in SLE. In a prospective study of women, patients with SLE developed significantly more CAD events than controls and the presence of SLE itself was an independent predictive factor for coronary artery disease [22]. In a recent study of 18 women with SLE and typical or atypical angina compared to ten reference controls, myocardial perfusion reserve index (MPRI) measured by MRI was decreased in the symptomatic women who had no obstructive coronary disease on CT coronary angiography. The mean MPRI in patients versus controls was 2.0 ± 0.4 versus 2.4 ± 0.4 ($p = 0.031$) in the subepicardium and 1.8 ± 0.3 versus 2.1 ± 0.4 ($p = 0.24$) in the subendocardium. Multivariate linear regression revealed that SLE was the only predictor of subepicardial ($p < 0.0025$; $\beta = -1.059$) and subendocardial ($p < 0.05$; $\beta = -0.529$) MPRI after adjustment for risk factors. Additionally, the visual analysis of the perfusion data was abnormal in 8/18 [23].

Yilmaz et al. have published a retrospective observation of the relationship between MRI myocardial perfusion and coronary microvascular dysfunction. They identified a group of 42 patients who presented with unstable angina but had no significant epicardial CAD at angiography. An adenosine-induced, reversible subendocardial perfusion defect was detected in 22/42 patients (52 %) without significant CAD. Coronary epicardial vasospasm was detected in 10/42 patients (24 %) while microvascular dysfunction was found

in 20/42 patients (48 %). Patients with a reversible stress-induced perfusion defect were more likely to have an abnormal response to intracoronary ACh testing than those without a perfusion defect (20/22 vs. 10/20 $p<0.01$) [24]. This relationship between adenosine induced perfusion abnormalities with MRI and abnormal response to ACh at angiographic coronary reactivity testing (CRT) suggests that these patients have both endothelium dependent and endothelium independent abnormalities in coronary vascular function – because the two forms of stress testing are examining different aspects of coronary reactivity.

The study by Yilmaz used visual evaluation of pharmacologic stress MRI. Quantitative rather than visual analysis of stress MRI was used in a recently completed study of women with MCD proven by a more comprehensive protocol of CRT that included Ach, adenosine and nitrate stimulation. Fifty-three symptomatic women with MCD and no obstructive coronary artery disease had stress perfusion MRI for calculation of MPRI (CASS MRV 3.3 software, Pie Medical Imaging B.V., Netherlands) and this group was compared to a reference control population of age and estrogen matched asymptomatic women (publication submitted). Women with MCD had lower MPRI values globally and in subendocardial and subepicardial regions compared to controls (1.63 ± 0.39 vs. 1.98 ± 0.38, $p=0.007$, 1.51 ± 0.35 vs. 1.84 ± 0.34, $p=0.0045$, 1.68 ± 0.38 vs. 2.04 ± 0.41, $p=0.005$, respectively).

The clinical utility of measurement of perfusion reserve non invasively requires further investigation. It is possible that perfusion MR may be a useful tool to evaluate response to therapy in women with microvascular disease. Mehta et al. recently published pilot data from a randomized double blind placebo control crossover trial of a novel anti anginal agent, Ranolazine in 20 women with angina in the absence of obstructive coronary artery disease. In addition to improved Seattle angina questionnaire symptoms score, there was a trend towards improved MPRI with the use of Ranolazine. In a subset of 13 patients who also had invasive coronary flow reserve measurement, those with $CFR<3.0$ had a significantly improved MPR with Ranolazine versus placebo compared to women with $CFR>3.0$ (Δ in MPRI 0.48 vs. −0.82, $p=0.04$) [25].

These recent studies in women were all performed at 1.5 T, using standardized clinical stress MR protocols and relatively simple quantitative analysis of data based on evaluation of stress and rest upslope curves for evaluation of the response to vasodilator stress. These studies build on the observations of Panting et al. and the MRS literature and demonstrate abnormalities in coronary flow reserve in women with chest pain and open coronary arteries.

The calculation of the MPRI from the first pass perfusion data required quantitative analysis using software that is not currently approved by the FDA for use in clinical MRI, and was performed in patients enrolled in IRB approved research studies.

Cold Pressor Stress

Vasodilator stress evaluates the adenosine receptor responsiveness of the coronary vascular bed and this is an endothelium independent response. Endothelium dependent responses to nitroglycerine and to acetyl choline are also examined as part of invasive evaluations of microvascular and macrovascular function.

Cold pressor stress is also a method for evaluating endothelium dependent response. The normal response to cold pressor stress is for the coronary artery to dilate, and a paradoxical vasoconstrictive response (or lack of vasodilation) is observed in atherosclerotic coronary arteries in the absence of significant epicardial stenosis [26]. Abnormal angiographic response to cold pressor stimulus has also been observed in patients with cardiac syndrome X, in measures of both coronary diameter and coronary flow [27]. These observations confirm the presence of endothelial dysfunction in syndrome X.

The cold pressor stress testing can be performed using several different methods, but most often involves immersion of the hand and forearm(s) in ice water for a period of 90–120 s. This technique is possible to perform in the MRI environment although access to the forearm may be limited when the patient is within the bore of the magnet, dependent upon patient size.

The use of cold pressor testing in the magnet was recently described for measurement of coronary flow reserve in a small group of asymptomatic women with cardiovascular risk factors who had evaluation of coronary sinus flow at 3 T at rest and during cold pressor stress. The coronary sinus flow reserve was 1.31 ± 0.2 in this population and the authors also noted a 45 % increase in rate pressure product during the cold pressor stimulus [28].

Approaches to Quantitation of Myocardial Perfusion

There are different approaches to interpretation of MR perfusion imaging, and a lack of consensus exists regarding the optimal approach. Visual analysis of the perfusion data requires a sufficient contrast bolus to allow the visual detection of the signal increase during first pass. Visual analysis has been effective for detection of epicardial coronary disease, when ischemic myocardium appears as a full thickness, or near transmural region of hypoperfusion within a coronary vascular territory. Figure 21.4 demonstrates single frame images at rest and stress to show the difference in first

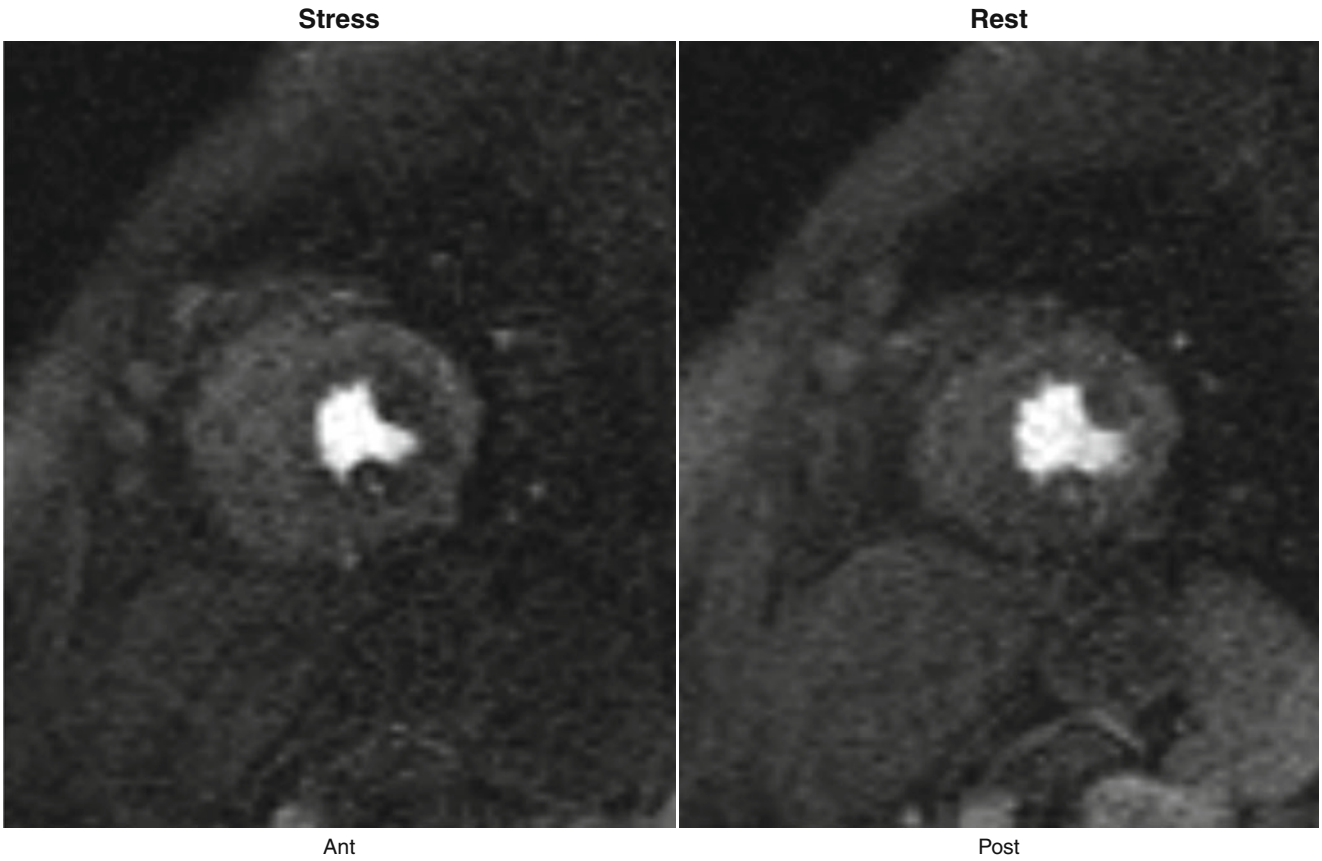


Fig. 21.4 Stress perfusion with diffuse subendocardial first pass hypoperfusion is contrasted with a representative image from the corresponding rest perfusion sequence that has a more uniform appearance of the myocardial contrast. The images are a mid ventricular level short axis image. The visual analysis of perfusion MRI is performed by inspection of cine images, looking for regional variation in the first pass of myocardial perfusion

pass perfusion patterns observed in the setting of diffuse microvascular dysfunction.

Quantitative analysis may be used to estimate absolute myocardial flow or more simply to evaluate relative difference in time intensity curve statistics for stress compared to rest perfusion data. Quantitative studies of perfusion MR have used a variety of different modeling methods, and either locally designed or commercially marketed software. The major MR system vendor perfusion quantitative software packages are not available for clinical use in the US due to lack of FDA approval. (Cardiac imaging with Gadolinium contrast is an off label use of this agent).

A recent study from the United Kingdom compared perfusion MR at 3 T to coronary fractional flow reserve (FFR) measured at the time of angiography in a group of 42 patients (including 9 women). Fractional flow reserve was measured in all vessels with >50 stenosis, and FFR <0.75 was considered significant. MR perfusion reserve was calculated for each vascular territory. The MPR in the 24 territories with an FFR < 0.75 was 1.35 ± 0.5. In the 90 territories in which FFR was > 0.75, MPR was 2.2 ± 0.5 ($p < 0.0001$). On ROC analysis, an MPR of 1.58 provided optimal sensitivity and specificity to detect coronary ischemia at the threshold of FFR < 0.75, with sensitivity 80 %, specificity 89 % ($p < 0.0001$) [29]. This study helps to define values for MPRI that may be anticipated for significant coronary luminal narrowing.

There is, however, a paucity of data defining normal limits for myocardial perfusion reserve, as evaluated by MRI, for different age groups or according to sex. There is also a paucity of data defining the repeatability of the measurements made using this perfusion imaging technique, which hinders interpretation of serial measurements in patients over time.

In Conclusion

Cardiac MRI may be used for the evaluation of women with suspected microvascular dysfunction. There are two main approaches using MRI: spectroscopic evaluation of cellular composition and the non invasive imaging and quantitation of myocardial perfusion reserve. Both techniques have demonstrated abnormalities in patients with

microvascular dysfunction in the absence of obstructive coronary artery disease and compare favorably to invasive angiographic measures of coronary reactivity. There is a potential clinical role for MRI for the detection of microvascular disease and monitoring of response to therapy. The advantage of the non invasive approach is in the avoidance of the need for invasive angiography. Further research is required to prove the clinical utility of MRI in this population but the early data is promising.

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Role of Echocardiography in Evaluation of Women with Chest Pain

22

Jannet F. Lewis and Brian G. Choi

Abstract

This chapter reviews the role of echocardiography in evaluation of women with chest pain. Stress echocardiography is a well-established and diagnostically reliable modality for assessment of women with chest pain and suspected myocardial ischemia due to epicardial coronary artery disease. The technique is particularly suitable in women because of the lack of radiation and applicability in individuals who are or are not able to exercise. The chapter addresses the difficult issue of chest pain in women with angiographically normal coronary arteries, including prognostic role of stress echocardiography in these women, and newer echocardiographic techniques for assessment of coronary flow reserve and detection of microvascular disease. The importance of coronary flow reserve abnormalities in women with chest pain is examined.

The chapter concludes with a discussion of the role of transthoracic echocardiography in assessment of two other important cardiac causes of chest pain in women with angiographically normal coronary arteries – hypertrophic cardiomyopathy and stress-induced cardiomyopathy. The typical echocardiographic features of both types of cardiomyopathies are reviewed. Also, the role of coronary flow reserve and myocardial contrast in clarifying the causes of ischemia in these entities is examined.

Keywords

Echocardiography • Chest pain • Women

Stress echocardiography is a well-established modality for assessment of women with chest pain and suspected myocardial ischemia. The technique has proven accuracy of 80–90 % for diagnosis of obstructive CAD. Diagnostic accuracy is reportedly similar to radionuclide perfusion imaging. Stress echocardiography is particularly suitable for evaluation of chest pain in women with suspected ischemic heart disease because of the lack of ionizing radiation and applicability to women who can or cannot exercise. This chapter reviews the literature on application of stress echocardiography in women, as well as the use of echocardiography for assessment of chest pain in women using standard transthoracic echocardiography. The role of more recent echocardiographic modalities in assessment of women with chest pain is also reviewed.

The chapter addresses the difficult issue of chest pain in women with evidence of stress induced ischemia and normal coronary arteries, including prognostic role of echocardiography in these women. Lastly, the role of echocardiography in diagnosis and management of women with angiographically normal coronary arteries and chest pain from less common causes is discussed.

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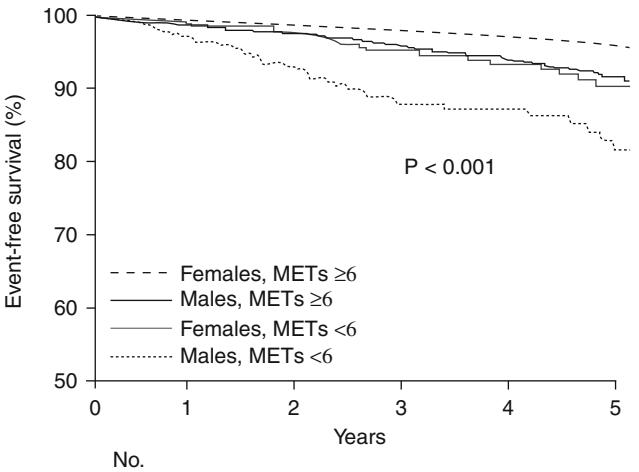
Stress Echocardiography

Studies using stress echocardiography in women with chest pain and suspicion for coronary artery disease have demonstrated good to excellent sensitivity for detection of occlusive epicardial coronary stenosis [1, 2]. Marwick et al. compared the accuracy of echocardiography to standard treadmill exercise ECG testing in 162 women [1]. Sensitivity and specificity of exercise echocardiography were 80 and 81 %, respectively, compared to 77 and 56 % with exercise ECG in women with interpretable electrocardiograms. A smaller study in women with chest pain who underwent both stress echocardiography and coronary angiography showed overall sensitivity and specificity of 86 % [2]. The authors point out the superior diagnostic accuracy of stress echocardiography in women with nondiagnostic exercise ECG studies. These studies infer that chest pain in women with abnormal stress echocardiograms and normal coronary angiography represents a limitation of test specificity rather than ischemia occurring in the absence of obstructive coronary artery disease.

An important aspect of stress echocardiography, in addition to demonstration of inducible myocardial ischemia, relates to the overall prognosis provided by both exercise and pharmacologic stress testing. Prognosis following normal stress echocardiography (both exercise and dobutamine) is consistently excellent [3]. Moreover, exercise capacity is related to outcome. In a study of 5,798 patients (including 2,476 women) undergoing stress echocardiography, exercise capacity and induced segmental wall motion abnormalities were echocardiographic predictors of death and nonfatal myocardial infarctions in both men and women [4] (Figs. 22.1 and 22.2). Overall survival and event-free survival were both worse in men compared to women. However, exercise echocardiography provided significant incremental predictive value for cardiac events compared to clinical findings and exercise ECG alone. The prognostic utility of exercise echocardiography appeared to be comparable in men and women, the best predictor being the extent and severity of exercise-induced segmental wall motion abnormalities. Similar incremental predictive value was observed in 1,488 elderly patients (44 % women) undergoing stress echocardiography [5], as well as women with high cardiovascular risk profiles. Heupler et al. performed exercise echocardiography in 549 consecutive women followed for a mean of 41 months, and found incremental value of stress echocardiography over clinical and exercise variables for identification of women at high risk for cardiovascular events [6].

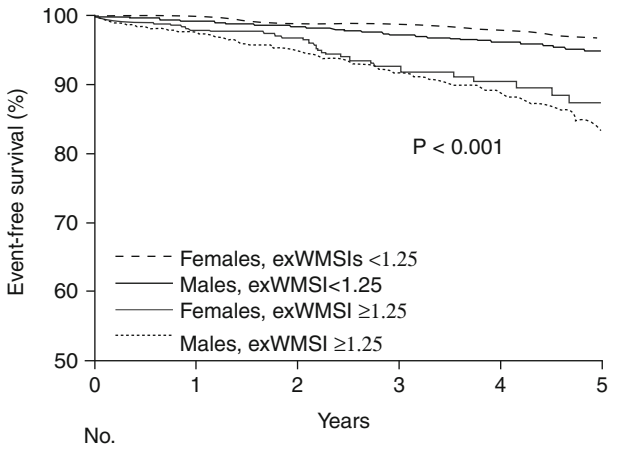
A recent study by Shaw et al. evaluated 4,234 women undergoing exercise or dobutamine stress echocardiography [3]. The greatest predictors of death over the 5 year follow up period included age, Duke treadmill score, resting left ventricular systolic function and extent of stress-induced left ventricular wall motion abnormalities. Of note, the extent of



No.

Category at risk						
F ≥6	1,999	1,845	1,340	870	487	274
M ≥6	2,981	2,621	2,016	1,321	807	459
F <6	468	420	335	230	151	88
M <6	366	266	206	150	106	61

Fig. 22.1 Survival free of cardiac death and myocardial infarction in men and women, with exercise capacity ≥6 metabolic equivalent (*METs*) and <6 METs (Reprinted from Arruda-Olson et al. [4]. With permission from Elsevier)



No.

Category at risk						
F < 1.25	1,929	1,808	1,348	890	518	299
M <1.25	1,945	1,783	1,376	920	568	321
F ≥1.25	538	457	327	210	120	63
M ≥1.25	1,372	1,104	846	551	345	199

Fig. 22.2 Survival free of cardiac death and myocardial infarction in men and women, with exercise wall motion score index (*WMSI*) <1.25 or ≥1.25 (Reprinted from Arruda-Olson et al. [4]. With permission from Elsevier)

stress-induced ischemia on echocardiography provided incremental information beyond resting left ventricular systolic function and Duke treadmill score. For women undergoing exercise echocardiography, 5-year survival was 99.4, 97.6, and 95 % for those with no, single, and multivessel ischemia, respectively ($p<0.0001$). Dobutamine stress echocardiography (DSE) in most studies has shown accuracy

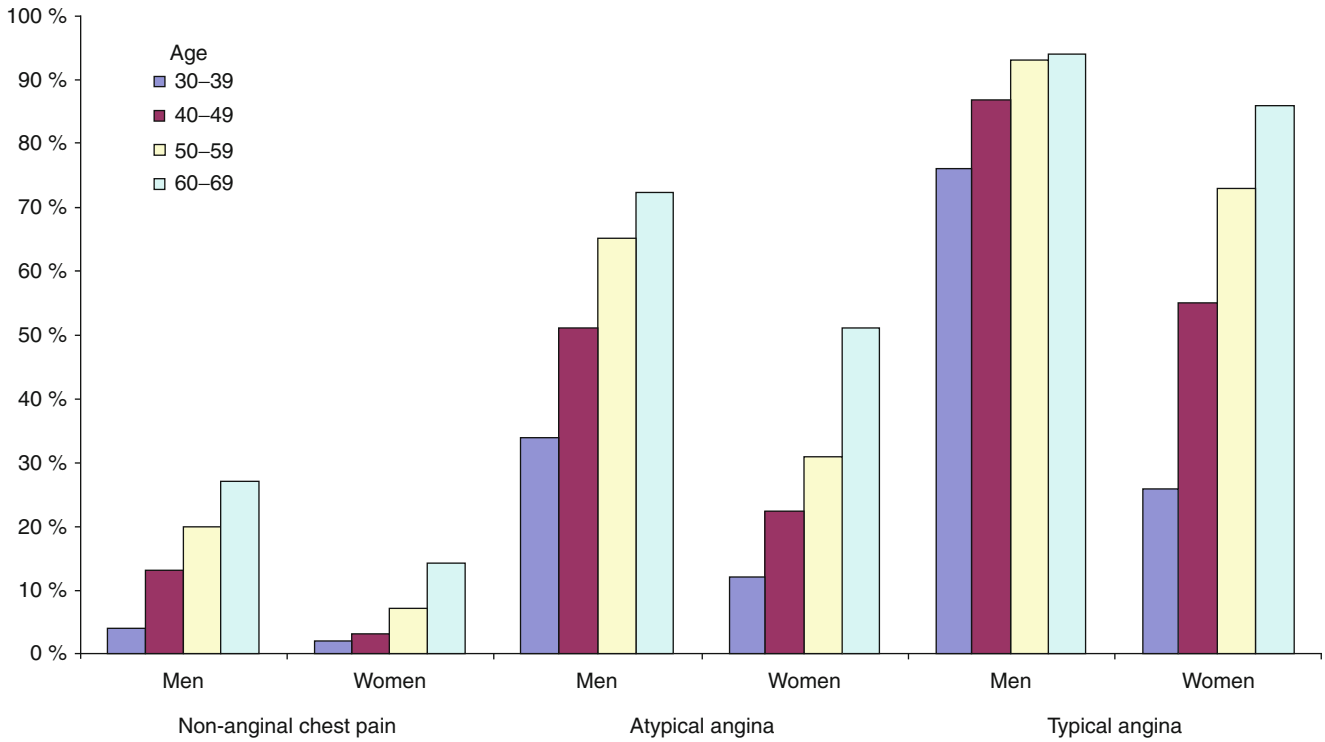


Fig. 22.3 Prevalence of obstructive coronary artery disease on catheterization by gender and symptoms (Adapted from Gibbons et al. [15]. With permission from Elsevier)

for detection of epicardial coronary artery disease, similar in women compared to men [7]. It should be noted that sensitivity of DSE for detection of single-vessel disease is substantially lower compared to diagnostic accuracy for multivessel disease [8, 9]. In addition, most studies are influenced by post-testing bias; that is, patients referred for cardiac catheterization are likely to have significant inducible ischemia, and are, therefore, more likely to have occlusive epicardial coronary artery disease. This referral bias may explain the discrepancies noted for sensitivities and specificities among studies using DSE in women for detection of coronary artery disease [9–13].

Despite this potential referral bias following stress testing, coronary angiography in women with chest pain has consistently shown a lower prevalence of obstructive CAD compared to men referred for cardiac catheterization [14]. Nearly 50 % of women undergoing cardiac catheterization have angiographically normal coronary arteries or minimally obstructive disease [15] (Fig. 22.3). The percentage of women undergoing cardiac catheterization with angiographically normal coronary artery disease is higher in women <60 years, and some studies suggest even more so in African American women [14]. In the past, such women were considered to have a benign prognosis. However, more recent studies, particularly from the WISE study, have demonstrated that many of these women with chest pain continue to have significant symptoms with functional disability, recurrent hospitalizations and repeated (sometimes invasive) testing [16]. Moreover, tests of endothelial and microvascular function are often abnormal in such women and associated with adverse cardiovascular events [17]. The majority of these events were repeat hospitalizations and percutaneous interventions, but nearly one-third were "hard events" including death, stroke, myocardial infarction or heart failure. The WISE study investigators proposed use of the term "microvascular angina" to describe women with chest pain in women with angiographically normal coronary arteries and evidence of ischemia [18]. These women often demonstrate, by noninvasive and invasive testing, evidence of microvascular or endothelial dysfunction. Importantly, the hypothetical model of microvascular angina also demonstrates why testing such as conventional stress echocardiography (either exercise or dobutamine) that relies on detection of left ventricular wall motion abnormalities, may not reliably detect subendocardial ischemia occurring as a consequence of microvascular or endothelial dysfunction.

Coronary microvascular abnormalities detected by measurement of coronary flow reserve have been associated with increased cardiovascular events in women without significant epicardial coronary stenosis. Cardiac magnetic resonance spectroscopy (MRS) has demonstrated metabolic evidence of stress-induced ischemia in women with chest pain and normal epicardial coronary arteries [19]. Although the numbers

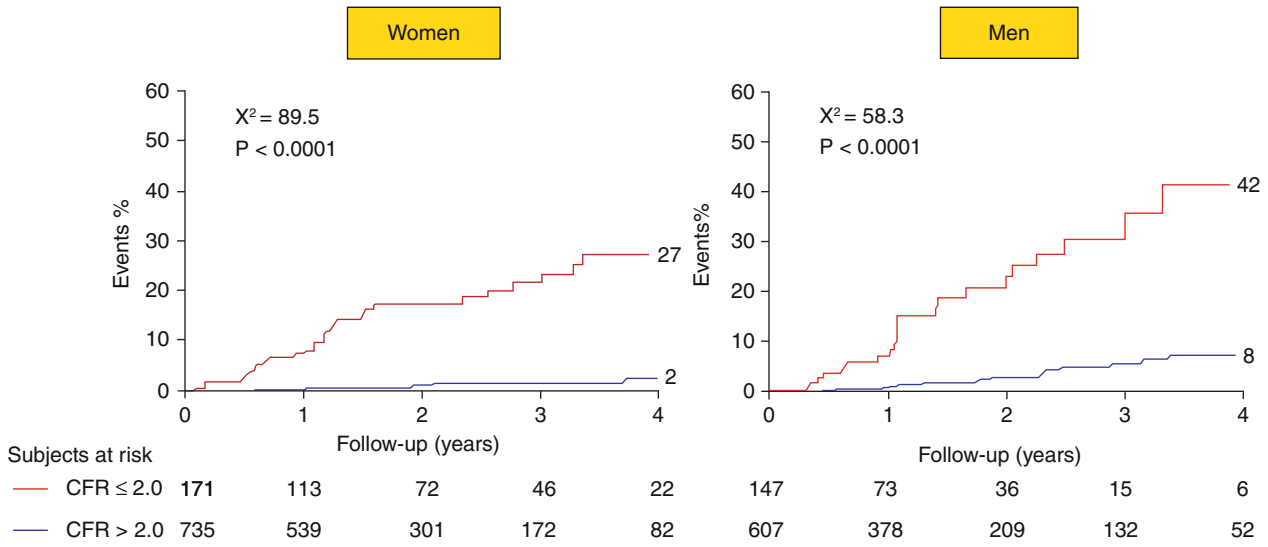


Fig. 22.4 Annual event rates for numbers of women and men with coronary flow reserve ≤2.0 or >2.0 (Reprinted from Cortigiani et al. [21]. With permission from Excerpta Medica)

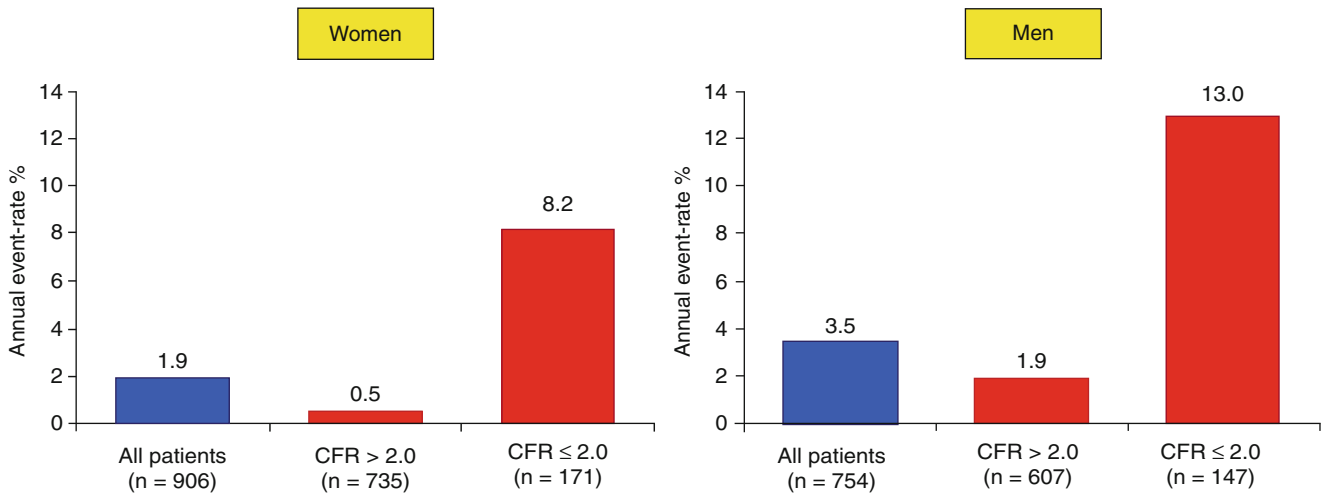


Fig. 22.5 Annual event rates in entire population of women and men and in groups with coronary flow reserves ≤2.0 and >2.0 (Reprinted from Cortigiani et al. [21]. With permission from Excerpta Medica)

were small, women with abnormal spectroscopy were more likely to have myocardial perfusion abnormalities on nuclear stress testing. Moreover, follow up of patients without epicardial coronary stenosis who underwent MRS showed an increased event rate among those with abnormal spectroscopy [20].

Coronary flow reserve measured in patients with normal stress echocardiograms (i.e., normal wall motion at baseline and no evidence of inducible myocardial ischemia) has been assessed noninvasively. Cortigiani et al. measured coronary flow reserve in the left anterior descending coronary artery in 1,660 patients, including 960 women with normal stress echocardiograms [21]. Coronary flow reserve was calculated by measuring peak diastolic flow velocities in the left anterior descending coronary artery at baseline and following high dose dipyrimadole: 19 % of both women and men showed abnormal coronary flow reserve. Event rate (including death, myocardial infarction and coronary revascularization) in this cohort of patients with normal stress echocardiograms (over a mean follow up of 19 months) was substantially lower in women compared to men (1.9 % vs. 3.5 %). However, among both women and men with abnormal coronary flow reserve, annual event rates were strikingly higher compared to patients with normal CFR (Figs. 22.4 and 22.5). Women with normal stress echocardiograms and normal CFR had an annual event rate of 0.5 % compared to

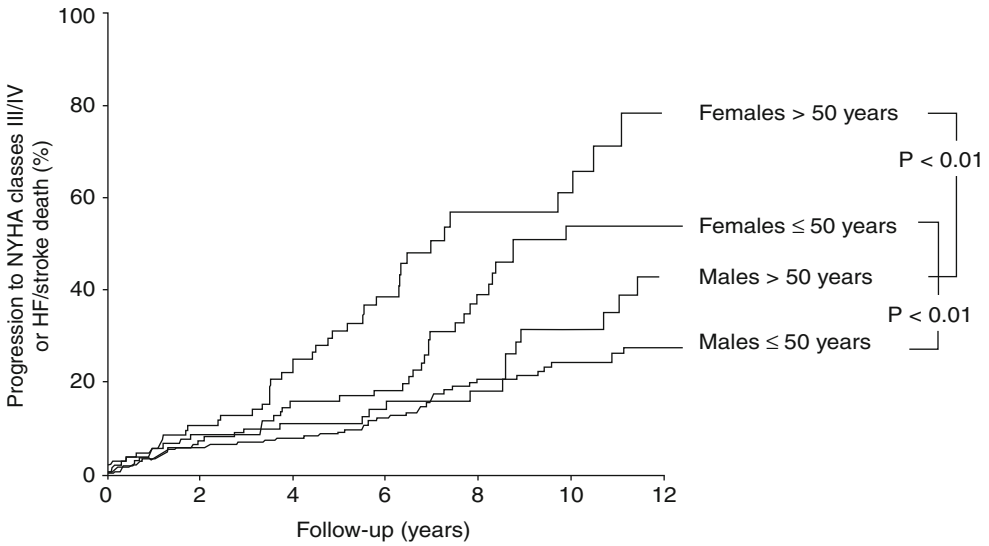


Fig. 22.6 Relation of age and gender to risk of poor outcome in HCM. Risk of progression to New York Heart Association (NYHA) functional classes III and IV, or heart failure (HF) or stroke death related to age at initial evaluation and gender. Analysis excludes patients with NYHA III or IV at initial evaluation. Female patients >50 years versus ≤50 years of age ($p<0.005$); male patients >50 years versus ≤50 years ($p=0.02$) (Reprinted from Olivotto et al. [27]. With permission from Elsevier)

a rate of 8.2 % among those with abnormal CFR. CFR is abnormal in both epicardial coronary artery disease and microvascular disease, and therefore does not provide localization of the site of abnormal myocardial blood flow. Thus, the lack of angiographic data in these patients is an important limitation to this study. Nonetheless, the presence of normal stress echocardiograms, without evidence of inducible ischemia, raises a potentially important issue regarding prognosis. Specifically, while prognosis among patients with normal stress echocardiograms is considered excellent, the findings of this study suggest that a subset of such individuals do not share in this favorable prognosis. These findings support previous investigations in patients with normal or near normal coronary arteries, and demonstrate the prognostic value of noninvasively measured CFR [22].

Similar findings have been reported using dobutamine echocardiography to measure coronary flow reserve [23]. Among patients with normal left ventricular systolic function at baseline and no evidence of inducible myocardial ischemia, important correlates of abnormal coronary flow reserve included diabetes mellitus, hypertension, and obesity. The high prevalence of these risk factors among women presenting for chest pain evaluation highlights the complex relation among risk factors, symptoms and inability to demonstrate ischemia using conventional techniques. These studies, demonstrating abnormal coronary endothelial and microvascular function in patients with angiographically normal coronary arteries and normal stress echocardiograms, challenge accepted approaches to evaluation of chest pain and ischemia in women.

Hypertrophic Cardiomyopathy

HCM is a disease caused by mutations of genes encoding the sarcomeric proteins, and is most commonly diagnosed or confirmed by transthoracic echocardiography [24–26]. The disease is autosomal dominant and would be expected to occur equally in men and women. Most studies of patients with HCM have shown a male predominance. The clinical impact of gender in HCM was evaluated in a multicenter, international study of 969 patients followed for an average of 6 years [27]. Men comprised 59 % of the study population. Women were notably older at diagnosis (mean age 47 years compared to 38 years in men), had more severe symptoms and more frequently demonstrated left ventricular outflow obstruction. Women were also more likely to progress to severe heart failure or death, especially those 50 years or older (Fig. 22.6). Sudden cardiac death was as common in women as in men. Of note, one-third of the study population had diagnosis of HCM made in the absence of cardiac symptoms or family history of disease. Women were 50 % less likely to have diagnosis made under these circumstances. However, treatment strategies did not differ among male and female patients with HCM. The authors proposed that the worse outcomes observed among women with HCM was in part a consequence of later diagnosis (on average 9 years older than men), but also due a greater prevalence of left ventricular outflow obstruction, and increased susceptibility to complications of atrial fibrillation.

Data from an HCM lay support group also suggest that women report more cardiac symptoms compared to men.

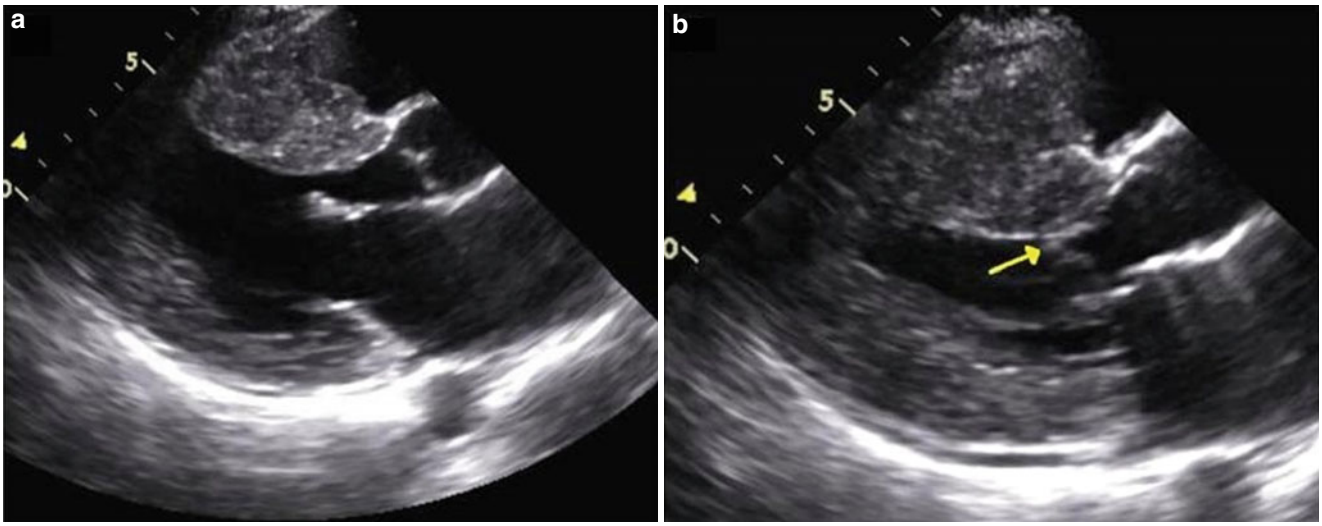


Fig. 22.7 Hypertrophic cardiomyopathy in a 42 year old woman with chest pain. Panel **a**. Diastolic frame showing marked asymmetric hypertrophy of the ventricular septum. Panel **b**. Systolic anterior motion of the mitral valve (*arrow*) consistent with left ventricular outflow obstruction

The Hypertrophic Cardiomyopathy Association, a patient support and advocacy group founded in 1996, evaluated symptoms among 1,228 patients, including 549 women [28]. The non-hospital or referral-based population was comprised of a diverse group of individuals. Compared to men, women more commonly reported chest pain, fatigue, lightheadedness and palpitations. Moreover, although men and women reported similar use of cardiac medications, including beta adrenergic blocking agents and calcium channel blockers, and similar numbers reported pacemaker implantation, women were more likely to be taking medications other than those prescribed for treatment of HCM.

Application of echocardiography in diagnosis of HCM has been primarily for demonstration of the typical features, i.e., asymmetric left ventricular hypertrophy, systolic anterior motion of the mitral valve, and left ventricular outflow gradient by Doppler echocardiography (Fig. 22.7). Three-dimensional echocardiography has more recently been utilized to refine the diagnostic reliability of echocardiography in distinguishing other forms of left ventricular hypertrophy from HCM [29]. Caselli et al. performed three-dimensional echocardiography in 68 subjects including healthy volunteers, athletes, hypertensives and 15 patients with HCM. These authors proposed use of a mass dispersion index, an assessment of left ventricular mass distribution, that demonstrated a specificity of 100 % for diagnosis of HCM.

The vast majority of HCM patients demonstrate normal to hyperdynamic left ventricular systolic function measured by ejection fraction. However, newer techniques challenge these observations. Tissue Doppler imaging (TDI) is a relatively new diagnostic technique that measures myocardial tissue velocities. The most commonly used clinical application has been with use of longitudinal velocities by pulsed wave or color Doppler. Several studies in patients with HCM have demonstrated abnormalities of systolic and diastolic tissue Doppler velocities, measures of left ventricular contractility and diastolic properties, that have important diagnostic and prognostic applications [30–32].

Vinereanu et al. evaluated patients with HCM, systemic hypertension as well as athletes and normal subjects. Using TDI peak systolic annular velocities, these investigators were able to distinguish pathologic from physiologic hypertrophy with a diagnostic accuracy of 92 % [30]. Several investigators have used TDI to identify patients with genotypic but not phenotypic evidence of HCM [31, 32]. Nagueh et al. identified patients with HCM mutation, but no left ventricular hypertrophy, with 100 % sensitivity and 93 % specificity [31].

The limitations of evaluating left ventricular systolic function using velocities obtained by tissue Doppler imaging have been largely negated by speckle tracking imaging, which uses "speckles" from the echocardiographic images to derive myocardial strain [33]. Abnormalities of left ventricular contractility in HCM patient with normal ejection fraction has also been demonstrated with use of two-dimensional strain determined by speckle tracking [34]. In a study of patients with HCM, secondary hypertrophy and cardiac amyloidosis, strain imaging clearly distinguished among the different causes of hypertrophy. In particular, HCM was characterized by decreased myocardial strain, as well as evidence of segmental dysfunction of the myocardium.

Myocardial ischemia has been well established in some HCM patients and appears to result primarily from disease of the small intramyocardial coronary arterioles [35], exacerbated by increased demand from the hypertrophied left ventricle and, in many patients, left ventricular outflow

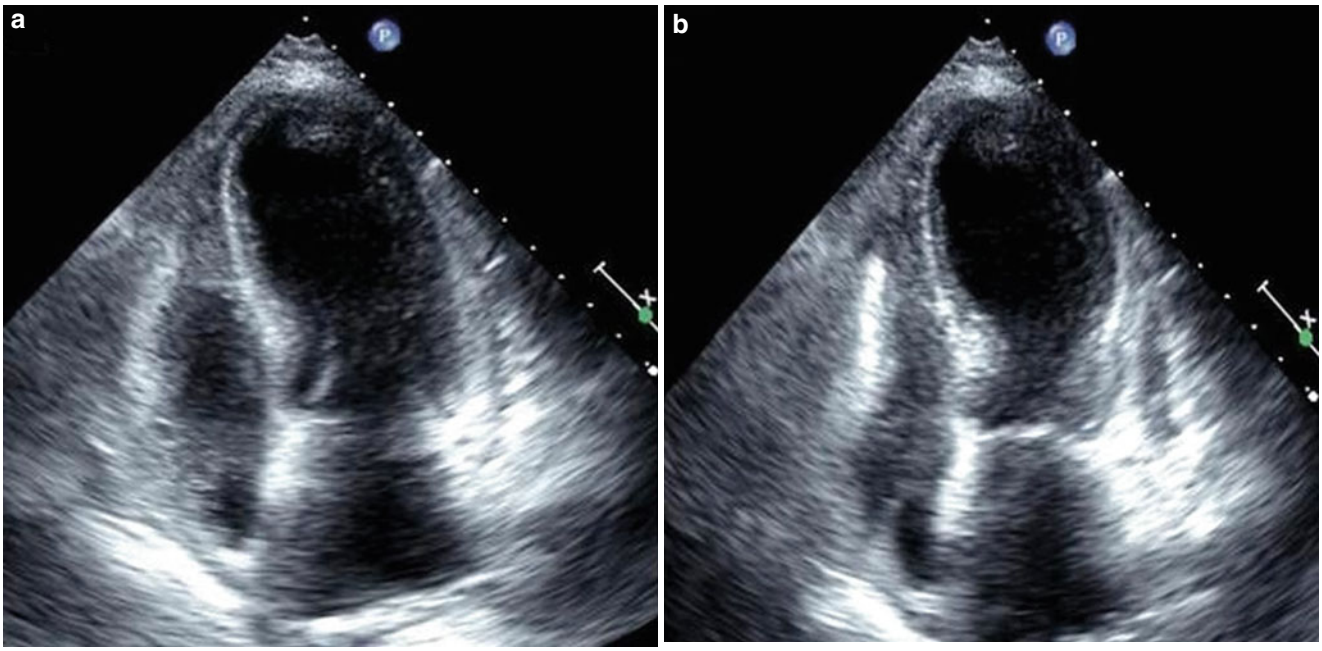


Fig. 22.8 Apical ballooning in a 62 year old woman with severe chest pain occurring after a heated argument. Panel **a**. Diastolic frame in apical 4-chamber view. Panel **b**. During systole, there is marked ballooning of the left ventricular apex. A thrombus is also seen in the left ventricular apex

obstruction. At autopsy, the intramural arterioles show intimal or medial thickening with reduced vessel area. Invasive studies performed more than 25 years ago, demonstrated evidence of myocardial ischemia after atrial pacing in patients with HCM and no epicardial coronary artery disease [36]. Noninvasive studies using a variety of modalities, including PET, cardiac MR and SPECT have demonstrated evidence of myocardial ischemia occurring from disease in the microvasculature [37–40].

Conventional stress echocardiography has rarely been reported to be useful in diagnosis of ischemia in patients with HCM [41, 42]. Okeie et al. performed exercise and dobutamine stress echocardiography in 39 patients with nonobstructive HCM and without epicardial coronary artery disease [42]. Stress-induced decrease in LV ejection fraction was observed in 43 % of patients, and among these patients, new wall motion abnormalities during dobutamine infusion occurred commonly. These findings have not been consistently confirmed in larger populations of patients with HCM. Stress echocardiography would be expected to have poor reliability in HCM given the underlying nature of ischemia in this disease.

On the other hand, chest pain in HCM may occur as a consequence of abnormal coronary flow reserve in the absence of epicardial coronary disease. Using Doppler echocardiography, Cortigiani et al. studied 68 patients, including 28 women, with hypertrophic cardiomyopathy to assess coronary flow reserve following dipyridamole in the left anterior descending coronary artery. Compared to age and gender matched controls, CFR was abnormal in the majority of symptomatic patients with hypertrophic cardiomyopathy (67 %), but also present in 17 % of asymptomatic patients [43]. Cardiovascular event rates over 3-year follow up were higher among patients with abnormal CFR, including asymptomatic individuals. An interesting study using myocardial contrast echocardiography in 56 patients with HCM (predominantly the apical variant) demonstrated perfusion defects in hypertrophied segments of the left ventricle. Perfusion defect size was related to impaired contractile function by tissue Doppler imaging. [44]. These findings support the role of microvascular disease as a cause of ischemia in HCM.

Stress-Induced Cardiomyopathy

Initially described as takotsubo cardiomyopathy [45] or apical ballooning [46], stress-induced cardiomyopathy is increasingly recognized as a cause of chest pain and severe left ventricular dysfunction in women with angiographically normal coronary arteries. Stress induced cardiomyopathy characteristically occurs after profound emotional or physiologic stress [47–49], and accounts for approximately 1–2 % of suspected myocardial infarctions [50]. The disease predominantly affects postmenopausal women, with men accounting for only 10 % of cases in most series [47]. The hallmark of the syndrome is segmental dyskinesis that does not correspond to a plausible single coronary distribution [51, 52], resulting in the description of left ventricular ballooning, most commonly of the apex (Fig. 22.8). Initially thought to have a benign prognosis with complete recovery

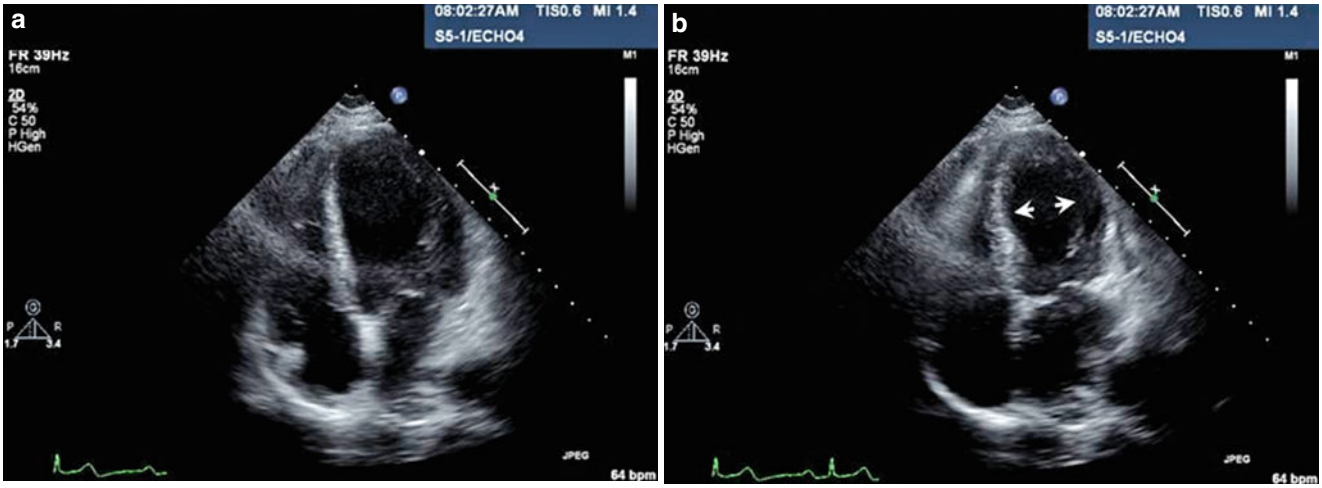


Fig. 22.9 Takotsubo cardiomyopathy. Representative images from a 65 year old woman presenting with chest pain after an emotionally stressful event demonstrate midventricular systolic ballooning (*arrowheads* in panel **b**), not present in diastole (panel **a**). Subsequent emergent catheterization demonstrated angiographically normal coronary arteries

of left ventricular function within the first 2 months, the acute episode can be complicated by death (in-hospital mortality of 2 %) [53] or embolic event from left ventricular thrombi. All-cause mortality exceeds that expected in the general population, and approximately 5 % of patients do not completely recover LV function [54, 55]. The proposed mechanism for the often profound decrease in left ventricular function observed in these patients appears to be marked adrenergic stimulation resulting in multivessel coronary vasospasm, microcirculatory abnormalities including endothelial dysfunction, or transient left ventricular outflow tract obstruction [56, 57].

The pathophysiology of takotsubo cardiomyopathy has been investigated using echocardiography. Myocardial contrast echocardiography indicates that dysfunctional wall segments have decreased perfusion [58, 59]. Furthermore, supporting the hypothesis that takotsubo cardiomyopathy is caused by microvascular dysfunction, adenosine stress contrast echocardiography in patients with takotsubo show decreased perfusion at baseline in segments with wall motion abnormalities. Adenosine infusion results in improved perfusion and contractility of the affected segments, consistent with vasodilation of coronary microcirculation [60]. Also, a transient decrease in coronary flow reserve assessed by echo in the acute phase of takotsubo occurs in the regions with dysfunctional myocardium [61, 62], further supporting the microcirculatory dysfunction hypothesis. Notably, the functional improvement seen with adenosine infusion is not seen during dobutamine stress echocardiography. Dobutamine infusion does not reverse the wall motion abnormalities seen in takotsubo cardiomyopathy [63], which is consistent with the hypothesis that catecholaminergic surge is the major underlying cause of this syndrome. Some investigators, based on these results, have proposed that a similar phenomenon may account for markedly false positive stress echocardiograms in postmenopausal women, suggesting that stress testing can be a trigger for takotsubo cardiomyopathy [64, 65]. Indeed, as the pathophysiology of Cardiac Syndrome X and takotsubo (or stress-induced) cardiomyopathy are strikingly similar, the two entities may represent a similar disease process, one chronic and the other acute – akin to coronary artery disease having a chronic manifestation (stable angina) and an acute presentation (myocardial infarction).

A maker of increased risk in stress-induced cardiomyopathy may be dynamic left ventricular outflow tract obstruction. Older women with a septal bulge may be predisposed to develop LVOT obstruction, which in one series was associated with worsened outcomes [66].

Echocardiography plays an important role in the diagnosis and management of patients with takotsubo cardiomyopathy. Echocardiography in these patients reveals profound left ventricular dysfunction and segmental wall motion abnormalities representing multiple coronary distributions. The classic apical ballooning is seen in the majority of patients, but other variants, including ballooning of the mid- or basal-walls (also referred to "inverted takotsubo") has also been described [51] (Fig. 22.9). Serial echocardiography is important to confirm the normalization of left ventricular systolic function, and to identify patients with persistent left ventricular systolic dysfunction.

Conclusions

Our understanding of chest pain in women has evolved significantly over the last several years. Standard testing used to assess for coronary artery disease and myocardial ischemia in men has often been negative or inconclusive in women. Assumptions regarding

the absence of myocardial ischemia based on these tests have been significantly challenged with testing of coronary endothelial and microvascular function. Echocardiography continues to play an important role in diagnosis of ischemia in women with epicardial coronary artery stenosis, and in assessing prognosis in women. However, further work is needed to assess the role of new techniques, including noninvasive assessment of coronary flow reserve and myocardial perfusion in women with chest pain and angiographically normal coronary arteries.

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Assessment of Coronary Vasomotor Responses: Clinical Usefulness

23

Peter Ong, Anastasios Athanasiadis, and Udo Sechtem

Abstract

Assessment of coronary vasomotor responses can be a helpful tool to detect coronary vasomotor abnormalities as the underlying cause for chest pain in patients with normal or unobstructed coronary arteries. Testing can be performed using intravenous or intracoronary administration of vasoactive substances such as ergonovine or acetylcholine. Intracoronary provocation testing for the assessment of coronary vasomotor responses is an integral part of coronary angiography in Asia. However, in the US and Europe it is only performed in few centres as part of daily clinical routine. This book chapter gives a detailed explanation on how to perform assessment of coronary vasomotor responses and how to interpret the test results. In addition, frequent pitfalls and limitations are described. Moreover, the different clinical scenarios where abnormal coronary vasomotion can explain angina symptoms in patients with normal or unobstructed coronary arteries, such as ACS, stable angina, etc. are highlighted. If vasomotor abnormalities have been demonstrated calcium channel blockers and nitrates are often the drugs of choice. In addition, patients should receive drugs to improve endothelial function or to reduce inflammation such as ACE-inhibitors and statins. The results of intracoronary provocation tests can serve as a basis to estimate prognosis. Patients with a pathologic test result have an increased morbidity and risk for cardiovascular events during follow-up. Patients with proof of epicardial spasm have been shown to be at an elevated risk for cardiac death and myocardial infarction (approx. 1–1.5 % per year). In patients with microvascular spasm/dysfunction prognosis regarding major cardiovascular events is generally good (0 % for cardiac death, ~0.5 % for myocardial infarction per year). However, persistent or ongoing angina represents a major problem.

Keywords

Acetylcholine • Ergonovine • Coronary spasm • Microvascular dysfunction • Coronary microcirculation • Myocardial ischemia

Assessment of Coronary Vasomotor Responses – How to and Interpretation

Assessment of coronary vasomotor responses can be a helpful tool to detect coronary vasomotor abnormalities as the underlying cause for chest pain in patients with normal or unobstructed coronary arteries. Testing can be performed using intravenous or intracoronary administration of vasoactive substances. Until today, intracoronary provocation

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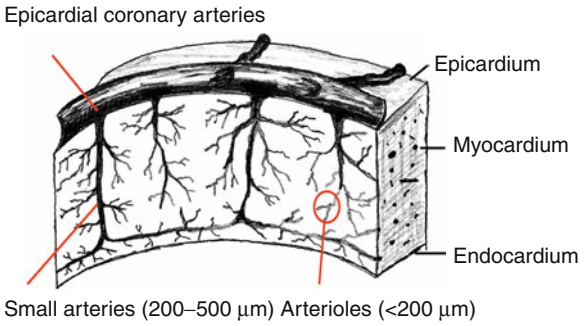

Fig. 23.1 Sketch of the coronary vasculature illustrating the potential locations of coronary spasm (microvessels = diameter <200 μm)

testing using substances such as acetylcholine or ergonovine has remained the gold standard for clinical evaluation of coronary vasomotion. Other provocative substances such as serotonin, histamine or, more recently, salbutamol [1] have so far only been used in research investigations. For all tests it is essential to discontinue any vasodilatory drugs that may alter the response of the coronary arteries to provocative stimuli such as calcium channel blockers and nitrates for at least 48 h. If a stringent protocol is followed, these tests can be performed with a low rate of serious complications (<1 %) [2, 3]. This rate is in the same order as reported for diagnostic coronary angiography [4]. Intracoronary provocation testing has been recommended for investigation of unexplained chest pain in patients with normal or unobstructed coronary arteries by the guidelines of the European Society of Cardiology [5], AHA/ACC [6] and the Japanese Circulation Society [7] to detect coronary artery spasm (Fig. 23.1).

Intracoronary Provocation Testing

Intracoronary provocation testing for the assessment of coronary vasomotor responses is an integral part of coronary angiography in Asia, especially Japan and Korea. However, in the US and Europe it is only performed in few centres as part of daily clinical routine. Acetylcholine and ergonovine are routinely used for intracoronary provocation tests [5]. Usually, a transfemoral approach is chosen. However, the transradial route has also been shown to be practicable [8].

Acetylcholine

Acetylcholine (ACH) is a transmitter of the parasympathetic nervous system and acts via nicotinic and muscarinic receptors. Muscarinic acetylcholine receptors (mAchR) play a key role for vascular homeostasis. ACH binds on mAchR in a non-selective way as an agonist. Activation of vascular endothelial mAchR leads to nitric oxide mediated vasodilatation whereas activation of vascular smooth muscle mAchR leads to vasoconstriction. Depending on the integrity of the endothelium, the net effect of intracoronary acetylcholine administration can be vasodilatation (endothelium intact) or severe constriction and spasm (dysfunctional endothelium) [9]. However, arteries can also respond with spasm in the presence of an intact endothelium if a hyperreactivity of the vascular smooth muscle layer is present [10]. It should be noted that ~25 % vasoconstriction as compared to baseline in response to intracoronary acetylcholine administration may still be within the range of normal responses as such a reaction can be observed in patients with angiographically normal coronary arteries without chest pain [11].

ACH can be administered via an infusion pump with a predefined speed and dose. However, manual injections via the diagnostic coronary catheter are easier to perform and have also been shown to be safe and reliable. Commonly used protocols either administer the substance over a period of 20 seconds as a bolus or as an injection over a period of 3 min directly followed by angiography. It is important to rinse the catheter before performing angiography as 1–2 ml of ACH solution are contained within the lumen of the catheter. An interval of 3 min should lie between the administration of increasing doses of ACH. Independent of the mode of administration, it is essential to follow a stepwise approach with increasing doses to avoid irreversible vasoconstriction/spasm with subsequent complications in patients with a very low threshold for provocation of severe spasm. Usually 2, 20 and 100 μg of ACH are used for provocation of the LAD and LCX when challenged selectively [12]. If an unselective injection is performed in the LCA, this corresponds to a dose of 200 μg ACH although many Japanese centres use only up to 100 μg as the maximum dose (Fig. 23.2). For provocation of the RCA a dose of 80 μg is used but some Japanese centres apply only up to 50 μg [13, 14] (Fig. 23.3).

Ergonovine

Ergonovine is an ergoline derivative and one of the primary ergot and morning glory alkaloids. Acting at alpha-adrenergic, dopaminergic and serotonin receptors (the 5-HT2 receptor), it exerts on vascular smooth muscle a powerful stimulant effect not clearly associated with a specific receptor type. Ergonovine is given in intracoronary doses of up to 40 μg into the RCA and up to 64 μg into the LCA if a continuous infusion pump is used [15]. If a stepwise approach is applied, graded doses of 1, 5, 10 and 30 μg of ergonovine are injected into the RCA and LCA [16].

Intravenous Provocation Testing

Ergonovine is the only provocative substance which is used for intravenous administration. Intravenous ergonovine administration may be performed during cardiac catheterisation (e.g. with incremental doses of 0.05, 0.1, 0.15 mg)

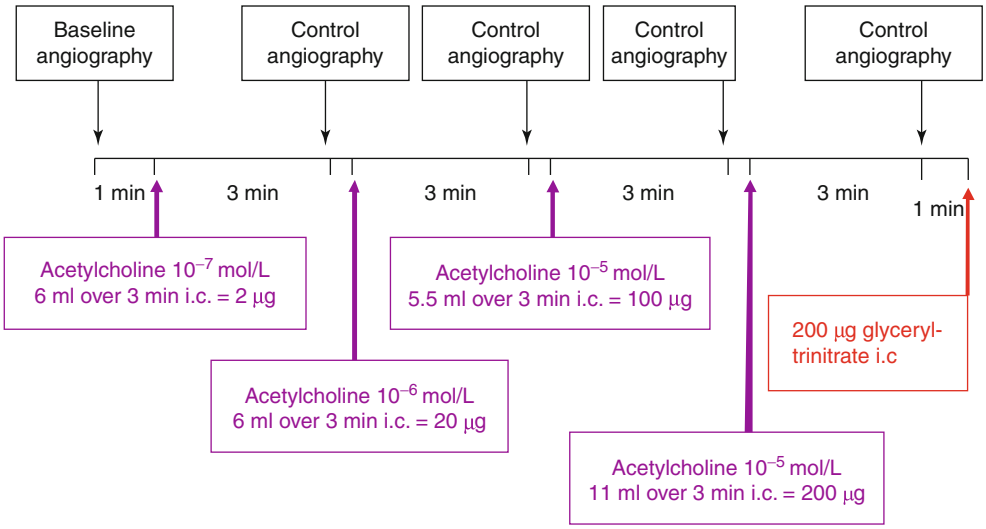

Fig. 23.2 Intracoronary acetylcholine provocation protocol for the LCA

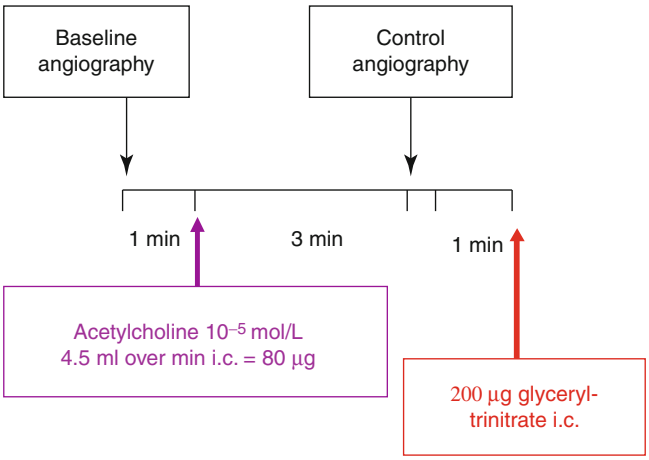

Fig. 23.3 Intracoronary acetylcholine provocation protocol for the RCA

instead of an intracoronary injection [17, 18]. However, this approach has a lower yield of a pathologic response [15] compared to the intracoronary administration. Intravenous ergonovine provocation testing has also been performed together with continuous 12-lead ECG registration outside the cath lab as a follow-up test after invasive documentation of coronary spasm and initiation of medical treatment or during stress-echocardiography [19]. However, this non-invasive, intravenous approach should be seen with caution as adequate management of any unforeseen complications may not be feasible.

General Recommendations and Interpretation of Test Results

During provocative testing continuous blood pressure and 12-lead ECG registration is obligatory. This usually requires special radiolucent electrodes in the catheterisation laboratory. After each injection, coronary angiography is performed to document the speed of coronary flow and epicardial diameter changes. Moreover, a 12-lead ECG should be registered after each injection to document any changes from baseline. Throughout the procedure frequent questioning of the patient about symptoms or discomfort experienced during testing is mandatory. It is important to find out whether the patient has such discomfort also occurring spontaneously. In addition, it is worth knowing if the intensity of the provoked discomfort is different but the character of the discomfort is identical.

In case of (re)production of intolerable symptoms, haemodynamic compromise or angiographic evidence of severe spasm, intracoronary glyceryltrinitrate (GTN, usually 200 µg) is given to relax the coronary arteries and relieve the chest discomfort. In case of mild or well known symptoms it is often sufficient to await the degradation of ACH after several seconds which usually leads to improvement or disappearance of symptoms. In this situation which is the usual one, sequential testing of the LCA and the RCA can and should be performed in order to detect multivessel spasm. GTN should be given routinely at the end of the test into the RCA (which is usually tested as the second vessel) and then into the LCA. Following such a protocol, the rate of serious complications (e.g. myocardial infarction, refractory spasm, sustained ventricular arrhythmias or need for resuscitation) is very low (<1 %) [2, 3]. However, transient AV-block is frequently observed, mostly during provocation of the RCA. It almost always resolves within seconds after reducing the speed of the manual injection. Following this approach, placement of a temporary pacemaker was not necessary in more than 3,000 ACH-tests performed at our institution since 2006.

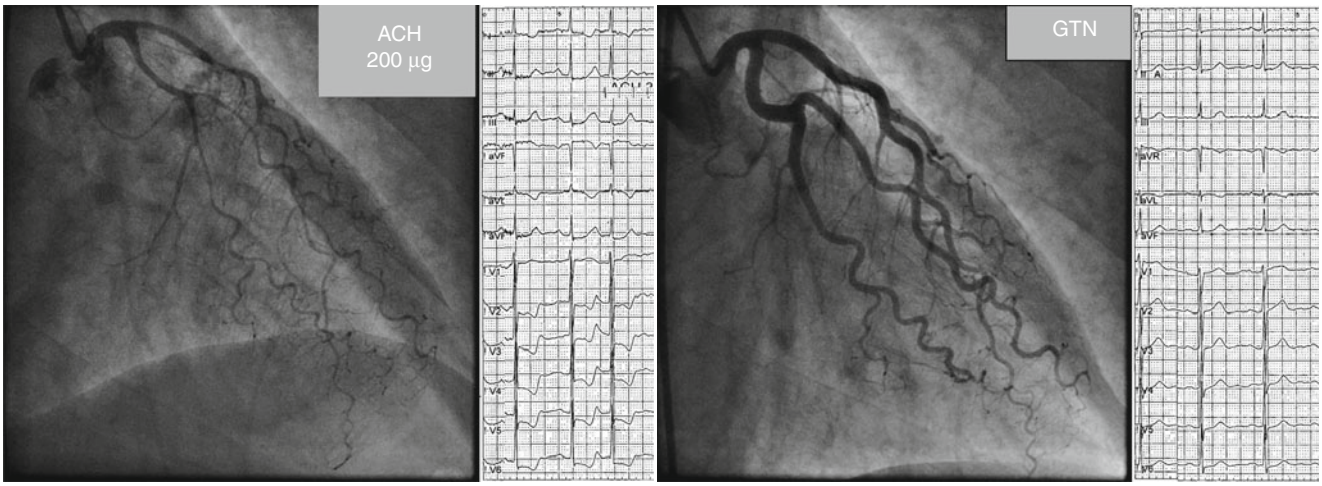

Fig. 23.4 Diffuse epicardial spasm. This was a 66 year old woman with exercise related angina without any cardiovascular risk factors. Exercise stress testing revealed ischemic ECG shifts in leads V4–V6 together with reproduction of her angina. Coronary angiography revealed curly but smooth arteries. Upon ACH challenge there was diffuse spasm in the LCA, ischemic ECG shifts in leads V2–V6 and the patient had reproduction of her usual angina (*left*). After intracoronary glyceryltrinitrate administration symptoms, vasoconstriction and ECG shifts resolved (*right*)

Interpretation of Provocation Testing Results Is Routinely Based on Three Criteria

1. Reproduction of the patient's usual symptoms.
2. Ischemic ECG changes on 12-lead ECG registration during administration of the provocative substance compared to baseline (ST-segment depression, ST-segment elevation including tenting of T-waves, T-wave alternans).
3. Epicardial coronary diameter reduction (≥75 % as compared to the relaxed state after GTN injection, quantified by quantitative coronary angiography, QCA) [20] although some Japanese centres consider only visual subtotal occlusion of an epicardial artery as a spastic reaction [7].

- Uneventful test: If none of the above criteria is met (no symptoms, no ECG changes, no relevant, i.e. <25 % epicardial diameter changes), the test is uneventful.
- Inconclusive test results: If one of the mentioned criteria (e.g. reproduction of chest pain without ischemic ECG shifts and without epicardial spasm or an ischemic ST response without symptoms or epicardial spasm) is observed during provocation testing, the test result should be termed inconclusive.
- Epicardial coronary spasm: If epicardial diameter changes ≥75 % in comparison to the relaxed state after intracoronary glyceryltrinitrate administration together with reproduction of the patient's symptoms are documented, epicardial coronary spasm can be diagnosed (Fig. 23.4) [20].
- As direct visualization of the coronary microcirculation in the clinical setting is not possible at present, microvascular spasm remains a diagnosis of exclusion. An accepted definition of microvascular spasm is the combination of a reproduction of the patient's symptoms together with ischemic ECG shifts (usually ST-segment depression) without epicardial diameter changes ≥75 % (Fig. 23.5) [20].

Limitations of Intracoronary Provocation Testing

Assessment of coronary vasomotor responses underlies some limitations. They should be taken into account when performing and interpreting such tests. Coronary vasomotor responses to provocative stimuli have been shown to follow a circadian variation with more pronounced or pathologic results in the morning as compared to the afternoon [21]. Therefore, assessment of coronary vasomotion may produce different results depending on the time of day they are performed. Hence, when sequential testing is employed, tests should be done at the same time of the day.

Discontinuation of vasodilatory drugs at least 48 h before provocation testing is essential. Otherwise the test result may be false negative due to sustained pharmacological effects of these drugs. Moreover, the substance used for assessment of coronary vasomotion may influence the test result. Although some authors have argued that acetylcholine and ergonovine are equally sensitive for induction of coronary spasm, others have shown that intracoronary injection of acetylcholine after uneventful intracoronary injection of ergonovine sometimes may elicit coronary spasm [22].

Regarding the coronary microcirculation, the main dilemma lies in the fact that its visualization is currently not possible. Therefore, microvascular spasm/dysfunction can

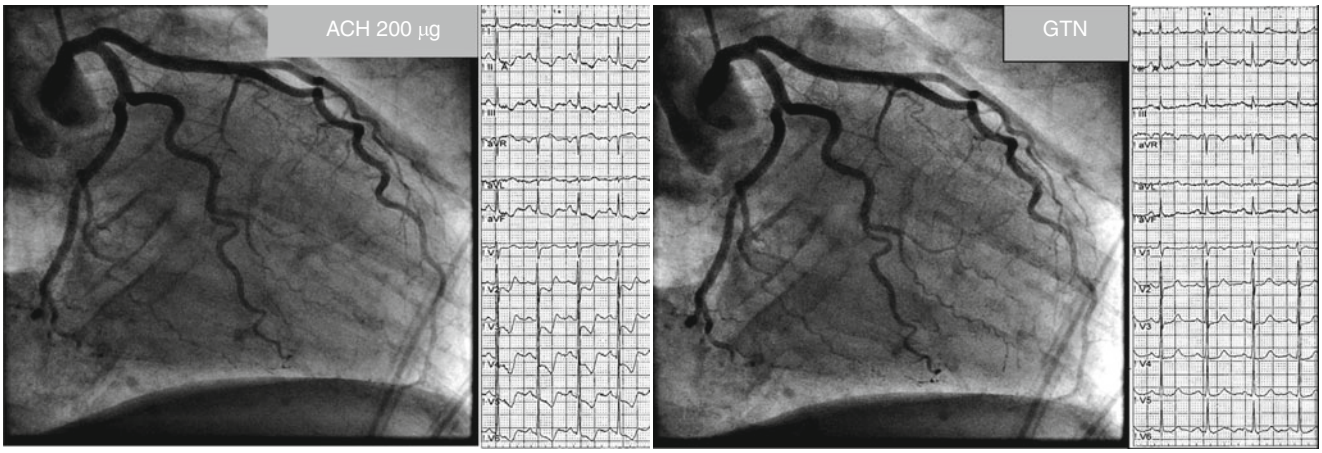

Fig. 23.5 Microvascular spasm. This was a 62 year old woman with exertional dyspnoea and occasional attacks of angina at rest. She had hypertension, hypercholesterolemia and a positive family history for cardiovascular disease. Exercise stress testing reproduced her dyspnoea and the ECG showed ST-segment depression ≥0.1 mV in leads V4–V6. The coronary angiogram revealed normal coronary arteries. Intracoronary acetylcholine provocation reproduced her angina together with ST-segment depression in leads V2–V6 but without epicardial coronary spasm (*left*). After administration of 200 µg glyceryltrinitrate the angina and the ST-shifts resolved (*right*)

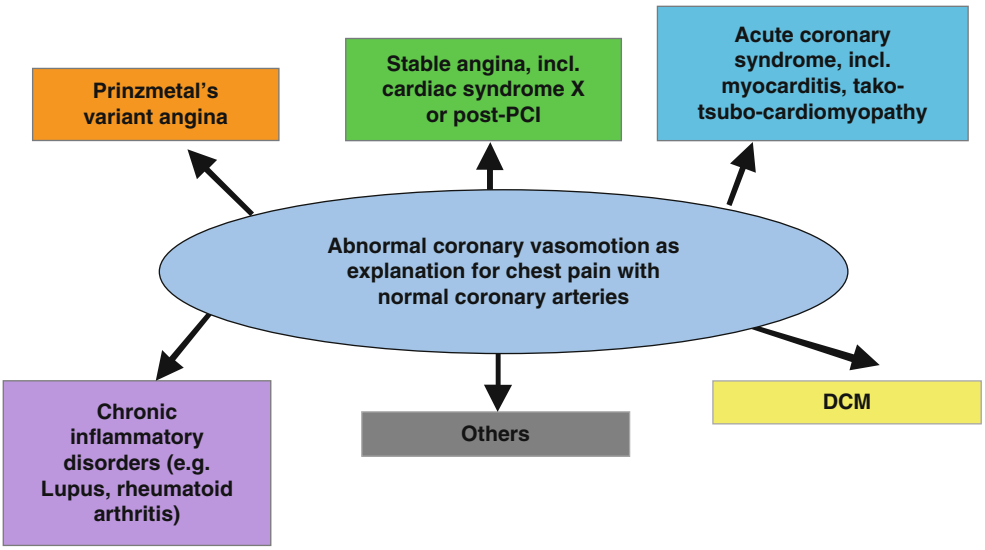

Fig. 23.6 Clinical scenarios where abnormal coronary vasomotion can explain angina symptoms in patients with normal or unobstructed coronary arteries

only be diagnosed indirectly via ischemic ECG shifts, reproduction of chest pain during provocative testing or measurement of markers from coronary sinus blood samples indicative of myocardial ischemia (e.g. lactate).

Measurement of lactate in the coronary sinus may not detect minor but clinically relevant (production of symptoms in the patient) amounts of microvascular spasm/dysfunction because coronary microvascular dysfunction can be patchily distributed along the microvasculature [23]. This dilemma may be overcome with more comprehensive methods to assess ischemic ECG shifts during provocation testing such as, for example, the 80-lead ECG vest [24].

Clinical Scenarios with Coronary Vasomotor Abnormalities, Chest Pain and Normal Coronary Arteries

Abnormal coronary vasomotion in the setting of normal or unobstructed coronary arteries can be the cause for angina in various clinical conditions (Fig. 23.6). It is, however, important to remember that even angiographically impressive stenoses may not necessarily be the cause of the patient's symptoms as fractional flow reserve measurements frequently demonstrate absence of relevant pressure drops during administration of adenosine [25].

Especially in patients with repetitive attacks of resting chest pain one should look for vasomotion abnormalities even if a critical stenosis has been identified. This is important as stenoses with a diameter reduction >70 % by coronary angiography but not impeding blood flow at rest should cause exercise related angina but not resting angina.

Identification of the exact cause of chest pain can serve to establish a diagnosis, initiate appropriate medical treatment and avoid unnecessary reassessments including repeated invasive coronary angiographies. Given the high sensitivity and specificity of intracoronary provocation tests [26], a negative test result indicates that a coronary vasomotor abnormality is unlikely to be the cause for the chest pain. In this case, further diagnostic tests for non-cardiac chest pain may be pursued [27]. In case of an inconclusive test result, abnormal coronary vasomotion cannot be fully excluded as provocation tests underlie some limitations (see above). As a consequence, a trial of treatment is often justified in these patients.

Acute Coronary Syndrome

Epicardial spasm is a frequent cause for a clinical presentation of acute coronary syndrome but with unobstructed coronary arteries. Up to 50 % of patients with ACS but unobstructed coronary arteries suffer from vasospastic angina. There is no difference between Asian and Caucasian patients [16, 28] ACS may, however, also be caused by microvascular spasm [29].

Another condition where patients present with the clinical picture of an acute coronary syndrome despite normal coronary arteries is stress-induced cardiomyopathy (takotsubo cardiomyopathy, TTC). It has been shown that patients with stress-induced cardiomyopathy may suffer from epicardial or microvascular coronary spasm [30, 31]. Although there is still limited knowledge regarding the pathophysiology of this syndrome it is conceivable that coronary spasm may at least in part explain the chest pain and the myocardial stunning in patients with stress-induced cardiomyopathy [32].

Acute viral myocarditis is another disease which can mimic an acute coronary syndrome. It has been shown that chest pain which usually occurs at rest in these patients can be caused by coronary spasm associated with viral inflammation with parvovirus B19 [33]. Other chronic inflammatory conditions such as rheumatoid arthritis, or lupus erythematodes or the Churg-Strauss syndrome may also predispose to coronary spasm sometimes leading to acute myocardial infarction [34].

Repeated Attacks of Resting Angina Associated with ECG Changes

Prinzmetal's variant angina [35] is characterized by resting chest pain associated with ST-segment elevations. In his original description of 1959, Prinzmetal did not have today's tools to examine the coronary arteries as Mason Sones had only on October 30, 1958 performed the first coronary angiogram in a living human being. Of his three cases [35] the coronary anatomy was only known in a 56 year old man who at post-mortem examination had severe coronary artery disease (CAD) although he had no symptoms on exertion but only at rest. The two other patients aged 42 years may have had "normal" coronary arteries. Only a few years later it became apparent during coronary angiography that focal occlusive coronary spasm may cause ST-elevation despite normally appearing coronary arteries [36]. Hence, the typical features of Prinzmetal's angina are that it occurs at rest in patients without angina induced by effort and that it is associated with ST elevations (when an ECG can be obtained during the attack). Angiographically, there may be coronary artery lesions or the coronary arteries may appear normal [37] (Fig. 23.7).

Although resting angina and ST elevation is the typical clinical presentation of focal spastic coronary occlusion, ST elevation may also be elicited in some patients by exercise [38]. In these patients, ST elevation with typical regional wall motion abnormalities can be provoked by exercise although no critical stenosis can be found during coronary angiography. However, at ACH provocation, focal occlusion of the coronary artery can be demonstrated at the site of a coronary plaque [38].

In other patients repeated attacks of resting angina may be associated with ST segment depression. The coronary arteries of these patients may appear smooth or be irregular sometimes with stenoses between 50 and 70 %. At acetylcholine challenge, these patients have diffusely spastic coronary arteries and the spasm is usually most pronounced distally. Clinically, these patients cannot be distinguished from patients with the Prinzmetal form of coronary vasospasm. However, treatment tends to be more difficult in patients with diffuse distal spasm than in those with the focal occlusive form.

Patients with the distal diffuse form of vasospasm tend to have ECG changes and symptoms during ACH testing before epicardial spasm can be documented [39]. Hence, one can conclude that microvascular spasm precedes the epicardial spastic reaction in these patients. This means that spasm begins distally in the microvasculature and then extends proximally into the distal epicardial coronary arteries. These patients tend to be more often female and often have prolonged resting chest pain. Treatment also tends to be more difficult in patients afflicted by this variety of coronary vasospasm.

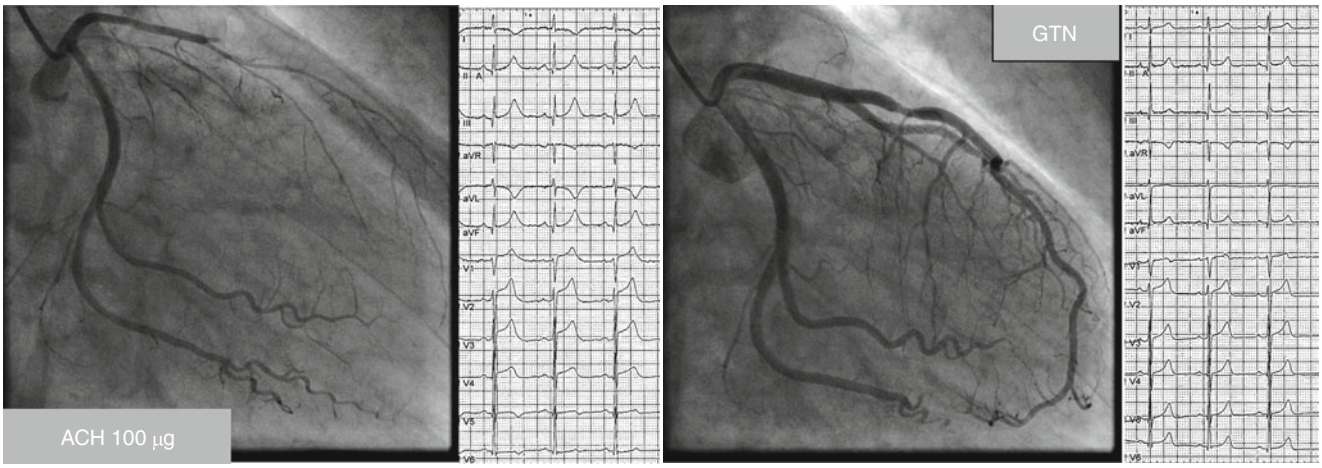

Fig. 23.7 Focal epicardial spasm (Prinzmetal's variant angina). This was a 47 year old male patient with a history of substernal resting chest pain starting 3 weeks ago. He had no apparent cardiovascular risk factors. Because of recurrent chest pain >20 min he was brought to the emergency room with signs of acute myocardial infarction. Upon arrival, initial ST-segment elevation in leads V2–V4 and chest pain had already resolved. Coronary angiography revealed unobstructed coronary arteries with a 30 % plaque in the mid LAD. Intracoronary acetylcholine provocation showed focal occlusive spasm in the area of the LAD plaque associated with reproduction of symptoms and ST-segment elevation (*left*) which resolved after administration of 200 µg glyceryltrinitrate (*right*)

Stable Angina and Cardiac Syndrome X

Patients with stable exertional anginal symptoms (or dyspnoea which is interpreted as an angina equivalent) and normal coronary arteries often exhibit diffuse and distal epicardial spasm when challenged with ACH [14]. As described above, these patients also often show signs of ischemia (angina and/or ST-segment depression) before epicardial spasm can be demonstrated [39]. This indicates that the abnormal response to ACH begins in the microvasculature. Therefore, reduced coronary reserve due to microvascular dysfunction may be the cause of the exertional angina symptoms. Upon careful questioning, these patients often report mild attacks of resting angina in addition to their exercise related symptoms.

There has been much debate about how to precisely classify patients with exertional angina (or dyspnoea) but normal coronary arteries as suffering from cardiac syndrome X [40]. This is because the definition of cardiac syndrome X varies from study to study. Initially, cardiac syndrome X was defined as stable angina in patients with normal coronary arteries and normal LV function who had no coronary risk factors or any other cardiac disease. Although such patients exist, the majority of patients with effort angina but normal coronaries has risk factors such as arterial hypertension (hypertensive heart disease), a family history of atherosclerosis or hypercholesterolemia or diabetes or combinations thereof. Therefore, a broader definition of "syndrome X" including such patients has been advocated [41]. This broader definition also acknowledges that these patients may also experience angina at rest.

Impaired vasodilation of the coronary resistance vessels has been demonstrated by various techniques in many but not all of the patients fulfilling the broader clinical definition of CSX [42]. The reduced coronary flow reserve has been suggested to be the cause of the exercise related symptoms in these patients. In such patients vasoreactivity testing often produces microvascular spasm often associated with distal and diffuse epicardial spasm as well [43]. This indicates that abnormal coronary vasomotion is part of the pathogenic framework of syndrome X. In order to avoid the use of the confusing term "syndrome X", we propose as others [44] to use the term "microvascular angina" instead.

Coronary spasm is often found in patients with persistent exercise-induced ischemia after successful stent implantation but without in-stent-restenosis (ISR) [45, 46]. Stable exercised-induced angina (with or without angina attacks at rest) is a common phenomenon after stent implantation and coronary angiography is often repeated to rule out significant ISR. However, a substantial proportion of patients do not have ISR [47]. In such cases assessment of coronary vasomotion may be useful to detect vasomotion abnormalities as a potential cause for the chest pain.

Finally, a substantial portion of patients with suspected dilated cardiomyopathy (DCM) suffer from exercise-induced but also occasional attacks of resting chest pain [48]. Several lines of evidence point to a reduced coronary reserve associated with angina in these patients [49, 50]. DCM patients

also show abnormal vasoconstriction in response to acetylcholine provocation [51, 52] which may serve as an indicator of abnormal vascular regulation in these patients. ACH testing is quickly performed during coronary angiography (which is often done in these patients to exclude coronary artery disease as the cause of their heart failure) and if positive may result in an impressive improvement both of symptoms and left ventricular function with antianginal drugs (calcium antagonists and nitrates). As many as 1/3 of all DCM patients may have abnormal coronary vasomotion explaining at least partially their "idiopathic" left ventricular dysfunction [53].

Coronary Vasoreactivity Test Results as the Basis for Therapy

If vasomotor abnormalities have been demonstrated strict control of cardiovascular risk factors should be pursued in all patients even if the coronary arteries appear entirely normal. In addition, patients should receive drugs to improve endothelial function or to reduce inflammation such as ACE-inhibitors [54] and statins [55]. Finally, medical treatment regimes should be tailored to the patient's clinical presentation and condition according to the current international guidelines.

Epicardial coronary vasomotor abnormalities should be treated with calcium channel blockers. In patients with a resting heart rate of >70/min. administration of diltiazem is recommended. If the heart rate is <70/min, amlodipine should be administered. If side effects such as leg oedema are not tolerable, lercanidipine can be used as an alternative. In Japan, benidipine has been shown to be more effective compared to other calcium channel blockers [56]. However, this drug is currently not available outside Asia.

Nitrates are also recommended for treatment of epicardial vasomotor abnormalities [6]. They should be administered together with calcium channel blockers in order to maximise the therapeutic benefits. Pentaerythrityltetranitrate may be helpful if symptoms occur at day and night times as it may not lead to nitrate tolerance [57]. Finally, nicorandil can be used to control chest pain associated with coronary vasospasm or reduced vasodilator capacity in response to exercise [58]. Beta blockers have shown mixed efficacy: they may have beneficial effects in patients with syndrome X and microvascular disease but they should be avoided in patients with proven focal epicardial spasm as they can sometimes aggravate this condition [59].

In patients with microvascular spasm and pure resting angina a similar treatment approach as described for epicardial spasm is justified. In patients with exertional anginal symptoms found to have microvascular dysfunction by provocative testing (and hence thought to have reduced vasodilatory capacity) calcium channel blockers and nitrates may also be used as first line therapy. However, the use of nitrates in these patients has shown variable efficacy. Nitrates do not seem to be better than beta blockers such as atenolol [60]. However, in some patients symptom control may only be achieved if medical treatment is complemented with nicorandil or ranolazine [61]. A novel treatment approach may be the administration of endothelin-1 receptor blockers to prevent vasoconstriction [62]. However, more convincing data are clearly needed before this expensive therapeutic concept may find a place in the guidelines.

Test Results as the Basis for Prognosis

The results of intracoronary provocation tests can serve as a basis to estimate prognosis. Patients with a pathologic test result have an increased morbidity and risk for cardiovascular events during follow-up. Patients with proof of epicardial spasm have been shown to be at an elevated risk for cardiac death and myocardial infarction (up to 1.5 % per year) [63–66]. Furthermore, it has been shown that patients with epicardial spasm can develop cardiac arrhythmias [67, 68]. It is currently not known how the prognosis is affected if patients also suffer from Brugada syndrome [69].

The differences in outcome among the studies published may be due to the mode of presentation (ACS patients have a better prognosis than those presenting with sudden cardiac death), the follow-up duration, type of spasm (diffuse vs. focal) as well as the type of medical treatment.

In patients with microvascular spasm/dysfunction prognosis regarding MACE is generally good (0 % for cardiac death, ~0.5 % for myocardial infarction per year) [70, 71]. However, persistent or ongoing angina represents a major problem. Therefore, medical treatment regimes should focus on symptom relief as studies have shown that patients with normal coronary arteries and persistent chest pain have a worse prognosis compared to patients without persistent chest pain [72].

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New Techniques for the Assessment of Coronary Microvascular Abnormalities

24

John Beltrame and Peter Ganz

Abstract

The assessment of abnormalities in the coronary microvasculature is particularly challenging since unlike the epicardial coronary arteries, the microcirculation cannot be readily imaged and thus its evaluation relies on functional techniques. These functional techniques infer the presence of microvascular coronary dysfunction by either (a) detecting the presence of myocardial ischaemia or one its ischaemic cascade surrogates, or (b) measuring coronary or myocardial blood flow as indicators of coronary resistance, in patients without obstructive coronary artery disease. The ischaemic cascade markers include the use of electrocardiography, metabolic imaging, transmyocardial metabolic studies, myocardial perfusion imaging, and imaging methods for the assessment of myocardial contractility. The blood flow techniques include coronary sinus thermodilution methods, myocardial perfusion reserve imaging, specialised angiographic techniques, coronary Doppler and pressure wire methods. As many of the earlier chapters have focussed on the ischaemic cascade markers, this chapter primarily focuses on the blood flow techniques, particularly those undertaken in the cardiac catheterisation laboratory setting.

Keywords

Coronary Microvascular Dysfunction • Slow Flow • Syndrome X • Microvascular Angina Coronary Heart Disease • Normal Angiogram • Coronary Flow Reserve • Microvascular Disease

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The comprehensive evaluation of the coronary vasculature requires both structural and functional assessments. In relation to the large epicardial coronary arteries, a plethora of clinical techniques are available including those involving luminal/structural vascular wall assessments (e.g. coronary angiography, intravascular ultrasound), dynamic functional assessment of coronary vascular reactivity (e.g. endothelial function assessment or provocative spasm testing), and assessment of the functional consequences of coronary vascular disease (e.g. myocardial ischaemia, impaired myocardial perfusion, transient myocardial dysfunction, or a reduced fractional flow reserve).

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In contrast, human coronary microvessels cannot be clinically imaged so that structural assessment of the microvasculature is very limited. Although myocardial biopsy allows structural assessment of microvessels < 200 μm in diameter, this precludes some of the important coronary microvascular resistance vessels such as the pre-arterioles that are generally 200–500 μm. As a consequence, clinical assessment of the coronary microvasculature is primarily dependent upon functional assessment methods. As these functional techniques are influenced by disorders of the upstream large coronary arteries and since large/microvascular dysfunction can co-exist, it is prudent to evaluate the coronary microvasculature in the absence of obstructive coronary artery disease. Hence consistent with the theme of this book, the remainder of the chapter will focus on the assessment of the microvasculature in patients with chest pain in the absence of obstructive coronary artery disease.

Coronary Microvascular Assessment Principles

The functional methods to assess the coronary microvasculature focus on two principles either (1) detection of the functional consequences of microvascular coronary dysfunction as evident in the ischaemic cascade (i.e. myocardial ischaemia, impaired myocardial perfusion or contractility), or (2) measurement of coronary/myocardial blood flow, which is inversely related to coronary resistance and which is primarily regulated by the coronary microvasculature. The techniques utilised may be either non-invasive or invasive and are summarised in Table 24.1.

Table 24.1 Functional assessment techniques clinically utilised to evaluate the human coronary microvasculature in the absence of obstructive coronary artery disease

Non-invasive techniques	Invasive techniques
Myocardial ischaemia methods	
Electrocardiography (stress ECG test)	Transmyocardial metabolic studies
Positron emission tomography (metabolic tracers)	
Magnetic resonance spectroscopy (^{31}P)	
Myocardial perfusion methods	
Single-photon emission computed tomography	Angiographic myocardial blush
Positron emission tomography (blood flow tracers)	
Magnetic resonance imaging (early contrast)	
Contrast echocardiography	
Myocardial contractility methods	
Echocardiography (stress echo)	
Magnetic resonance imaging (stress MRI)	
Coronary/myocardial blood flow methods	
Positron emission tomography (blood flow tracers)	Coronary sinus thermodilution
Magnetic resonance imaging (perfusion reserve)	Angiographic TIMI frame count
Contrast echocardiography (perfusion reserve)	Coronary Doppler flowire
Transthoracic echo Doppler	Index of microvascular resistance

Assessment of Functional Consequences of Microvascular Coronary Dysfunction

Detection of myocardial ischaemia in the absence of obstructive coronary artery disease is usually attributed to microvascular coronary dysfunction. For example, the initial description of Cardiac Syndrome X was in the context of ischaemic ECG changes and transmyocardial lactate production [1]. Similarly, as described in the preceding chapters, inducible myocardial ischaemia has been demonstrated in Cardiac Syndrome X patients using ^{18}F-fluoro-deoxyglucose positron emission scanning [2] (PET) and also with ^{31}P nuclear magnetic spectroscopy imaging [3].

In the traditional ischaemic cascade model, myocardial ischaemia arises from an imbalance of myocardial oxygen demand and supply, firstly resulting in impaired myocardial perfusion with the subsequent development of diastolic and then systolic dysfunction; thereafter ECG changes are evident and finally the patient may experience angina symptoms [4]. Accordingly, impaired myocardial perfusion in the absence of obstructive coronary artery disease may potentially be an early marker of microvascular coronary dysfunction. These perfusion imaging techniques are typically performed under exercise or pharmacological stress testing (e.g. dipyridamole, adenosine or dobutamine) and compared with resting images. The imaging techniques require blood flow markers such as ^{99m}Tc-sestamibi, Rubidium-82, gadolinium, or microbubble contrast agents to be administered, which can then be respectively imaged by single-photon emission computed tomography (SPECT) [5], PET [6], cardiac magnetic resonance imaging (MRI) [7], or contrast echocardiography [8]. Since many of these perfusion techniques have been described in detail in the preceding chapters, they will not be further discussed in this chapter.

Transient impaired myocardial contractility (especially transient regional wall motion abnormalities) during stress imaging (echocardiographic, SPECT, PET or MRI) is also used as indirect markers of myocardial ischaemia, utilising the traditional ischaemic cascade model. However in microvascular coronary dysfunction, transient myocardial dysfunction is frequently absent despite documented ischaemia prompting some researchers to propose an alternative ischaemic cascade in microvascular disorders [9]. Accordingly, assessing myocardial contractility may not be an optimal approach in assessing microvascular coronary dysfunction.

Coronary/Myocardial Blood Flow Assessment

An alternative approach to assessing the coronary microvasculature is to measure impaired coronary or myocardial blood flow to a vasodilatory stimulus rather than attempting to induce myocardial ischaemia. This can be performed non-invasively using the above myocardial perfusion imaging techniques but rather than qualitatively assessing perfusion, refining the techniques to quantitatively measure myocardial blood flow. Other more invasive techniques are used to measure coronary blood flow, such as thermodilution or Doppler techniques.

The interpretation of coronary/myocardial blood flow measurements is more difficult than the 'ischaemic cascade' related techniques since the former involves a continuum between a normal physiological response and an inappropriate pathological response whereas the later is clearly a pathological state. Simply assessing resting coronary/myocardial blood flow is often inadequate since it is dependent on myocardial oxygen demand and thus heart rate, myocardial contractility and cardiac preload. To minimise this variability, the concept of coronary flow reserve or myocardial perfusion reserve were developed. Coronary flow reserve is defined as the maximal achievable coronary blood flow (typically induced by a hyperaemic stimulus such as pacing/exercise tachycardia or dipyridamole administration), relative to the resting blood flow. Admittedly, rapid pacing may be only a submaximal stimulus and maximal vasodilators such as dipyridamole or adenosine are generally preferred. A normal response is usually considered to be a coronary flow reserve above 2.0 (i.e. at least a doubling of the resting blood flow). A similar principle can be applied to myocardial perfusion reserve where myocardial blood flow rather than coronary artery blood flow is measured. Thus a coronary flow reserve or myocardial perfusion reserve of <2.0 is usually considered pathological and a marker of microvascular coronary dysfunction. Since a reduced reserve could also reflect an inadequate stimulus, measurements in healthy control subjects are highly recommended to establish a normal range.

With the principles for assessing microvascular coronary dysfunction elucidated, the remainder of the chapter will focus on the individual techniques utilised. Since the non-invasive techniques had been previously discussed in the earlier chapters, this chapter will focus of the invasive techniques including (1) angiographic methods, (2) coronary sinus catheterisation methods, (3) coronary Doppler methods, and (4) coronary pressure wire methods.

Coronary Angiographic Methods

Selective invasive coronary angiography was developed over 50 years ago as a method of imaging the large coronary arteries to ascertain the presence of obstructive coronary artery disease. Although not the most sensitive technique, it has since become the standard clinical structural assessment technique for coronary artery disease. Although not a validated measure of coronary blood flow, the real time, dynamic nature of invasive coronary angiography provides the basis for assessing coronary angiographic contrast flow which is frequently used clinically as a marker of microvascular coronary dysfunction. These angiographic techniques have primarily been developed by the TIMI (Thrombolytic In Myocardial Infarction) Study Group and include (a) the TIMI flow grade, (b) the TIMI frame count, and (c) the TIMI blush score. These techniques are detailed below.

Definitions of perfusion in the TIMI Trial

Grade 0 (no perfusion): There is no antegrade flow beyond the point of occlusion.

Grade 1 (penetration without perfusion): The contrast material passes beyond the area of obstruction but "hangs up" and fails to opacify the entire coronary bed distal to the obstruction for the duration of the cineangiographic filming sequence.

Grade 2 (Partial perfusion): The contrast material passes across the obstruction and opacifies the coronary bed distal to the obstruction.However,the rate of entry of contrast material into the vessel distal to the obstruction or its rate of clearance from the distal bed (or both) are perceptibly slower than its entry into or clearance from comparable areas not perfused by the previously occluded vessel—e.g., the opposite coronary artery or the coronary bed proximal to the obstruction

Grade 3 (complete perfusion): Antegrade flow into the bed distal to the obstruction occurs as promptly as antegrade flow into the bed proximal to the obstruction, and clearance of contrast material from the involved bed as rapid as clearance from an uninvolved bed in the same vessel or the opposite artery.

Fig. 24.1 The TIMI flow grade (Reprinted from Chesebro et al. [10]. With permission from Wolters Kluwer Health License)

TIMI Flow Grade

This qualitative technique was developed for assessing the angiographic extent of restoring coronary artery patency following thrombolytic therapy in acute ST elevation myocardial infarction [10]. As shown in Fig. 24.1, angiographic flow is graded on the basis of contrast moving beyond the coronary artery occlusion, with TIMI-0 flow being no flow and TIMI-3 flow being normal distal coronary artery opacification. In the context of acute ST elevation myocardial infarction, establishing no less than TIMI-3 flow is essential to improving prognosis [11].

The TIMI flow grade has also been used as a marker of microvascular coronary dysfunction, particularly in relation to TIMI-2 or lesser flow. The no-reflow phenomenon during percutaneous coronary interventions is often clinically defined as TIMI-2 flow following successful dilation of the coronary artery lesion. Furthermore as described in the coronary slow flow phenomenon chapter in this book, TIMI-2

flow in the absence of obstructive coronary artery disease is the hallmark of this microvascular coronary disorder.

In the assessment of microvascular coronary dysfunction in patients without obstructive coronary artery disease, the TIMI flow grade is only useful to categorise patients in a bimodal manner on the presence of TIMI-2 or lesser (abnormal) or TIMI-3 (normal) flow. Although this is clinically useful, it reflects the limitations of the TIMI flow grade given its qualitative nature. Furthermore, this method may have limited sensitivity compared with other techniques. For example in the context of acute myocardial infarction, all those with TIMI-2 flow had impaired microvascular coronary function on contrast echocardiography however it was also evident in 16 % of patients with TIMI-3 flow [12]. Also of note, agreement between observers is poor in assigning TIMI-2 flow with 52 % (kappa = 0.38 ± 0.05) agreement being reported [13]. Hence more detailed quantitative techniques may provide more useful information than this simple clinical technique.

TIMI Frame Count

The TIMI frame count (TFC) method was developed by Gibson et al. [13] as a quantitative technique to assess coronary artery contrast flow. Using well-defined start points and distal landmarks, the number of cine frames required to opacify a coronary artery is calculated. The technique has been shown to have good intra- and inter-observer reproducibility [14]. In the original study [13], reference controls were established using a cohort of 78 patients with no history of prior myocardial infarction and TIMI-3 flow during elective angiography. In this population, the left anterior descending artery filled in 36.2 ± 2.6 frames, the circumflex 22.2 ± 4.1 frames, and the right coronary artery 20.4 ± 3.0 frames. To adjust for the longer length of the left anterior descending artery, a correction factor of 1.7 was developed so that the 'corrected TIMI frame count' for this vessel was 21.1 ± 1.5 frames [13]. Furthermore, this study and others [14] have shown good intra- and inter-observer reproducibility in assessing TFC.

The TFC method has been used as a marker of coronary microvascular dysfunction. As detailed in the coronary slow flow phenomenon chapter, some researchers have used it to define a population of patients with this disorder. Other uses for the TFC technique include (a) the quantitative assessment of cardiac transplant-associated arteriosclerosis [15], (b) the effect of interventions on the coronary microvasculature [16, 17], and (c) the documentation of microvascular coronary dysfunction in non-infarct related arterial territories amongst patients with acute myocardial infarction [18]. Moreover in acute myocardial infarct patients, the TFC has been shown to be predictive of subsequent left ventricular function [19] and in-hospital mortality [20]. This may indicate the importance of microvascular coronary function in acute myocardial infarction although the patients did have co-existing coronary artery disease.

Validation of the TFC against coronary Doppler wire techniques has produced variable findings. Coronary average peak velocity (APV) as measured by the coronary Doppler wire assesses blood velocity at one point within the blood vessel whereas TFC is a measure of average blood velocity over a distance within a vessel. In patients without obstructive coronary artery disease, TFC and APV have been shown to correlate well [21, 22]. Furthermore the 'frame count reserve' (i.e. TIMI frame count following adenosine-induced hyperaemia relative to the resting frame count) compares favourably with Doppler wire derived 'coronary flow reserve' in comparative studies [23, 24]. However in one investigation involving patients undergoing elective percutaneous coronary intervention, no relationship was observed between the TFC and APV derived 'flow reserves' either before or after the intervention [25]. Thus more studies are required to evaluate the relationship between these blood velocity/flow measures.

The ready availability and simplicity of the TFC method makes it attractive for coronary microvascular studies. However there are some limitations with the technique. Firstly, angiographers must ensure that adequate images are recorded which cover the entry of the contrast into the vessel and its arrival at the distal landmarks. Secondly, the TFC can be influenced by the contrast injection technique. Although the catheter size and rate of injection have minimal [26] or no impact on TFC [14], dye injections at the beginning of diastole can decrease the TFC [14]. Finally, heart rate can influence TFC with an increase in heart rate reducing the TFC [14]. Hence the TFC is a useful measure of coronary flow velocity provided these limitations are appreciated.

TIMI Myocardial Perfusion Grade

This qualitative angiographic technique was developed to assess microvascular tissue perfusion by examining contrast washout within the myocardium. The technique involves continuing to acquire cine images for at least three cardiac cycles during the arterial contrast washout phase (i.e. during contrast emptying out of the epicardial vessels), in order to assess the washout of the myocardial blush. The extent of myocardial blush is graded from 0 to 3 as described in Fig. 24.2.

The technique has principally been used in the context of assessing reperfusion therapy for acute myocardial infarction and shown to predict 30-day mortality [27]. It has been validated against the more quantitative digital subtraction angiography technique and shown to correlate well with ST segment

TMP Grade O: failure of dye to enter the microvasculature. Either minimalor no ground-glass apearance ("blush") or opacification of the myocardium in the distribution of the culprit artery, indicating lack of tissue-level perfusion.

TMP Grade 1: Dye enters but fails to exit the microvasculature. There is the ground-glass appearance ("blush") or opacifiction of the myocardium in the distribution of the culprit lesion that fails to clear from the microvasculature, and dye staining is present on the next injection (~30 s between injections).

TMP Grade 2: Delayed entry and exit of dye from the microvasculature.There is the ground-glass appearance ("blush") or opacification of the myocardium in the distribution of the culprit lesion that is strongly persistent at the end of the washout phase (i.e. dye is strongly persistent after three cardiac cycles of the washo phase and either does not or only minimally diminishes in intensity during washout).

TMP Grade 3: Normal entry and exit of dye from the microvasculature.There is the ground-glass appearance ("blush") or opacification of the myocardium in the distribution of the culprit lesion that clear normally and is either gone or only mildly/moderately persistent at the end of the washout phase (i.e. dye is gone or is mildly/moderately persistent after three cardiac cycles of the washout phase and noticeably diminishes in intensity during the washout phase), similar to that in an uninvolved artery, Blush that is of only mild intensity throughout the washout phase nut fades minimally is also classified as grade 3.

Fig. 24.2 TIMI perfusion grade definitions (Reprinted from Gibson et al. [27]. With permission from Wolters Kluwer Health)

resolution in acute infarction [28]. Although a simple technique, it is subjective, must be prospectively undertaken and requires additional radiation exposure. It has limited uses in the study of patients with chest pain and normal coronary angiogram.

Merits and Limitations

The above angiographic techniques are useful clinical tools that can be used to diagnose or monitor microvascular coronary dysfunction. The TIMI flow grade and TFC can often performed retrospectively in good quality angiographic images whereas images for the TIMI myocardial perfusion grade must be prospectively acquired. All the techniques are suitable for use in large-scale clinical trials. However, in contrast to other microvascular assessment techniques, these methods are limited by their quantitative sensitivity in detecting microvascular coronary dysfunction.

Future Directions

With the rapid evolution of non-invasive coronary computed tomographic (CT) angiographic imaging, techniques are now available to assess myocardial perfusion, including stress perfusion imaging with adenosine. This non-invasive angiographic technique has recently been shown to be as accurate as cardiac MRI stress perfusion studies [29]. Hence the future role of coronary CT angiographic imaging in the study of microvascular coronary disorders, now needs to be defined considering the availability of stress perfusion imaging.

Coronary Sinus Catheterisation Methods

Coronary thermodilution techniques were first clinically utilised over 40 years ago [30] and involve placing a catheter into the coronary sinus or great cardiac vein and injecting an indicator solution (typically room temperature saline) into the coronary blood flow stream. The change in temperature of the downstream fluid-blood mix is then detected via a sensitive thermosistor, with the transit time reflecting coronary blood flow. The technique was commonly used in earlier coronary microvascular investigations but is less often used with the development of coronary Doppler techniques.

Merits and Limitations

The advantages of the thermodilution technique include (a) it is a volumetric measure of coronary blood flow, and (b) the coronary sinus catheter placement allows for metabolic studies to be simultaneously performed (e.g. assessing transmyocardial lactate changes). However the technique also has a number of limitations. Firstly, the placement of the catheter requires skill; the thermodilution catheter should be optimally placed in the great cardiac vein which more selectively drains the left anterior descending blood territory, whereas the coronary sinus includes both left anterior descending and circumflex artery drainage. Hence any migration of the catheter tip may influence the blood flow sampling and thus recording. Secondly, the thermodilution technique does not allow instantaneous or phasic (systole and diastolic) blood flow measurements to be recorded. Changes in blood flow can only be made after a period of at least several seconds to allow the cold injectate and the warm blood to come to equilibrium temperature. Thirdly, the technique has a limited ability to detect subtle changes (<30 %) in coronary blood flow and should be avoided if this level of precision is required [31]. For these reasons, coronary venous thermodilution techniques have largely been supplanted by coronary arterial Doppler measurements.

Coronary Doppler Methods

In 1842, Johann Doppler hypothesized that sound waves reflected from a moving structure shift frequency (Doppler shift) proportional to the velocity of the moving structure

relative to the transmitter. The change in frequency (f_D or Doppler shift) can be expressed by the following equation:

$$f_D = (2fv\cos\Theta)/c$$

Where f is the frequency of the transmitted ultrasound, v is the velocity of the moving structure, $\cos\Theta$ the angle between the transmitter and moving object, and c the velocity of sound in medium. This principle is fundamental to a number of clinically useful cardiac investigations such as Doppler echocardiography and coronary Doppler techniques. These techniques use a pulse wave Doppler approach where a single crystal firstly emits an ultrasound signal and then reverts to being a receiver crystal after a pre-specified time period. The emitted, ultrasound signal into the blood is reflected off red blood cells (generating Doppler shift), which is detected by the crystal, thereby allowing red blood cell velocity (and thus blood flow velocity) to be estimated.

Coronary Doppler Flow Wire

Coronary Doppler probes were initially mounted on the tip of diagnostic coronary angiogram catheters but these were of limited value since they could not be advanced down the coronary artery. With the development of smaller crystals, they could be mounted on smaller catheters which could be advanced into selected coronary arteries but ultimately the crystals could be mounted onto a guide wire which allowed considerable clinical flexibility in their use. Thus the 'workhorse' for the measurement of coronary blood flow velocity is the coronary Doppler flow wire (often referred to as a Flowire – Volcano Products), which consists of a 20 MHz piezoelectric crystal mounted at the tip of a 0.014 in. floppy guide wire. The Doppler flow wire may also be combined with a coronary pressure wire, such as in the ComboWire (Volcano Products).

In the investigation of microvascular coronary dysfunction, the Doppler flow wire is usually used to assess the coronary flow reserve (CFR) in the setting of angina in the absence of obstructive coronary artery disease. As mentioned previously, it is important to exclude significant large vessel coronary artery disease since CFR can be influenced by both large and microvascular coronary disease. The use of the combination flow/pressure wire may be useful if coronary artery disease of uncertain significance exists since the pressure wire enables the assessment of fractional flow reserve, which can pinpoint any large vessel disease.

The Doppler flow wire procedure involves deploying the flexible wire into the artery of interest, at a position where there is a stable resting signal. The resting average peak velocity (APV) is measured and then a hyperaemic stimulus applied where-after the peak APV is determined. The hyperaemic stimulus used to assess CFR is typically a potent resistance vessel vasodilator such as dipyridamole, adenosine or papaverine. Since volumetric coronary blood flow is determined by multiplying the coronary flow velocity with the vessel cross-sectional area (at the point of the Doppler probe), then provided that the cross-sectional area remains constant during the hyperaemic stimulus, CFR can be calculated by peak APV/resting APV. If volumetric coronary blood is required to be calculated, then cross-sectional area can be estimated by assessing the luminal diameter by quantitative coronary angiography and applying the geographic principle of area $= \pi r^2$, where r is the radius of the vessel (or alternatively, area $= \pi d^2/4$ where d is the vessel diameter) (see Fig. 24.3).

The measurement of CFR provides insights into the coronary microvasculature's ability to respond to a vasodilatory stimulus. An impaired CFR in the context of normal epicardial coronary arteries suggests reduced maximal blood flow and/or that the microvessels have an increased resting blood flow. The increased resting blood flow may reflect an appropriate compensatory reduction in baseline coronary resistance in response to increased metabolic demand (e.g. increased resting heart rate or blood pressure) and thus the CFR will be arithmetically reduced even if the resistance vessels have an entirely normal maximal vasodilatory capacity to vasodilatory stimuli. Alternatively, reduced CFR may reflect dysfunctional microvessels that cannot achieve maximal vasodilation. Unfortunately, the CFR does not provide a distinction between these two scenarios, one pathological and the other indicating no microvascular coronary dysfunction at all.

In addition to determining the presence/absence of microvascular coronary dysfunction (i.e. making a diagnosis of microvascular angina), the coronary Doppler flow wire has been used to assess the presence of microvascular coronary endothelial dysfunction by determining the blood flow velocity in response to acetylcholine [32]. Furthermore by utilising specific antagonists (e.g. nitric oxide synthesis blockers or endothelin antagonists) the contribution of individual mediators (e.g. nitric oxide, endothelin) to microvascular coronary tone can be assessed [33]. This methodology has also been used to assess the potential benefits of therapeutic agents in the treatment of microvascular coronary dysfunction [34].

Other Coronary Doppler Techniques

In addition to the coronary Doppler flow wire, piezoelectric crystals have been mounted on small suction cups enabling them to be placed on native coronary arteries or grafts during open-heart surgery. Of more relevance for patients with angina

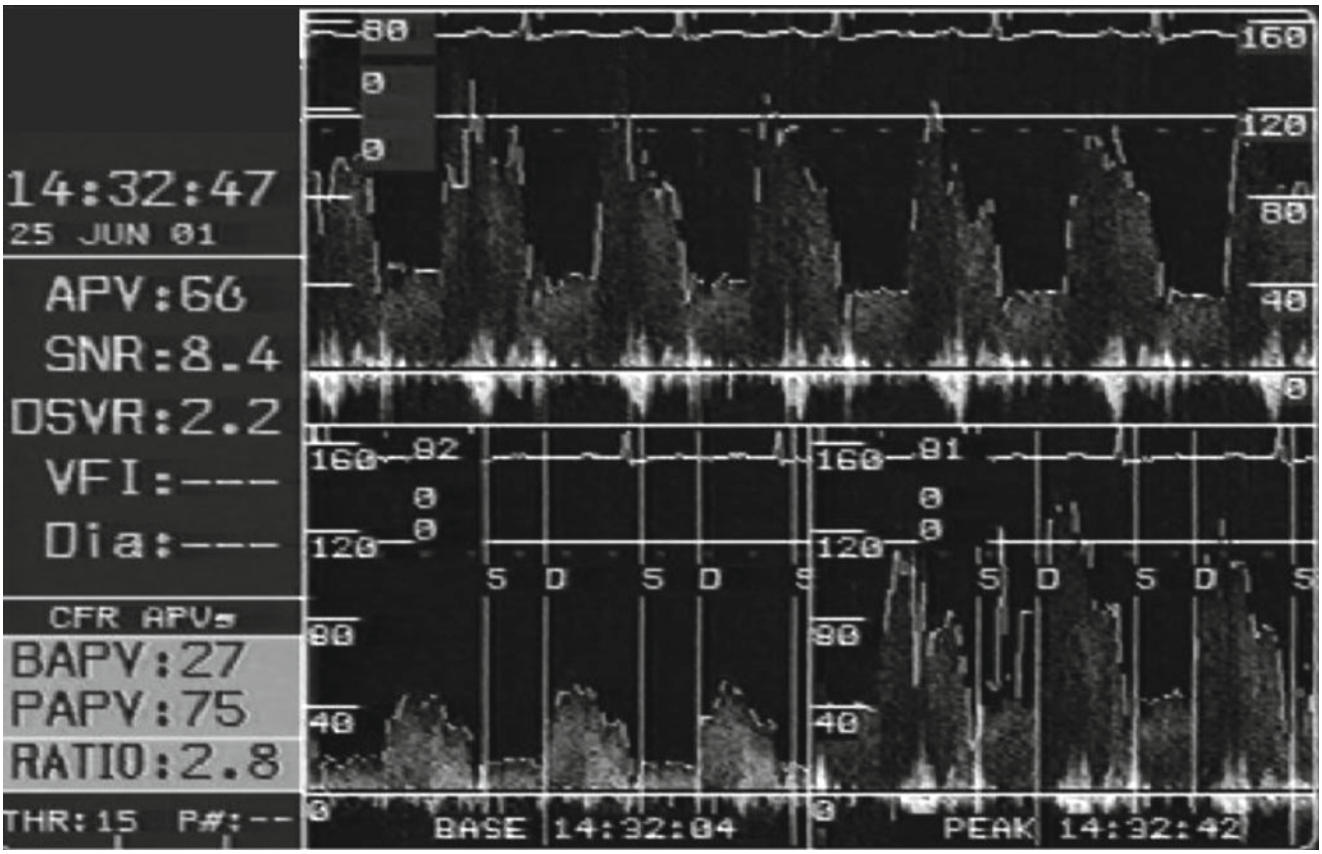

Fig. 24.3 Coronary Doppler flow wire recording example. In the recording below, the right upper panel shows the ECG recording and the continuous flow velocity trace (with the scale of 0–160 cm/s) measured by the coronary Doppler flow wire. The centre bottom panel marked "BASE", shows the baseline flow velocity recording with the systolic (S) and diastolic (D) start-points indicated. The adjacent panel marked "PEAK" shows the maximal hyperaemic velocity recording following the administration of adenosine. The left-hand panel summarises the demographic data, instantaneous velocity measurements (*APV* average peak velocity, *SNR* signal to noise ratio, and *DSVR* diastolic-systolic velocity ratio), and the coronary flow reserve calculation (Ratio), calculated from the baseline APV (BAPV) and peak APV (PAPV). Thus in this patient the coronary flow reserve is 2.8

and normal angiography, coronary blood flow velocity in the left anterior descending artery has been assessed non-invasively using transthoracic pulse wave Doppler echocardiography. This approach is very attractive considering its non-invasive nature however not all patients have a suitable acoustic window to allow imaging of the left anterior descending artery.

Merits and Limitations

The coronary Doppler flow wire has been the work-horse for coronary haemodynamic assessments of the coronary microvasculature. Its ability to be performed during routine diagnostic coronary angiography and its favourable safety profile make this technique attractive for use in microvascular coronary studies, despite its invasive nature. Despite the many positive attributes of coronary blood flow velocity assessment with the above Doppler techniques, there are some important limitations. Firstly, a stable resting coronary blood flow velocity signal must be obtained since small changes in the position of the Doppler probe will influence the Doppler shift signal and thus measurements. Secondly, flow in adjacent side-branches will influence the measurements so that the transducer must not be position near side-branches, which may limit its utility in certain studies. Thirdly, although a CFR above 2.0 is considered normal by many researchers [35], the threshold value may vary between 1.7–2.0 [36] so that many studies warrant a control reference group. Finally, although impaired CFR is used to define microvascular angina, it provides limited insights into the mechanism(s) responsible for the microvascular coronary dysfunction, unless it is coupled to the administration of agents that probe specific mechanistic pathway (e.g. acetylcholine to probe endothelial function).

Coronary Pressure Wire Methods

The development of miniature, high-fidelity, pressure transducers that can be fixed to a guide wire tip, have enabled the measurement of distal coronary artery pressure.

The capacity to measure coronary artery pressure beyond a coronary artery stenosis is particularly useful for the functional assessment of the lesion and given rise to the concept of myocardial fractional flow reserve (FFR). In the assessment of patients without obstructive coronary artery disease, the utility of FFR is limited to excluding an intermediate severity coronary artery stenosis as being of functional significance thereby implicating the microvasculature as the source of any documented myocardial ischaemia or abnormal coronary blood flow. Thus in the context of coronary haemodynamic assessment, two approaches have been used to simultaneously assess coronary blood flow with distal coronary artery pressure thereby permitting assessment of the coronary microvasculature. The first of these is the combination pressure Doppler flow wire that allows the simultaneous assessment of CFR and FFR. The second utilises the thermodilution principle to assess coronary arterial blood flow (in distinction to aforementioned venous thermodilution method) and has led to the development of a novel approach to assess the coronary microvasculature, referred to as the index of microvascular resistance (IMR). These two pressure wire approaches to assess the coronary microvasculature are discussed below but firstly it is important to understand the principles concerning the FFR concept.

The ability to measure distal coronary pressure and the appreciation that many coronary artery stenoses have minimal gradients at rest that become significant at maximal hyperaemia, are fundamental tenets in the FFR concept. The measurement of FFR involves the passage of 0.014 in. guide wire containing a miniature pressure transducer at its tip (pressure wire) beyond the coronary artery stenosis to allow the measurement of distal coronary pressure. A vasodilator stimulus (typically adenosine) is then administered to achieve maximal hyperaemia with the distal coronary pressure (P_d) measured from the pressure wire and the proximal arterial pressure (P_a) simultaneously measured from the guiding catheter. Although the trans-stenotic pressure gradient can be assessed, this is of limited value since the P_d is the major driving pressure for myocardial perfusion. Indeed the myocardial perfusion pressure is the gradient from P_d to the central venous pressure (P_v); P_v is typically negligible compared to P_d.

Since myocardial blood flow (Q) is related to the pressure change across the myocardium divided by the myocardial resistance (R), then in the absence of obstructive coronary artery disease, flow is expressed by the following relationship:

$$Q\ (\text{normal vessel}) = \frac{(P_a - P_v)}{R}$$

In contrast in the presence of an obstructive coronary artery stenosis, myocardial blood flow will be dependent on the P_d and thus determined by the following relationship:

$$Q\ (\text{stenotic vessel}) = \frac{(P_d - P_v)}{R}$$

Since the FFR is the ratio of the stenotic vessel blood flow relative to a normal vessel blood flow during maximal hyperaemia and since P_v is typically negligible, then the relationship is simplified to the following where theoretically a ratio of 1.0 is normal:

$$FFR = \frac{P_d}{P_a}$$

Clinical studies have revealed that a FFR less than 0.70 is indicative of a coronary artery stenosis producing inducible myocardial ischaemia [37] and that deferring revascularisation of lesions with an FFR ≥0.75 did not alter 5-year outcomes compared to those treated on the basis of angiographic appearance [38]. Hence an FFR > 0.75 suggests that the interrogated artery is not responsible for any observed myocardial ischaemia or impaired CFR.

Combination Coronary Pressure-Doppler Flow Wire

Since the CFR reflects both microvasculature dysfunction and the obstructive coronary artery disease whereas the FFR only reflects the epicardial coronary stenosis severity, then an abnormal CFR in the presence of a normal FFR infers microvascular coronary dysfunction. Although Doppler flow wire derived CFR is regularly used in studies of patients with chest pain and non-obstructive coronary artery disease, the use of the combination pressure-Doppler flow wire has rarely been utilised in the assessment of this condition, in part because these patients are assumed to have no significant coronary disease on the basis of their angiographic findings.

Another reason may be the concern that FFR is not completely independent of microvascular coronary dysfunction. The above derivative of the FFR formula assumes that the resistance in the normal circulation and the stenotic circulation are the same at maximal hyperaemia [36]. However this may not be valid in patients with microvascular coronary dysfunction where maximal hyperaemia may not be achieved. Although not directly assessed in patients with primary microvascular coronary dysfunction, FFR has been assessed in patients with left ventricular hypertrophy [39] or diabetes [40, 41] (who presumably have microvascular coronary dysfunction) and reported not to be effected by co-existing

microvascular coronary dysfunction. However one study evaluating FFR in the context of acute myocardial infarction with presumed microvascular coronary dysfunction, reported that it underestimated lesion severity [42], whereas others reported that it was unaffected [43].

Another assumption in the FFR simplified formula is that P_v is negligible compared to P_d. However, it has been reported that one in six patients will be miss-classified as having an abnormal FFR unless the central venous pressure is incorporated into the calculation [44]. In the context of chest pain and non-obstructive coronary disease where other co-morbidities need to be considered, this may become particularly important and warrant consideration.

Considering the limitations of the combination pressure-Doppler flow wire are few and not overarching, it would appear that this approach is underutilised in the assessment of patients with chest pain and non-obstructive coronary artery disease and warrants greater consideration in the future.

Index of Microvascular Coronary Resistance

This novel index for the assessment of microvascular coronary resistance has been developed using a pressure wire and employing the thermodilution principle to estimate coronary blood flow. The transducer at the tip of the wire simultaneously measures pressure and temperature. By detecting changes in temperature-dependent electrical resistance along the shaft of the pressure wire, proximal temperatures can be determined. Thus by detecting temperature changes to a 3 mL bolus of room temperature saline between the proximal and distal "thermistors", the mean transit time (T_{mn}) can be calculated which is inversely proportional to the coronary blood flow. Following administration of adenosine to induce maximal hyperaemia, the hyperaemic T_{mn} can be determined. Since resistance is determined by the change in pressure ($P_d - P_v$) divided by the blood flow, then assuming $P_v = 0$, then the following resistance index can be calculated during hyperaemia: Index of Microvascular Resistance (IMR) = $P_d \times T_{mn}$ (during maximal hyperaemia).

This index has been validated in an animal model of microvascular dysfunction [45] and shown to be independent of obstructive coronary artery stenoses in both animal [45] and clinical [46] models; thus it is a useful compliment to the FFR measurements. Moreover, IMR has been shown to be more reproducible than CFR and was not influenced by tachycardia, hypotension or increased contractility [47]. Considering these attributes, it is an ideal tool for the investigation of microvascular coronary function.

To date, IMR has mainly been used for the presence of microvascular coronary dysfunction in patients with obstructive coronary artery disease. In this context, it has been shown to be a better predictor of outcomes in patients with ST elevation myocardial infarction, than other markers of microvascular coronary dysfunction (such as CFR, TIMI frame count, or TIMI perfusion grade) [48]. In patients with chest pain and non-obstructive coronary artery disease, the index has been used to confirm the presence of microvascular coronary dysfunction. For example, Fineschi et al [49] demonstrated an abnormal IMR in patients with the coronary slow flow phenomenon despite the presence of a normal CFR. Other microvascular coronary disorders that have been assessed using IMR include tako-tsubo cardiomyopathy [50] and cardiac transplantation associated microvascular coronary dysfunction [51]. Furthermore, the index has been used to assess the effect of therapeutic interventions on the microvasculature such as rapamycin in transplant-associated vasculopathy [52].

Merits and Limitations

The use of coronary pressure wire methods has advanced our ability to assess the microvasculature, particularly in the context of co-existing obstructive coronary artery disease. The experience of utilising these techniques in patients with chest pain and non-obstructive disease remains somewhat limited although expanding. More studies are required, for example, to ascertain if assumptions concerning the negligible contribution of P_v and the hyperaemic response of a dysfunctional microvasculature are valid in the context of primary microvascular coronary disorders.

Peripheral Microvascular Assessment Techniques

As previously discussed, assessment of the coronary microvasculature is limited and requires the use of invasive techniques and/or indirect measurements. An alternative approach is to assess the more accessible peripheral microvasculature as a surrogate for the coronary microvasculature. This warrants a brief discussion as to the methods that are available and those that are evolving.

Assessment of peripheral microvascular function has been used to infer that microvascular dysfunction is widespread in syndrome X and thus could potentially be used as a marker of microvascular coronary dysfunction [53]. In these studies, forearm blood flow is measured by plethysmography and used as a marker of peripheral microvascular function. In patients with angina and normal angiography, forearm plethysmography has been used to examine mechanisms [54] and potential therapies [55] for this elusive disorder.

Other peripheral circulatory beds which can potentially be used as surrogate models for assessing the coronary microvasculature include the retinal and cutaneous circulations. Unlike the coronary microcirculation, the retinal microcirculation can be readily visualised in-vivo thereby allowing these microvessels to be photographed and vessel calibres measured. While microvascular retinopathy has long been recognised in hypertension and diabetes, only in recent years has the calibre of the retinal microvessels been shown to predict outcomes in coronary artery disease [56]. Whether the retinal microvessel calibre is associated with microvascular coronary disorders such as syndrome X requires further evaluation.

The cutaneous microcirculation can also be assessed in-vivo using cutaneous laser Doppler techniques with vasomotor responses to endothelium-dependent vasodilators determined. These cutaneous microvascular endothelium-dependent responses have been shown to be predictive of the coronary heart disease risk score (an index of developing coronary heart disease over a 10 year period) [57]. Similarly, nail fold capillary recruitment (visualised via capillary microscope) following 4-min digital arterial occlusion was predictive of the coronary heart disease score [57]. Subcutaneous vessels can also be assessed in-vitro following excision biopsy and suspension of the isolated microvessels in a myograph. Although a few studies have employed the myography technique to evaluate microvascular coronary disorders [58–60], these techniques are generally underutilised and may provide further insights into the mechanisms and potential therapies for these conditions.

Concluding Remarks

The investigation of coronary microvascular disorders in humans is challenging due to the inability to image the microvessels directly. Therefore functional assessments must be undertaken to assess either the ischaemic outcomes of the microvascular coronary dysfunction or coronary/myocardial blood flow as a marker of coronary resistance. Alternatively peripheral microvessels may be used as surrogate models for the coronary microvasculature. Of the various approaches described in this chapter, the most commonly used in studies investigating patients with angina and normal coronary angiography would be stress myocardial perfusion imaging studies and measures of coronary flow reserve. However many of the other techniques are still evolving and require re-evaluation in the future.

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Part V

Prognosis

Cardiac Syndrome X Prognosis

25

C. Noel Bairey Merz, Wafia Eteiba, Leslee J. Shaw, and Raffaele Bugiardini

Abstract

While historically Cardiac Syndrome X (CSX), characterized by the triad of chest pain, abnormal stress testing and no obstructive coronary artery disease (CAD), has been believed to have a benign prognosis, newer data documents otherwise. Multiple findings in larger, better characterized populations with longer follow-up time periods document a relatively high risk for major adverse cardiac events in those subjects with mechanisms related to microvascular coronary dysfunction (MCD) and manifestations of ischemia. Specifically, CSX related to MCD has an adverse prognosis and health care cost expenditure comparable to obstructive CAD in both stable angina and unstable acute coronary syndrome patient populations. Invasive assessment of coronary reactivity testing, including endothelial and non-endothelial pathway testing provides potent prognostic information in subject with normal and minimal diseased coronary arteries. Additional assessment by non-invasively determined coronary or myocardial blood flow reserve provides additive prognostic value to routine coronary angiography. The presence of persistent chest pain alone at 1 year following index coronary angiography predicts an adverse prognosis. MCD predicts a relatively greater proportion of heart failure events compared to myocardial infarction, suggesting potential links between MCD and heart failure with preserved systolic function, although longer term follow-up of ventricular function has not been performed. The high prevalence of this condition, adverse prognosis and substantial health care costs particularly in women, coupled with the lack of evidence-base regarding treatment places intervention trials in this patient population as a research priority area.

Keywords

Cardiac Syndrome X • MCD • Prognosis

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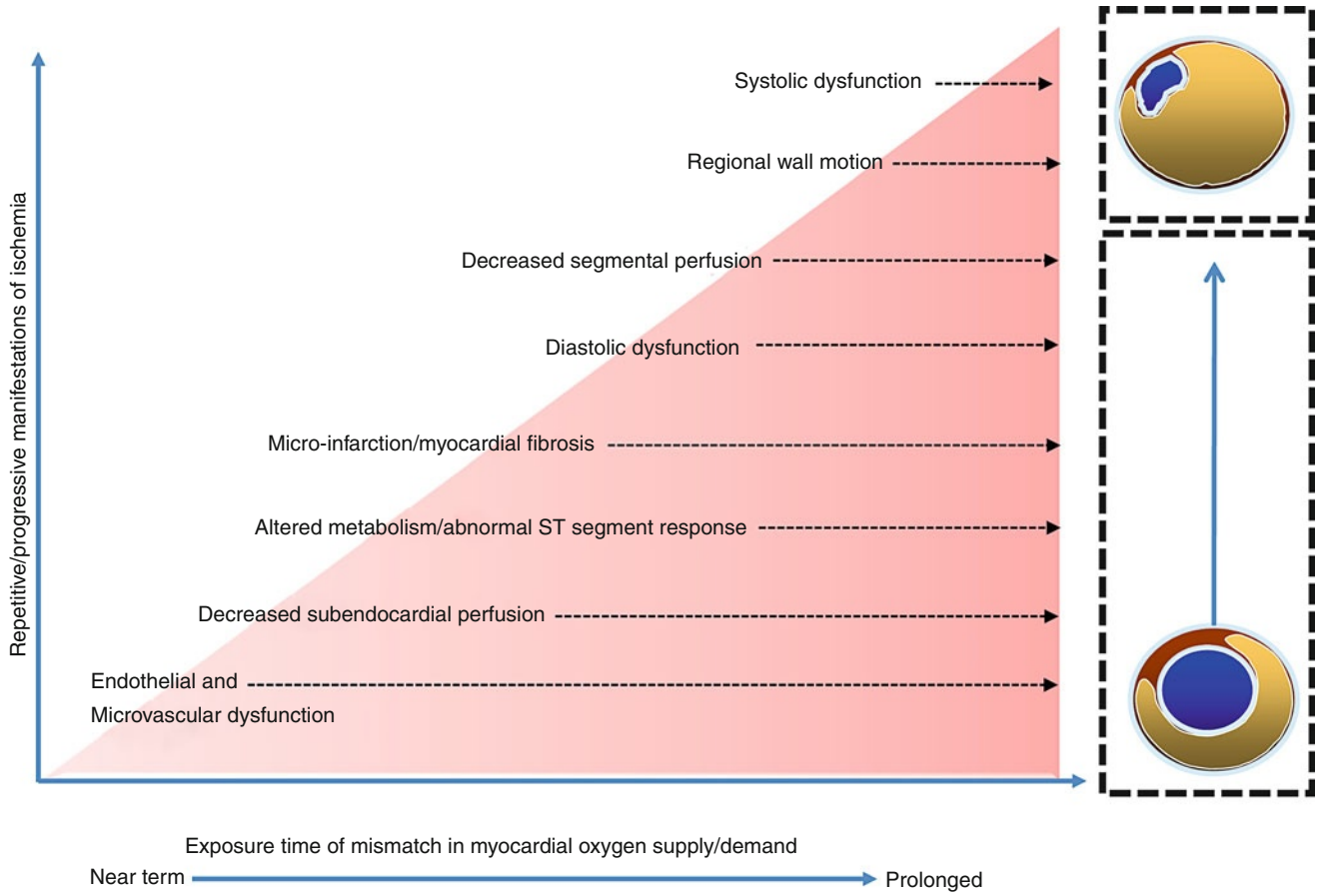

Fig. 25.1 Cascade of mechanisms and manifestations of ischemia impacting risk (Reprinted from Shaw et al. [9]. With permission from Elsevier)

Introduction

While the triad of angina, abnormal stress testing and no obstructive CAD historically has been labelled Cardiac Syndrome X (CSX), the term *ischemic heart disease* (IHD) now appears to be more appropriate for a discussion of this many of these patients. Among clinical cohorts, paradoxical sex differences are observed where women have less anatomical obstructive coronary artery disease (CAD) and relatively preserved left ventricular function yet higher rates of myocardial ischemia and mortality compared to similarly-aged males [1–4]. Data from the NIH-NHLBI-sponsored Women's Ischemia Syndrome Evaluation (WISE) and related studies implicate adverse coronary reactivity pathophysiology [5], MCD (MCD) [6], and plaque erosion/distal micro-embolization [7, 8] as contributory to a female-specific IHD pathophysiology. Specifically, this newer body of knowledge suggests that relatively higher risk patients exist within the CSX population, with risk related to mechanisms and manifestations of these IHD variables. Accordingly, knowledge beyond an anatomical description of obstructive CAD may provide important clues to CSX risk stratification. The cascade of mechanisms and manifestations of ischemia impacting prognostic risk is demonstrated in Fig. 25.1.

In addition to the issue of prognostic risk assessment for CSX, it is clear that symptom-driven care for patients is costly in the absence of obstructive CAD [10]. The WISE study has documented that for women with no obstructive CAD, the average lifetime costs for IHD is $767,288 USD, relatively similar in magnitude to the lifetime cost on average of >$1 million USD for women with obstructive CAD. Based on these data, the societal economic burden for IHD care for women with angina could exceed $162 billion USD annually, with an estimated half of this expenditure on women with no obstructive CAD [10]. A better understanding of risk relative to morbidity, mortality and cost is needed for the CSX population. Accordingly, we outline pathogenesis and pathophysiology here in order to better understand the prognostic literature. Furthermore, we will identify knowledge gaps with regard to future research needs.

Pathogenesis

The etiology of CSX appears non-homogenous and despite the considerable effort of research over the last four decades [11], there is no universally accepted understanding of the etiopathophysiology of chest pain with normal coronary

angiograms [11, 12]. Suggested mechanisms and contributing factors [11–13] of CSX include MCD, altered regulation of coronary microcirculation through autonomic dysregulatory mechanisms and/or imbalance state between endothelial-derived vasodilator and vasoconstrictor factors, generalized vascular disorder, abnormal subendocardial perfusion, inflammation, hyperinsulinemia, enhanced sodium-hydrogen exchange, hormonal deficiency, abnormal pain perception and lastly inherent pathogenetic pathways [14]. Furthermore, the notion that these subjects have "normal coronary arteries" should be reconsidered in light of the IVUS substudy from the WISE study showing that among a sample of 100 women studied, over 80 % had coronary atherosclerosis which was concealed by vascular remodeling [15].

Angina with No Obstructive CAD

The mode of presentation of chest pain with normal coronary angiograms ranges from uncomplicated chest pain to severe ischemia and acute myocardial infarction in patients with angiographically normal smooth coronary arteries. Authors have labelled this syndrome in a number of different ways, such as CSX, vasotonic and microvascular angina [16–18].

Prior selected retrospective studies had suggested in the past a benign outcome with normal or near normal angiograms [17, 19]; however this is not the case for more rigorous contemporary prospective cohort studies [20]. Other studies of women who presented with chest pain symptoms or suspected myocardial ischemia have suggested an impaired outcome in subsets of patients with angina and normal coronary angiograms [21, 22]. Furthermore, patients with angina and no obstructive CAD who have evidence of myocardial ischemia or impaired coronary flow reserve have particularly poor outcome [23, 24]. The assumption that prognosis of all subjects with angina and "minimal or no obstructive CAD" by angiography is benign should be, therefore, discouraged.

Pathophysiology of MCD

It is increasingly recognized that a large proportion of patients with chest pain and no obstructive CAD have symptoms of ischemia due to abnormal coronary vasomotion and microvessel coronary disease and that these may be the mechanisms leading to adverse outcomes. MCD refers to abnormalities in the vasomotor or metabolic regulators of the small coronary arterioles (<500 um). However, structural abnormalities of vessel wall of microcirculation (for example smooth muscle cell hypertrophy) have been described by some [25], but not all studies [26]. Although small coronary arterioles are not visualized during coronary angiography, they are the major determinants of coronary vascular resistance [27]. This may be caused by both endothelium and non-endothelium dependent mechanisms. Abnormal endothelium dependent coronary vasomotion in response to acetylcholine has been independently linked to adverse cardiovascular outcomes [5, 28] as has impaired coronary endothelium-independent vasodilatory reserve in response to adenosine, an index of microvascular coronary function [29, 30]. Also slow coronary flow as an indicator of increased microvessel resistance with transient myocardial perfusion defects has been linked to adverse outcome [31]. While experimental studies and clinical observations emphasize the role of sex in influencing the microvascular mechanisms that may reflect upon microvascular pathophysiology [32], prevalence data suggest that sex ratios for women and men may be 60:40 [4, 33]. Evidence from autopsy data suggests that women may have a higher frequency of coronary plaque erosion and microembolization [34], which could result in greater microvascular dysfunction. Results from research with retinal photography also implicate sex-specific dysfunction of the microvasculature. Retinal arterial narrowing, a measure of microvascular disease, is related to cardiovascular disease risk and mortality in women but *not* in men [6]. Specifically, for women, every standard deviation decrease in retinal arteriole-to-venule ratio was associated with a 37 % increase in coronary heart disease death and myocardial infarction (MI) that was independent of the presence of hypertension or diabetes [7]. Figure 25.2 demonstrates a proposed model of MCD.

Relation to Myocardial Ischemia

Documenting the presence of myocardial ischemia as etiological for chest pain in individuals with normal coronary angiograms remains the focus of many current studies [35–39]. Testing of CSX is not well defined, however non-invasive imaging has been used to determine whether ischemia is present or not and also to risk stratify patients with no obstructive CAD and/or MCD [3, 40]. The use of SPECT imaging revealed myocardial perfusion defects in response to exercise in some patients with CSX [36]. An abnormal response of coronary resistance vasculature to acetylecholine during diagnostic coronary angiography is also suggested to identify patients likely to have myocardial perfusion defects in response to stress [36]. Using PET in women with chest pain and no coronary obstruction by angiogram, the adenosine-induced changes in myocardial perfusion reflected a heterogeneous pattern of MCD [37]. In a cohort of women with chest pain and no obstructive CAD studied by cardiac magnetic resonance imaging (CMR), almost half of them showed an abnormal decrease in myocardial high-energy phosphate (a metabolic marker of ischemia) during light handgrip exercise [38]. The magnitude of the decrease was equal to or greater than that observed in patients with at least 70 % epicardial stenosis of the left anterior descending artery.

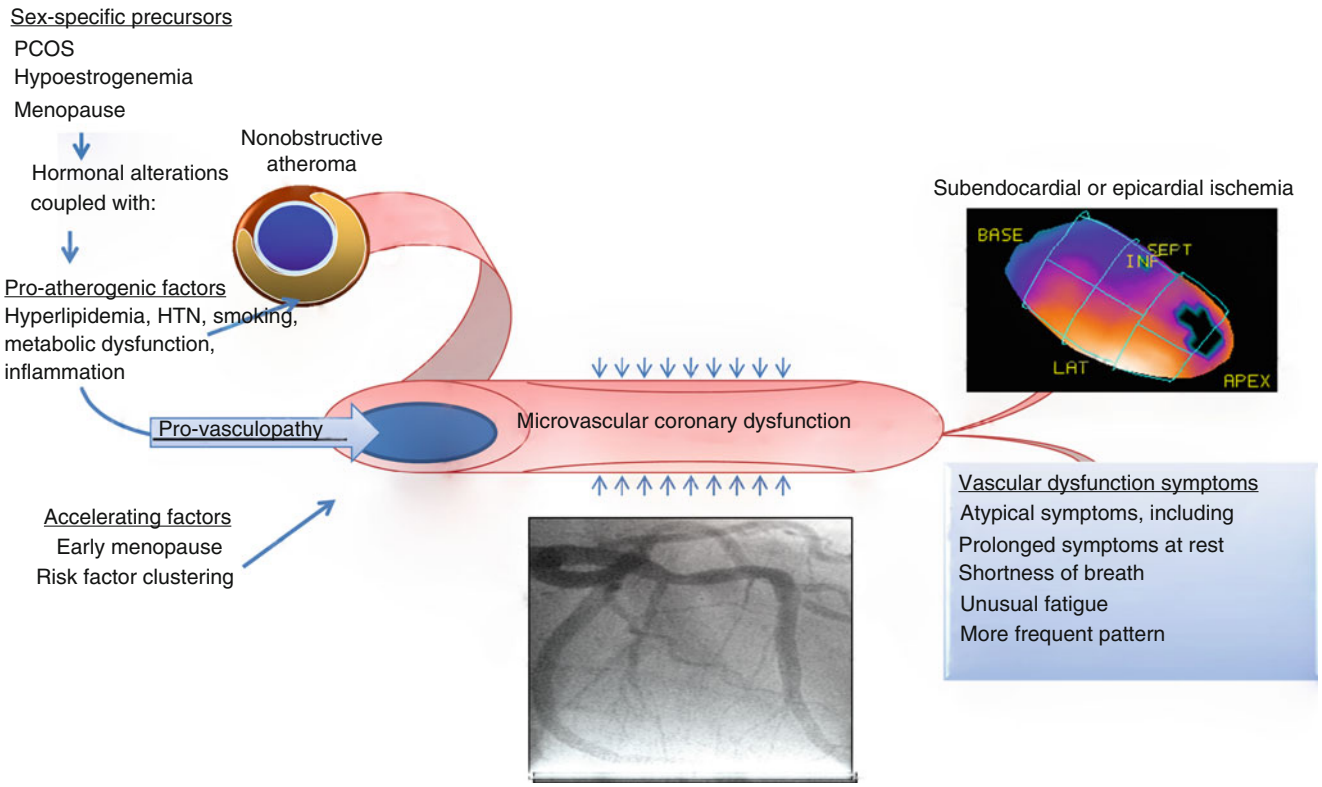

Fig. 25.2 Model of MCD. *HTN* hypertension, *PCOS* polycystic ovary syndrome (Reprinted From Shaw et al. [9]. With permission from Elsevier)

Endothelial dysfunction in the absence of obstructive CAD may not consistently cause myocardial ischemia that can be detected non-invasively [33, 41]. This can be explained by the fact that the commonly applied nuclear-based techniques for ischemia depend upon regional differences in perfusion and/or function that identified by normalizing radiotracer uptake across the myocardium. This will reduce detection of diffuse microvascular coronary flow abnormalities. Further analyses demonstrated that even in apparently normal scans, the majority of patients with CSX showed reduced thallium-201 uptake and washout in comparison to their controls [42]. Given the fact that traditional nuclear imaging techniques rely on detection of abnormalities that are compared to a normalized myocardium, diffuse CAD will appear as normal [3, 41]. Stress cardiac magnetic resonance imaging (CMRI) is capable of defining epicardial as well as subendocardial hypoperfusion following administration of IV adenosine in women with signs and symptoms of ischemia but no obstructive CAD [39]. Adenosine may also induce global and regional left ventricular diastolic dysfunction as demonstrated by both radionuclide imaging and stress echocardiography in patients with MCD. In the same study, the long axis diastolic dysfunction detected by tissue-Doppler study of the mitral annular was also suggestive of subendocardial of ischemia [43]. Figure 25.3 depicts the factors impacting risk of ischemia heart disease events.

Prognosis

Based on existing evidence, it appears that CSX encompasses a heterogeneous patient group; differences in case mix may explain differences in prognosis in various studies. Therefore, the majority of subjects in this group who do not have myocardial ischemia could drive the overall benign prognosis described in many studies. The subgroup that has ischemia or microvascular coronary dysfunction appears to be at increased risk for subsequent events and mortality.

Historical CSX prognosis studies indicated an overall good prognosis [44, 45]. Longer term follow-up in larger sample sizes suggest an alternate more adverse prognosis [46, 47]. Also, better characterization of the patients, specifically by identifying mechanistic pathways of the signs and symptoms of ischemia identifies an at-risk group. Specifically, evidence of MCD indicated by a lower coronary flow reserve determined invasively in a population of women and men [29] or exclusively women [30] predicts an adverse prognosis. Notably, among women with persistent signs and symptoms of ischemia, a relatively higher proportion of adverse events include heart failure rather than myocardial infarction [29] (Fig. 25.4), suggesting possible links between MCD and heart failure with preserved systolic function. Further research evaluating serial ejection fraction in these patients over time is needed.

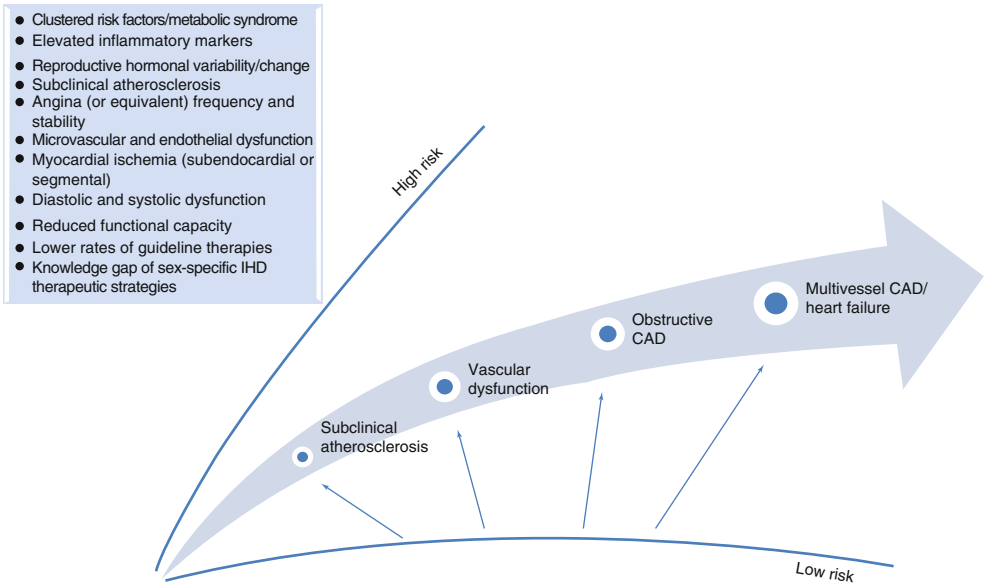

Fig. 25.3 Factors associated with risk of events. (Based on data from [21])

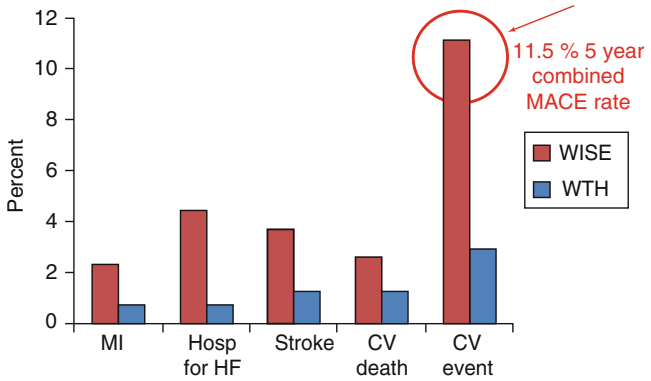

Fig. 25.4 Women's ischemia syndrome evaluation (*WISE*) patients with and without documented ischemia have elevated major adverse cardiac events (*MACE*) compared to asymptomatic Women Take Heart (*WTH*) with no ischemia by exercise treadmill testing (Reprinted from Shaw et al. [9]. With permission from Elsevier)

Prognosis by Coronary Angiography – Acute Coronary Syndromes

"Normal" coronary angiograms, defined as no visible obstructive CAD (luminal irregularities <50 % stenosis) are also reported more frequently in women with acute coronary syndromes (ACS). In a recent large series from 600 US hospitals in 459,941 acute coronary syndrome (ACS) patients, the adjusted odds for obstructive CAD were 50 % lower for women as compared to men [4]. For women presenting with ACS/ST segment elevation myocardial infarction (STEMI), 10–25 % of women as compared to 6–10 % of men have no obstructive CAD [41, 48–50]. Of the estimated 1.4 million patients discharged following an ACS each year, 600,000 are women [51]. Among women, the 10–25 % rate of "normal" angiography [52] translates into 60,000–150,000 women with ACS/MI having non-obstructive CAD. Specific investigation is needed to understand the paradox whereby women have less obstructive CAD and less severe MIs yet worsening clinical outcomes. The higher mortality compared to men has been attributed to advanced age, co-morbidity [1, 3, 53, 54], and underutilization of guideline care among women [55]; yet the largest mortality gap is seen in younger women with a number of studies demonstrating persistent sex differences despite covariate adjustment [22, 56].

Prognosis by Coronary Angiography – Stable Syndromes

The prognosis with "normal" coronary arteries co-occurring with signs and symptoms of myocardial ischemia has historically been interpreted as benign [17, 57, 58]. A recent investigation demonstrated that 30 % of women with chest pain, "normal" angiograms, and endothelial dysfunction developed obstructive CAD during 10-year follow-up [28]. A pooled analysis of women from recent, large randomized trials reveals that women with mild CAD have a worsening prognosis as compared to those with normal coronaries [20]. Results from the WISE [21] documented 5-year adverse cardiovascular event rates of 16.0 % for those with mild CAD (stenosis 1–49 %), 7.9 % for those with no coronary stenosis, and 2.4 % in asymptomatic women ($p \leq 0.002$); following adjustment of cardiac risk factors. Despite these compelling

findings, treatment for women with open coronary arteries remains often reassurance, sedative-hypnotic prescriptions, and/or repeated hospitalization and coronary angiography in response to refractory symptoms [41].

Prognosis by Signs and Symptoms of Ischemia

Prognosis is also determined by its components including chest pain, endothelial dysfunction defined by reduced coronary blood flow (CBF) to acetylcholine and myocardial ischemia. Women with chest pain and no obstructive CAD by angiography, persistent chest pain defined as chest pain (typical or atypical), that lasts over a year during follow-up, occurred in 45 % of them and yet was associated with significantly more than twice the cardiovascular events, including MIs, strokes, congestive heart failure and cardiovascular death compared to those without chest pain [59]. Subsequent functional disability secondary to chest pain was reported in half of women with non-obstructive CAD, the repeated angiography rate was 13.2 %, and the repeated hospitalization after 1-year follow-up was 1.8-fold higher than those with 1-vessle disease [10]. An abnormal coronary flow reserve in response to dipyridamole and non-invasive imaging [24] was the strongest independent predictor of an adverse prognosis in patients with no obstructive CAD. This remained true in an additional study despite normal perfusion scan results [60]. Cold pressor testing is also useful with a more adverse prognosis predicted by a blunted or absent myocardial blood flow increase [61].

Prognosis by Coronary Reactivity Testing

Endothelial dysfunction predicts accelerated development of obstructive CAD [33, 43, 62]. In a recent report [30] from the WISE, 189 women were followed-up for a mean period of 5.4 years after having their basal coronary flow reserve (CFR) measured using intracoronary adenosine. In their study, lower CFR was associated with adverse cardiovascular outcome whether women had or had no significant coronary obstruction. Also, CFR significantly improved the prediction of adverse cardiovascular outcome over angiographic severity and other risk factors. Prior results from the same study have shown that in women suspected to have myocardial ischemia, abnormal response to intracoronary acetylcholine was an independent predictor of adverse cardiovascular events including hospitalization for worsening angina, MI, congestive heart failure, stroke, revascularization and death [5]. The inter-relation between the vessel wall structure versus its function has been suggested as critical in the prognosis of atherosclerotic disease, whereas endothelial dysfunction seems to modulate the impact of a given atheroma burden [42]. Thus, the worst expected prognosis occurs when severe grades of endothelial dysfunction are concomitant with high degrees of atheroma burden [42]. Follow-up results of 157 patients with mild coronary atherosclerosis associated with microvascular coronary endothelial dysfunction revealed that cardiac events occurred only in those with severe degree of endothelial dysfunction while no adverse events were detected in individuals with normal or mild dysfunction [63].

As previously reported [1], the expected cost of initial conventional diagnostic investigations including coronary angiography approximately ranged from $3,500–6,000 USD. Recently, Shaw et al. reported an expected consumption of nearly $750,000 USD of cardiovascular health care resources related to the burden of ongoing symptoms and medications (4.8 % is directed to anti-ischemic therapy) throughout the lifespan of women with chest pain but normal angiogram [10]. Hence, the authors' reasoning that such women be reclassified as being at intermediate risk, compared to those with obstructive CAD, appears to be justified.

Psychological Well-Being and Quality of Life

The role of psychological symptoms in relation to physical symptoms in CSX is often questioned as being at least in part, responsible for or comes as a sequence of such a disease with unsure/uncertain etiology. Few studies focused primarily upon possible mental health profile and social factors peculiar to CSX [6]. When women with CSX, obstructive CAD, and age matched healthy controls were compared, women with CSX had significantly higher levels of anxiety and felt their health interfered more with everyday lives (QOL) compared to CAD patients and controls. CSX women with larger social network were significantly less anxious and less depressed than those with a small social network. Defining the psychosocial characteristics of CSX may give some directions to its management and treatment strategies [64].

Panic disorder was reported in 40 % of patients with CSX [65] and panic disorder is believed to have the potential to perpetuate the symptom and reduce the CFR in susceptible patients [66]. Patients with persistent chest pain but no coronary obstruction had higher prevalence of depression and anxiety and were more likely to use psychotropic medication [67]. In a group of women with chest pain and insignificant coronary stenoses, those with reduced CFR in response to adenosine administration, were likely to have reduced functional capacity as measured by Duke Activity Status Index (DASI), when compared to those with higher CFR [66]. Physical deconditioning may be in part a responsible factor. In female patients with CSX, planned moderate exercise for 8 weeks resulted in improvement of exercise capacity, time to pain, tendency to increased endothelium dependent blood

flow, and a decrease in urine cortisol level. The latter was considered a marker of better coping with stress [68]. These results have important implications in the area of risk stratification and treatment of MCD [66].

While psychological and quality of life followup studies are few, the case of chest pain with no obstructive CAD appears to often be a chronic condition, affecting many patients for a decade or more [69].

Summary

While historically CSX, characterized by the triad of chest pain, abnormal stress testing and no obstructive CAD, has been believed to have a benign prognosis, those CSX patients with MCD have an adverse prognosis and health care cost expenditure comparable to obstructive CAD in both stable angina and unstable acute coronary syndrome patient populations. MCD predicts a relatively greater proportion of heart failure as well as death and stroke events compared to myocardial infarction, suggesting potential links between MCD and heart failure with preserved systolic function, although longer term follow-up of ventricular function has not been performed. The high prevalence of this condition, adverse prognosis and substantial health care costs particularly in women, coupled with the lack of evidence-base regarding treatment places intervention trials in this patient population as a research priority area.

Knowledge Gaps and Future Research

Future outcome studies of patients with signs and symptoms of ischemia but no obstructive CAD should include well-characterized cohorts where the mechanisms for MCD are thoroughly studied. In the clinical setting, additional invasive testing aimed at determining the "type" of MCD, for example acetylcholine or adenosine testing during coronary angiography, is required to assess the etiological pathophysiological mechanisms of chest pain and further risk stratification in selected subgroups. Further knowledge gaps include whether MCD is predictive of heart failure with preserved systolic function, and further investigation regarding links to symptomatic, psychological and quality of life outcomes. The high prevalence of this condition, adverse prognosis and substantial health care costs particularly in women, coupled with the lack of evidence-base regarding treatment places intervention trials in this patient population as a research priority area.

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Impaired Quality of Life – Causes, Assessment and Management

26

Thomas Rutledge

Abstract

Sometimes considered outside of the scope of standard medical care, quality of life is indirectly the most important goal of most patient-provider encounters. Improving physical function, reducing symptom burden, improving energy levels and endurance, managing pain, helping patients return to work, decreasing depression and anxiety, and increasing independence are among the many dimensions of quality of life enhanced from care received in cardiology and primary care settings. Poor quality of life is a frequent concern among patients with chest pain and normal coronary arteries or no obstructive coronary artery disease (CAD), with evidence that this population may endure greater quality of life impairment relative even to those with chest pain and obstructive CAD. In light of the bidirectional relationships between pain, functional status, mental health, and quality of life among these patients, providers may feel underequipped to address these enmeshed treatment goals. Therefore, providing physicians with a practical guide to understanding, measuring, and treatment quality of life factors among patients with chest pain and no obstructive CAD is an objective with potential utility and clinical significance. This chapter presents an illustrated roadmap to assessing and maximizing quality of life outcomes among patients with chest pain and normal coronary arteries, with particular emphasis on methods that are suited to the time-limited medical context and consistent with recommended care guidelines for patients with CAD.

Keywords

Quality of life • CSX • Coronary heart disease • Treatment • Women

Americans now enjoy a near record average life span of 77.8 years based upon 2010 mortality statistics (www.cdc.gov), however, standards for quality of life have not maintained the same progressive pace. Instead, living longer lives often translates into living more years burdened by chronic diseases, mental health conditions such as depression, and consequent disability. This is particularly true for women, who both live longer (80.3 vs. 75.3, respectively) than men and are more likely to suffer from disabling conditions such as coronary heart disease, stroke, depression, and social isolation at older ages [1]. As the average length of life approaches or exceeds 80 years in the U.S. and other industrialized countries, and medical standards achieve diminishing returns for further extending lifespan, promoting equally high standards for quality of life becomes an increasingly important objective.

Quality of life concerns are common among patients with obstructive CAD. High rates of depression, anxiety, poor perceived health, and impaired functional capacity accompany CAD in many studies and across numerous measures (e.g., [2–4]). Among patients with CAD, an impaired quality of life may represent a psychosocial consequence of living

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with a serious health condition, one that limits physical abilities, decreases social interaction, and increases preoccupation with death. However, a less intuitive pairing with impaired quality of life are patients symptomatic with chest pain that prove to be free of obstructive CAD. These are the men and women presenting with chest pain and no evidence of CAD on angiographic testing, a population sometimes referred to as "cardiac syndrome X" (CSX) patients to characterize the combination of persistent chest pain, positive exercise test results, and normal coronary arteries [5]. For reasons that presently offer only a partial accounting, women comprise approximately 70 % of the CSX population [6, 7]. Despite the assurance of an absence of CAD, multiple studies show that rates of psychiatric distress and impaired quality of life among CSX patients equal or exceed those of patients diagnosed with CAD [8, 9]. Whether these impairments result from pre-existing factors or are even an iatrogenic result of the uncertainty caused by the absence of a clear medical diagnosis for their pain symptoms is unclear. However, when combined with the sometimes poor response to standard medical treatments for chest pain symptoms among CSX patients, this patient population becomes prone to a pattern of persistent anxiety over their pain symptoms, recurrent medical visits, failed treatment trials, and increased medical costs [10].

For patients with chest pain and obstructive CAD, quality of life concerns are often secondary to medical interventions prioritizing risk reduction and cardiac symptom management. In fact, the heightened risks for premature morbidity and mortality among CAD patients makes the patient experience of side effects potentially damaging to quality of life a necessary tradeoff in CAD treatments such as antihypertensives, cholesterol lowering agents and revascularization strategies [11]. Because most studies of patients with chest pain and no obstructive CAD, however, suggest relatively lower adverse event and mortality risks associated with the condition relative to those with obstructive CAD [12–14], the usual medical management priority for risk reduction over quality of life goals is questionable in this population. With studies indicating that upwards of 60 % of women with symptoms indicative of myocardial ischemia are free of obstructive CAD based upon angiographic findings [7, 15], it becomes clear that this is a common patient presentation for women and the objective of understanding and addressing quality of life factors in this population suddenly carries substantial implications for clinical practice.

Figure 26.1 illustrates the logical argument for appreciating quality of life concerns among patients with chest pain and no obstructive CAD. The case of chest pain with no obstructive CAD is a widespread condition; it often responds poorly to standard angina medication interventions [12];

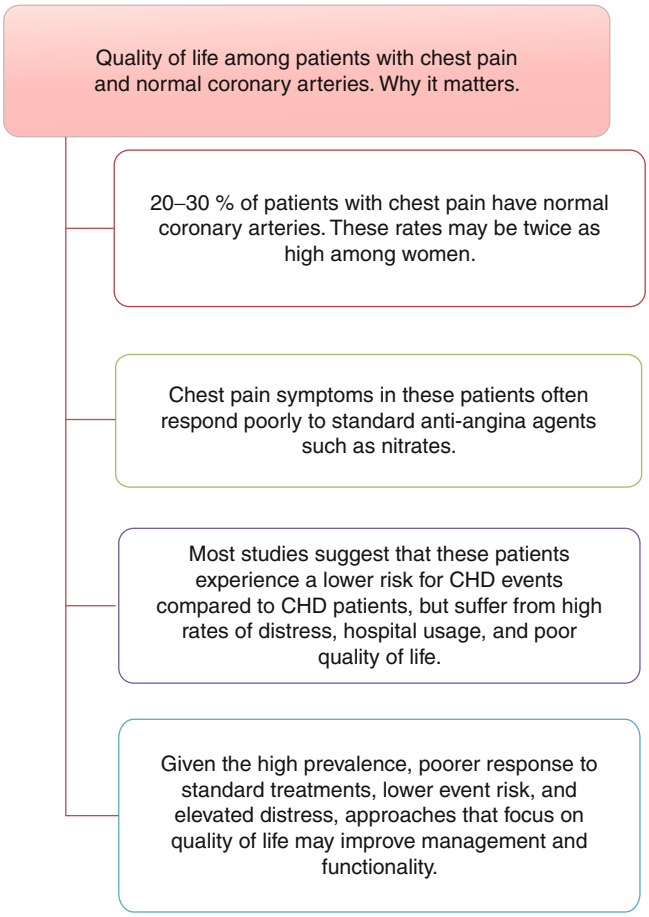

Fig. 26.1 Why quality of life goals are important to patients with chest pain and normal coronary arteries/no obstructive CAD

and it is often a chronic condition, affecting many patients for a decade or more [16, 17]. Therefore, for a sizeable percentage of patients presenting with chest pain – and perhaps even a majority of women – an alternative treatment algorithm, one that emphasizes improved pain management and quality of life on a level equal to medical management objectives, appears warranted for this population. However, the physician may feel comparatively unprepared concerning evidence-based methods for assessing and enhancing quality of life in this population. Providing a practical template towards these goals is the intent of this chapter.

For providers assisting patients with chest pain and normal coronary arteries, this chapter pursues two chief objectives: (1) to briefly define quality of life, characterize dimensions of quality of life commonly affected in this population, and identify methods of measurement suited to time-limited patient encounters; and (2) to describe the evidence for and application of strategies for improving chest pain symptoms and quality of life outcomes consistent with physician's treatment resources.

Fig. 26.2 Common dimensions of quality of life

Definition, Dimensions, and Measurement of Quality of Life

Quality of life is a broad, heterogeneous, and subjective entity. In daily use, quality of life is synonymous with overall life satisfaction and happiness. Unlike a blood pressure reading or glucose test result, however, the meaning of even the same quality of life rating differs across individuals. Although patients may consider a similar set of factors in evaluating their quality of life, the weight they apply to these factors can vary appreciably. Across the thousands of published studies regarding quality of life, reviews attempting to integrate dimensions of quality of life suggest, as illustrated in Fig. 26.2, the existence of a core set of factors. These include physical health, emotional health, social and environmental factors, material and living necessities, and spiritual/personal growth areas [18]. The most important theme to capture from Fig. 26.2 is that pain and physical function are not distinct from quality of life. These factors are, in fact, inherent to what quality of life represents to patients, making the treatment of quality of life a process complementary to standard medical goals rather than a separate clinical objective.

It may surprise readers familiar with frequently bulky psychological instruments to learn that meritorious quality of life measures exist in forms as brief as a single item. The general life satisfaction item from the World Health Organization Quality of Life measure ("In general how satisfied are you with your life?"), for example, is one such brief quality of life indicator [19]. As a health-related dimension, the single-item self-rated health question (a question asking the patient to rate their health as poor, fair, good, very good, or excellent; [20]) is an excellent alternative. Self-rated health is a robust predictor of cardiovascular and total mortality outcomes [21], including among patients with chest pain and normal coronary arteries. In the NHLBI-sponsored Women's Ischemia Syndrome Evaluation (WISE) study, for example, poorer self-rated health predicted a greater risk of total mortality and cardiovascular events even after controlling for CAD risk factors and angiographic disease severity [22]. Further analyses revealed that the degree of functional impairments, not disease severity, best accounted for the self-reported health association in this sample of symptomatic women.

Single item measures such as the above offer tremendous value in applicability but offer limited potential for interpretation. A broader, but still practical, quality of life measure is the Satisfaction with Life Scale (SWLS; [23]), a 5-item questionnaire assessing a person's contentment with their life across several areas. The SWLS has the advantage of being widely used in medical populations, including those rehabilitating from serious medical circumstances such as stroke and spinal cord injury [24]. This wealth of medical population normative data allows one to compare a patient's score on the SWLS to those with a similar health status; providing a template for interpreting whether a patient is experiencing a relatively impaired quality of life. Finally, there exist multiple examples of lengthier and more detailed quality of life measures such as the Short Form Health Survey (SF-36; [25]). By design, this category of quality of life measures captures dimensions of physical function, pain, mental health, and social functioning, among others, at least partially offsetting reduced practicality with greater depth of information. Scores from these longer instruments offer greater interpretability into what aspects of quality of life are impaired, thus potentially guiding recommendations or treatment efforts towards improving quality of life. Among the longer instruments, the Questionnaire for Quality of Life in Syndrome X [26] is the only measure specifically designed and validated for CSX patient populations; like the SF-36, the latter measure comprehensively assesses quality of life across multiple dimensions, ranging for emotional and social functioning to pain and physical health.

Table 26.1 offers a summary of some of the most common quality of life measures, including their respective lengths and content areas and relative advantages and disadvantages for employment among patients with chest pain with or without angiographic obstructive CAD. The measures included in Table 26.1 are but a sampling of those available; however, many of the most commonly used quality of life measures in research contexts (e.g., the Sickness Impact Profile, at 136 items; [27]) are much less practical for clinical settings and intentionally not included among the short list of more practical instruments described here.

Table 26.1 Six common measures of quality of life applicable to patients with angina or chest pain symptoms

Questionnaire	Item length and dimensions	Advantages and disadvantages
Nottingham Health Profile	38-items assessing multiple quality of life domains	A: Assesses multiple dimensions of quality of life; validated with angina populations. D: Lengthy.
HALex	13-items developed for National Health Interview Study	A: Strong focus on functional impact of health problems; includes self-rated health item. D: Generic items not specific to CAD; does not assess emotional or social aspects.
Quality of Life Questionnaire for Syndrome X	45-items measuring nine dimensions of quality of life	A: Designed and validated specifically for syndrome X patients; multidimensional. D: Lengthy
Satisfaction with Life Scale (SWLS)	5-item scale assessing global perceptions of quality of life	A: Short; validated with many medical populations. D: Unidimensional.
Seattle Angina Questionnaire	19-item measure of five areas of chest pain and quality of life	A: Validated with angina/chest pain/CAD populations; assesses chest pain and functional aspects. D: Does not assess emotional or social aspects of quality of life.
Self-rated Health	1-item rating overall perception of health quality	A: Brevity; independent predictor of mortality; validated with CAD populations. D: Unidimensional.
SF-36	36-item measure containing eight subscales. A 12-item short version is also available.	A: Widely used and normed with many medical populations; multidimensional. D: Lengthy; copyrighted.

Improving Quality of Life Among Patients with Chest Pain and Normal Coronary Arteries/No Obstructive CAD

In the first two sections of this chapter, we established that the clinical scenario of chest pain without angiographic evidence of obstructive CAD is a common presentation and associated with an impaired quality of life. An impaired quality of life in these patients, however, is not simply a consequence of the condition but also a contributor to increased healthcare usage over time. Without understanding and intervention, therefore, quality of life effects may contribute to a vicious cycle of greater symptoms, increased healthcare visits, poor emotional health, and impaired functioning. Section "Improving Quality of Life Among Patients with Chest Pain and Normal Coronary Arteries/No Obstructive CAD" overviewed the diverse field of quality of life research to identify core aspects through which patients define quality of life. Further, we reviewed a number of validated quality of life instruments, with an emphasis on those that are brief enough to employ in a healthcare context. From these sections, the objective was to demonstrate that quality of life effects are important to consider among patients with chest pain and normal coronary arteries and to provide a practical plan for measuring these effects. We now turn to the topic of enhancing quality of life among patients with identified impairments in these areas.

Targets for improving quality of life may include one or more of the specific areas indicated in Fig. 26.3. As suggested by the multiple quality of life dimensions identified in Fig. 26.3, approaches to improving quality of life are often multidisciplinary, involving specialty services such as occupational rehabilitation, physical therapy, and mental health and social work programs in addition to medicine. As such,

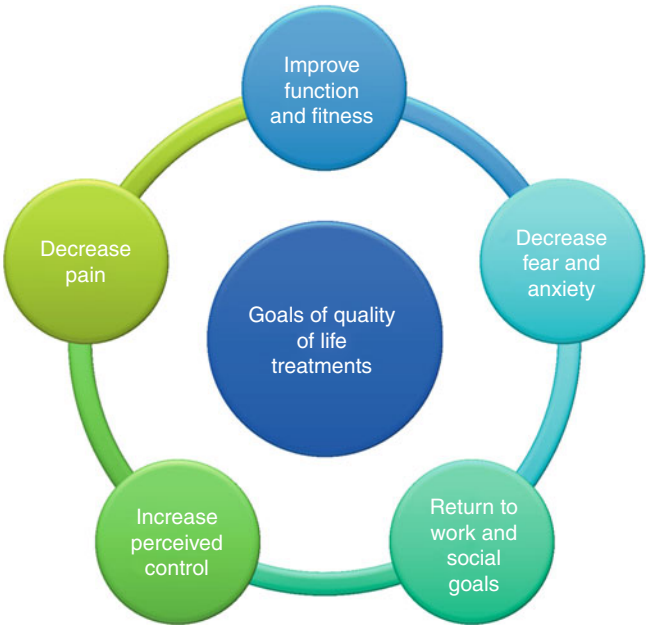

Fig. 26.3 Goals of quality of life treatments

the development of quality of life goals by the physician for patients with chest pain and normal coronary arteries should always include consideration of resources available through allied health disciplines. The specific focus of this section, however, is to describe treatment approaches for quality of life in this population that are both effective and complementary to usual cardiology practice.

In contrast to the complexities inherent in defining and measuring quality of life, the evidence regarding how to improve quality of life among patients with chest pain and normal coronary arteries offers several highly practical approaches for medical providers. Perhaps even more

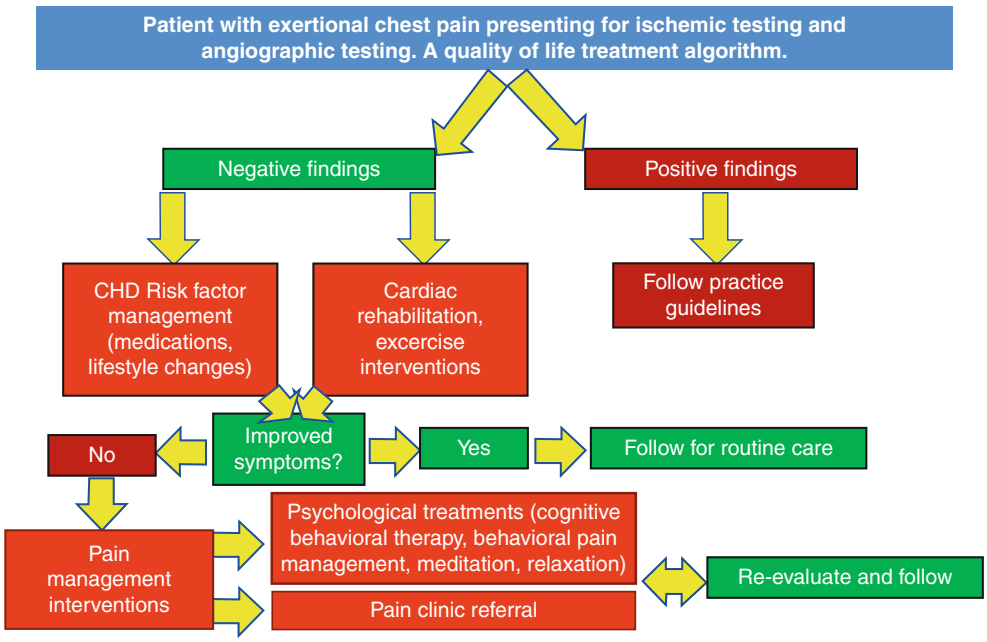

Fig. 26.4 A quality of life treatment algorithm for patients with chest pain and normal coronary arteries/no obstructive CAD

interesting to medical providers is that these methods for improving quality of life overlap with standard treatment approaches for CAD and related chronic medical conditions, dually improving objective as well as subjective aspects of well-being. Therefore, it is possible to address quality of life concerns in this patient population as part of usual care in the hospital, with three specific treatment approaches described.

For example, research examining exercise and cardiac rehabilitation interventions indicates that these treatments improve mood, functional capacity, pain symptoms, anxiety, and other quality of life domains among patients with chest pain irrespective of obstructive CAD status (e.g., [28, 29]). This literature includes specific trials of cardiac rehabilitation among women with chest pain and normal coronary arteries/no obstructive CAD, a patient group typically underrepresented in traditional cardiac rehabilitation studies. Thus, for the clinician working with patients with chest pain, the appreciable quality of life benefits of exercise interventions among those with or without angiographic evidence of disease simplifies the treatment algorithm: Cardiac rehabilitation referrals are an evidence-based treatment for both groups. As illustrated in Fig. 26.4, a follow-up assessment to exercise interventions is a prudent act, permitting the identification of patients not benefiting from the treatment and consideration for alternative management approaches.

Secondly, there is also evidence that aggressive cardiac risk factor management can result in favorable clinical and quality of life outcomes in this patient population [30]. Numerous studies indicate that patients with chest pain and normal coronary arteries/no obstructive CAD commonly present with elevated cardiac risk factor profiles. Treatments that result in reductions in these risk factors carry the twin benefit of lessening symptom burden and improving quality of life while also being proven approaches for reducing the risk of cardiovascular events.

Finally, chest pain in the case of normal coronary arteries/no obstructive CAD is often definable as a type of chronic benign pain and treatable using many of the same validated treatments for chronic pain [31]. Similar to chronic benign pain – back pain, headaches, fibromyalgia, and other pain conditions – chest pain is commonly associated with psychiatric comorbidities, an impaired quality of life, and threatening interpretations of their pain symptoms that produce fear and anxiety [32]. Women more frequently present with chest pain with normal coronary arteries/no obstructive CAD just as they do with many other forms of chronic pain syndromes [33, 34]. Given these multiple common features across common subtypes, it is also not surprising that psychological treatments such as cognitive behavior therapy – a robust treatment for pain, mood, and quality of life domains in other chronic pain populations – are effective treatments for those with chest pain and normal coronary arteries/no obstructive CAD [6, 31].

Cardiac Rehabilitation and Exercise Therapies

At first brush, the application of cardiac rehabilitation to a patient population without angiographic CAD appears to be contradiction in terms. Although cardiac rehabilitation is a proven intervention for reducing secondary event rates [35], the relatively lower coronary event risk among patients with chest pain and normal coronary arteries/no obstructive CAD compared to those with obstructive CAD would seem to mitigate any potential benefit. However, cardiac rehabilitation offers other benefits that make participation highly

beneficial for these patients. For example, in addition to reducing secondary CAD event risk, cardiac rehabilitation is also effective at reducing depression and anxiety [36]. Many studies show that depression rates or depressive symptom severity are reduced by 50 % or more among cardiac rehabilitation participants (e.g., [37]), and is as beneficial in these regards for women as for men (e.g., [38]). Similarly, regular exercise in a supervised environment may help patients alter their perceptions of chest pain symptoms, learning to interpret pain symptoms as more benign and less harmful. Modifying dangerous interpretations of pain symptoms – often measured as "pain catastrophizing" – is a frequent goal of pain management therapies, and correlates with improvements in patient's pain severity reports [39]. Cardiac rehabilitation and other exercise treatments designed for CAD patients also commonly combine with psychological treatments such as relaxation therapy and stress management that can further enhance quality of life benefits. The addition of psychological treatments is associated with further improvements in cardiac rehabilitation program effectiveness based upon meta-analytic reviews [40].

Several studies demonstrate the potential of cardiac rehabilitation and related exercise interventions specifically for patients with chest pain and normal coronary arteries/no obstructive CAD. In a 2008 randomized controlled trial comparing women with CSX assigned to an 8-week cardiac rehabilitation or control [28], rehabilitation participants reported significant decreases in depression, anxiety, interference, pain, and health worries, along with improvements in energy, physical functioning, and general health. Rehabilitation participants also enjoyed decreased blood pressure and increased physical fitness. Participants in the control condition did not experience these benefits. A separate trial of CSX patients randomized to usual care or exercise training showed that exercise treated patients doubled their time to pain onset from exertion following the intervention [29]. A third trial assigned women with CSX to either control, exercise, or relaxation, with the results indicating that, compared to controls, exercise participants experienced improved physical function and health related quality of life. Relaxation-treated participants also improved on the health related quality of life dimensions [41].

Criticisms of the above studies include their relatively small samples and low rates of male participation for the purposes of generalizing results. However, the consistent pattern of benefits across multiple domains of reductions in pain and emotional distress and improvement in physical function suggests that cardiac rehabilitation and exercise therapies are viable and cost-effective treatment alternatives for improving quality of life while also improving CAD risk factor status among patients with chest pain and normal coronary arteries.

CAD Risk Factor Management

Prior reviews of medical management approaches for patients with CSX highlight the multifactorial nature of the pathophysiology contributing to the condition, the importance of linking underlying mechanisms to appropriate treatments, and the many options available for achieving improved symptom management [42, 43]. Mechanisms such as microvascular coronary dysfunction, inflammation, insulin resistance, and hormonal deficiencies are frequently associated with a CSX diagnosis, suggesting an important role for CAD risk factor management in these patients. Similar to the evidence presented regarding exercise therapies, medical therapies effective for improving pain and physical capacity also have broadly favorable benefits on quality of life.

Thus, a recurring theme is that the physician can enhance quality of life outcomes among patients with chest pain and normal coronary arteries/no obstructive CAD even in course of usual care of cardiac risk management and often even in the context of minimal multidisciplinary resources. For example, a randomized placebo controlled trial showed that the antiglycemic agent metformin improved pain and exercise tolerance among patients with chest pain and normal coronary arteries [44]. A 2004 trial of CSX patients comparing ramipril, atorvastatin, and placebo found that both the ACE inhibitor and statin groups experienced significantly improved endothelial function and quality of life as measured by exercise duration and the Seattle Angina Questionnaire [45]. Nitrates, beta blockers, and calcium channel blockers may also enhance quality of life outcomes to the extent that they improve pain symptoms and exercise tolerance [46]. At least one previous placebo-controlled trial combined conventional anti-anginal medications with imipramine in patients with CSX, resulting in significantly fewer chest pain episodes [47]. High rates of side effects experienced by patients receiving the imipramine treatment, however, may have mitigated broader quality of life improvements in the latter trial. Thus, for patients presenting with chest pain, normal coronary arteries, and elevated CAD risk factor profiles, attention to CAD risk factors may carry the additional benefit of improving pain, physical function, and other areas of quality of life.

Pain Management Therapies

A 2010 Cochrane review of psychological treatments for chest pain in patients with normal coronary arteries identified ten randomized controlled trials including 484 participants participating in psychological interventions for pain management [31]. The authors concluded that, relative to participants in comparison conditions, patients in the psychological therapies showed significantly reduced reports of pain

frequency, severity, and number of days free of chest pain. Benefits from these treatments remained stable over 3–9 month follow-up intervals and were particularly strong for studies including cognitive behavioral therapies. Thus, there is at least moderate statistical support from randomized trials indicating that improved chest pain symptoms among patients with normal coronary arteries/no obstructive CAD commonly results among those engaged in psychological treatments and that these treatments confer improvements in other quality of life domains as well.

Cognitive behavioral treatments include multiple components. Relaxation, for example, is frequently among the skills taught to patients as a behavioral strategy for reducing muscle tension, pain, and anxiety. Randomized studies addressing relaxation therapies independent of other treatment aspects are effective at improving quality of life among patients with chest pain and normal coronary arteries/no obstructive CAD [48, 49]. Cognitive behavioral therapies also help patients to identify associations between physical symptoms, cognitive interpretations, and emotional reactions, with the objective of patients learning to identify, evaluate, and correct inaccurate appraisals. Along with physiological pathways such as microvascular and endothelial coronary dysfunction, abnormalities in pain perception are a common mechanism invoked to account for disabling pain symptoms among patients with chest pain and normal coronary arteries [12, 30]. A common vicious cycle among patients with pain is to "catastrophize" symptoms, interpreting symptoms as precursors of serious events, escalating anxiety, and often worsening the severity of the original pain symptom. Figure 26.5 illustrates the causal pathway theorized between pain symptoms, symptom of interpretation, and their impact on quality of life. Reductions in pain catastrophizing often correlate with overall reductions in pain reports. For example, in a 2011 randomized controlled trial assessing the application of a cognitive therapy (pain coping skills training) and sertraline treatments in patients with non-cardiac chest pain, both treatments significantly reduced pain intensity compared to placebo. Further, the combination of the two treatments reduced pain reports and pain catastrophizing scores [39]. Pain catastrophizing and associated anxiety predict the degree of physical and psychosocial disability among patients with chest pain and normal coronary arteries [49], indicating that psychological and/or psychotropic treatments improving pain and pain catastrophizing have widespread benefits across other quality of life domains.

The importance of the pathway highlighted in Fig. 26.5 is that it identifies that pain symptoms affect quality life indirectly through cognitive, emotional, and behavioral mechanisms. Interventions that modify the latter responses in more adaptive ways, even in the absence of changes in pain or disease severity, can reduce the impact of pain on quality of life. As shown in the earlier Fig. 26.4, the application of pain management therapies is appropriate as either a first line therapy for patients with chest pain and normal coronary arteries/no obstructive CAD or as a secondary treatment among those failing to response to initial medical therapies (cardiac rehabilitation and CAD risk factor management).

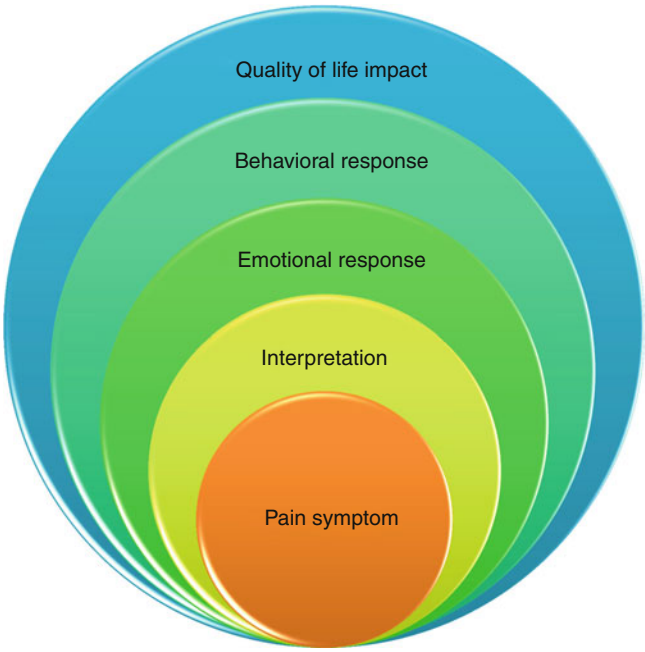

Fig. 26.5 The relationship between pain symptoms and quality of life

Summary

This chapter focused on defining quality of life among patients with chest pain and normal coronary arteries/no obstructive CAD and describing practical, cost-effective ways for physicians to measure and improve quality of life in the course of medical management. Quality of life is a multifarious characteristic, encompassing aspects of physical function, physical and mental health, social status, and spirituality. Many, if not all, of these areas are vulnerable among patients with chest pain and normal coronary arteries/no obstructive CAD, with studies indicating that the quality of life among those with chest pain and normal coronary arteries/no obstructive is even more impaired relative to those with chest pain in the presence of obstructive CAD [50]. Because of the broad nature of quality of life, it can be a vague and challenging outcome to incorporate into cardiology care. However, we identified a number of brief tools that can fit into the time-limited context of patient-physician interactions while yielding information that can reliably identify those with impaired quality of life and helping to guide consideration for interventions.

The focus on quality of life enhancement is this chapter was treatments that: (1) are demonstrated effective for

improving quality of life in randomized controlled trials of patients with chest pain and normal coronary arteries/no obstructive CAD; (2) cost-effective; and (3) most likely to be available as a treatment resource to physicians working with this patient population. Using these criteria, we summarized evidence for three distinct therapeutic approaches. Perhaps surprisingly, our summary of quality of life treatments indicated that the algorithm for patients with chest pain and normal coronary arteries/no obstructive CAD closely parallels that of patients with obstructive CAD [51] and complement standard medical management approaches. Cardiac rehabilitation, exercise therapies, aggressive CAD risk factor management, and pain management therapies, for example, enhance physical function and quality of life for both populations, a conclusion that may reduce the complexity of decision making for the physician, promote management strategies that dually improve cardiac risk status and quality of life, and normalize the experience of care for patients without angiographic CAD.

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Part VI

Treatment

Cardiac Syndrome X: Management Algorithms

27

Gaetano Antonio Lanza and Juan Carlos Kaski

Abstract

The management of cardiac syndrome X (CSX) often represents a challenging task for the managing physician. The syndrome encompasses heterogeneous patient categories with different pathophysiological and etiological backgrounds. Each of these patient subgroups may require different therapeutic approaches, depending on the prevailing pathogenic mechanism. In addition, within groups, some patients but not others may respond favourably to different forms of treatment.

Coronary microvascular dysfunction is one of the prevailing pathogenic mechanisms and can result in impaired coronary vasodilation, excessive coronary vasoconstriction or both. Identifying the prevailing pathogenic mechanisms should result in the implementation of effective treatment strategies.

This chapter focuses on the practical management of patients with CSX.

Keywords

Treatment • Management algorithms • Pharmacotherapy

Introduction

The management of cardiac syndrome X (CSX) often represents a difficult task for the managing physician, as the syndrome encompasses heterogeneous patients with different pathophysiological and etiological backgrounds. Each of these patient subgroups may require different therapeutic approaches, depending on the prevailing pathogenic mechanism. In addition, within groups, some patients may respond poorly to various forms of medical therapy.

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Symptoms, including exertional angina and chest pain at rest, fatigue, dyspnoea, tiredness, etc., may be a reflection of different mechanisms operating in different patients. It is now apparent that most of the patients presenting with typical symptoms of angina pectoris despite normal coronary angiograms or non-obstructive coronary artery disease, have microvascular angina (MVA), i.e. angina caused by coronary microvascular dysfunction (CMVD) [1–3], and this entity is discussed in detail in other chapters of this book.

In clinical practice, however, the diagnosis of MVA is often questioned or assumed on an "exclusion criterion" only, based on the absence of coronary artery stenosis. In several patients with chest pain and normal coronary arteries, however, symptoms may be non-cardiac in origin, such as gastro-oesophageal or musculo-skeletal chest wall disorders. In these latter cases, therapy directed to CMVD will most likely fail in preventing or controlling symptoms. Thus, documentation of the presence or absence of CMVD should be desirable to identify a suitable therapeutic strategy. Likewise, the identification of other pathogenetic mechanisms is crucial for the rational management of these patients [1–3].

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When present, CMVD can be related to different causes and can result in impaired coronary vasodilation, excessive coronary vasoconstriction or both. Identifying the prevailing mechanisms should result in the implementation of more effective treatment.

It is important to highlight the fact that, as shown by several studies [4, 5], in a sizeable proportion of CSX patient, chest pain is mainly related to the presence of abnormal pain perception. In these patients, severe chest pain can be elicited by cardiac stimuli that would not trigger a painful response in the general population. In most CSX patients, this nociceptive abnormality occurs concomitantly with CMVD. The combined effects of these two pathogenic mechanisms can result in the occurrence of severe chest pain even when minor reductions in blood flow take place and stimulate pain receptors in the myocardium [3]. It has been suggested that alterations in cardiac autonomic (sympathetic) nerve endings might be the mechanism underlying CMVD and abnormal pain perception, and that, in some patients, CMVD may damage sensitive cardiac fibres and this could result in nociceptive disorders [6]. Unfortunately, objective demonstration of this hypothesis is unlikely to happen in the very near future given that technical limitations exist at present that preclude the specific assessment of nociceptive cardiac function.

Management of MVA is at present based on current understanding of the pathogenic mechanisms suggested by research work in the past 20 years. Therapeutic efforts are mainly directed at improving microvascular function and preventing microvascular myocardial ischaemia. In addition, analgesic treatments can complement therapies directed to antagonising CMVD [7].

Importantly, long-term follow-up studies have consistently shown that chronic forms of CSX are not associated with an increased risk of major cardiovascular events [8, 9]. Therefore the primary objective of treatment should be the prevention of chest pain symptoms and the improvement of quality of life, which is in many cases significantly impaired due to severe and recurrent symptoms [8, 9].

As chest pain is the symptom that most frequently impairs quality of life, followed closely by dyspnoea and generalised fatigue, the efficacy of therapy in these patients should be judged mainly on its effects on chest pain and other major symptoms rather than on surrogate end-points such as ischaemic ECG changes, perfusion defects on myocardial scintigraphy or coronary blood flow (CBF) impairment.

A further issue about therapeutic recommendations in CSX patients is that most of the studies assessing patient treatment have important limitations, including small patient numbers, lack of appropriate randomization and suitable control groups, and heterogeneity of study end-points, which do not often allow appropriate comparisons between the various forms of treatment proposed.

This chapter briefly reviews the evidence available regarding the efficacy of the various forms of therapy used in clinical practice. We will also propose a therapeutic algorithm for a rational management of these patients.

Anti-ischaemic Drugs

Anti-ischaemic medications used for management of angina pectoris associated with obstructive coronary artery disease are also used for treatment in CSX patients. These medications, used as single agents or in different combinations, are often effective in preventing the occurrence of chest pain in patients with documented MVA [7]. The main characteristics and results of the studies that investigated the effects of classical anti-ischaemic drugs are summarized in Table 27.1.

Beta-Blockers

As in angina patients with obstructive coronary artery disease, beta-blockers (BBs) may have several beneficial effects in patients with effort MVA. They reduce myocardial oxygen consumption, prolong diastolic time and therefore improve coronary perfusion, improve left ventricular dynamics, particularly in subjects with increased sympathethic activity, and reduce exercise and stress induced myocardial ischaemia.

Of note, by reducing myocardial inotropism, BBs might also blunt the stimulation of mechanoceptors involved in the origin and transmission of cardiac pain, in patients with increased cardiac pain sensitivity.

The few studies that assessed the effects of BBs on angina symptoms in CSX patients have all concordantly reported significant beneficial effects. In a small single-blind, placebo-controlled study, Fragasso et al. [10] reported beneficial actions of atenolol on chest pain episodes in 22 CSX patients. In another small randomized, double blind crossover trial, Lanza et al. [11] showed that atenolol, but not amlodipine or isosorbide-5-mononitrate, significantly reduced angina symptoms over a period of 4 weeks of treatment (Fig. 27.1). Similarly, Leonardo et al. [12], in 16 CSX patients, reported that atenolol, but not trimetazidine, was effective in reducing chest pain episodes.

Data are less consistent when exercise test end-points are considered. Some studies, reported an improvement in both ischaemic and angina threshold, as well as in exercise capacity [10, 12], whereas others failed to show significant effects [13, 14]. Of interest, acebutolol was found to improve exercise stress test (EST) results only in a subgroup of patients with increased adrenergic activity, in contrast to verapamil, which had favourable effects in all patients [13].

Another study, however, showed that propranolol, but not verapamil, reduced the number of episodes of ST-segment depression during 24-h ECG Holter monitoring [15].

Table 27.1 Main results of studies assessing the effects of traditional anti-ischaemic drugs in patients with cardiac syndrome X

	Drug	Angina	QoL	EST	Holter	NTG use	Other
Beta-blockers							
Fragasso et al. [10]	Atenolol	↑		↑			Improved diastolic function
Lanza et al. [11]	Atenolol	↑					
Leonardo et al. [12]	Atenolol	↑		↑			Improved diastolic function
Romeo et al. [13]	Acebutolol			↔			
Ferrini et al. [14]	Propranolol			↔			
Bugiardini et al. [15]	Propranolol				↑		
Calcium-antagonists							
Cannon et al. [17]	Verapamil, Nifedipine	↑		↑		↓	
Cannon et al. [18]	Lidoflazine	↑		↑	↔		Severe arrhythmic adverse effects
Ozçelik et al. [19]	Nisoldipine	↑		↑		↓	
Romeo et al. [13]	Verapamil			↔			
Montorsi et al. [20]	Nifedipine sl	↑		↑			↑ CBF
Montorsi et al. [22]	Nifedipine sl						Variable coronary vasomotor response
Bugiardini et al. [15]	Verapamil				↔		
Lanza et al. [11]	Amlodipine	↔					
Ferrini et al. [14]	Diltiazem			↑			
Sutch et al. [21]	Diltiazem						↔ CFR
Nitrates							
Lanza et al. [25]	sl ISDN			↓			
Radice et al. [26]	sl NTG			↓			
Bugiardini et al. [27]	i.c. ISDN						↓ CBF
Lanza et al. [11]	ISMN	↔	↔				

NTG nitroglycerin, *QoL* quality of life, *ISDN* isosorbide di nitrate, *ISMN* isosorbide mononitrate, *CBF* coronary blood flo, *CFR* coronary flow reserve, *s* sublingual, *i.c.* intracoronary, *EST* exercise stress test

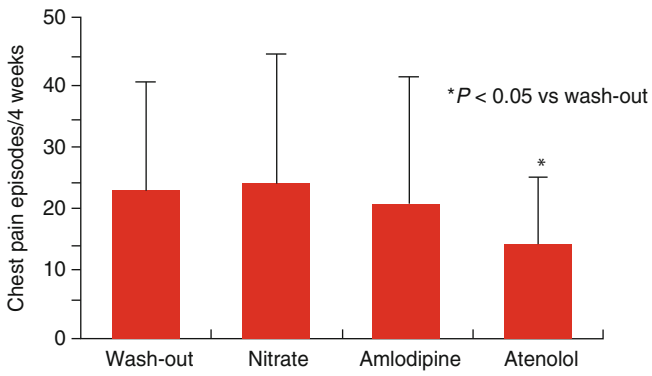

Fig. 27.1 Effect of atenolol, amlodipine and isosorbide-5-mononitrate on angina episodes in ten patients with cardiac syndrome X (Modified from Lanza et al. [11]. With permission from Elsevier)

These studies have obvious limitations, particularly the small number of patients included, which in the presence of such a heterogeneous syndrome, makes it difficult to draw definitive conclusions regarding the true role of BB treatment in these patients.

It is reasonable to conclude that BBs are useful in patients with CSX, particularly in those who show evidence for increased adrenergic activity, including those with increased heart rate at rest, a rapid increase of heart rate and/or blood pressure during exercise, abnormal heart rate circadian rhythm and sympatho-vagal imbalance, as suggested by heart rate variability analysis [16].

Calcium-Antagonists

Calcium antagonists (CAs) are powerful vasodilator drugs and are therefore used in patients with CSX in an attempt to prevent microvascular ischaemia by improving the reduced vasodilatory capacity of the coronary microcirculation. These agents also reduce cardiac afterload which can be beneficial. In addition, non dihydropyridine CAs reduce myocardial oxygen consumption mainly as a result of their negative chronotropic effect. In some patients CAs, mainly dihydropyridine drugs, reduce blood pressure and this effect causes a reflex increase in adrenergic activity, which may antagonise their favourable vasodilatatory effects.

A beneficial effect of CA therapy on angina symptoms of CSX patients has been shown in several studies [13, 17–20]. Cannon et al. [17], in 26 patients with evidence of MVA, showed that verapamil or nifedipine significantly reduced the number of anginal episodes and nitroglycerine consumption and improved exercise tolerance, during a 4-week

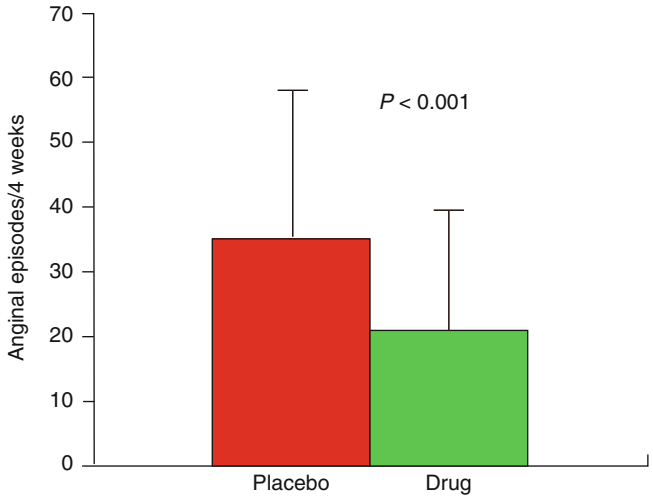

Fig. 27.2 Effect of verapamil or nifedipine on episodes of angina in 26 patients with evidence of microvascular angina (Based on data from Cannon et al. [17])

follow-up (Fig. 27.2). In this study, however, patients received a determined optimal dose of the study drugs and those unresponsive (four patients) were excluded from the trial.

Using a similar approach, Cannon et al. [18] showed significant antianginal effects with the CA lidoflazine, which, however, caused severe arrhythmic adverse effects in some patients.

Favourable effects of CAs have been reported on exercise-induced angina and ST-segment depression, as well as on exercise tolerance [13, 19]. Montorsi et al. [20] showed, in an open trial, that nifedipine for 4 weeks improved both ST segment depression and exercise-induced angina. Similarly, Romeo et al. [13] reported beneficial effects with verapamil on exercise tolerance in CSX patients, compared to the BB acebutolol.

However, no significant improvement of angina symptoms were observed with amlodipine in a study [11] (Fig. 27.1), and verapamil failed to reduce spontaneous episodes of ST-segment depression during daily life, as assessed by ambulatory ECG Holter monitoring, in a randomized study [15].

Some studies have also assessed the effects of CAs on CBF in CSX patients, with variable results. Sütsch et al. [21] showed no effects of diltiazem on coronary flow response to dipyridamole, whereas an improvement of coronary microvascular function in response to sublingual nifedipine was observed by Montorsi et al. [22]. Of note, in the latter study nifedipine was associated with a worsening of exercise-induced angina and ECG changes in a few patients, similarly to what has been shown in some patients in response to the acute administration of nitrates (see below) [22].

In summary, like with BB, studies carried out with CAs have important limitations and it is unfortunate that no large well designed studies have been carried out to clarify their real therapeutic effect. From a clinical perspective, non dihydropyridine CAs constitute a valid therapeutic first-line option, particularly in patients in whom the prevailing mechanism of angina appears to be an abnormal vasodilatory capacity of the coronary microcirculation or microvessel spasm.

Nitrates

The anti-ischemic effects of nitrates in patients with coronary artery disease are mainly related to their capacity to reduce cardiac work through a reduction of pre-load, and to their coronary vasodilator effects. However, the effects of nitrates on the coronary microcirculation seem to be variable and rather limited [23].

As in patients with coronary artery disease and in those with epicardial coronary artery spam (i.e. Prinzmetal's variant angina), short-acting sublingual nitrates are the first-choice drugs to treat chest pain attacks also in patients with CSX. However, the efficacy of sublingual nitrates seems less consistent in these patients, compared to those with obstructive coronary artery disease (CAD) or variant angina, as a good response seems to be achieved in only about 50 % of patients [8, 24].

The effect of nitrates on daily life angina symptoms, i.e. spontaneous chest pain or exercise-induced angina and ST-segment changes in these patients is positive in only approximately 50 %, as mentioned for acute chest pain episodes. In two studies and in contrast with data in patients with obstructive CAD, the administration of short-acting nitrates before exercise stress testing failed to significantly improve the time to 1 mm ST-segment depression and angina [25, 26]. Intriguingly, some patients in these series showed a worsening of these variables. The reasons for the different effects of acute nitrates in CSX patients are not fully known, but may include myocardial hypoperfusion caused by hypotension, a limited effect on coronary microvascular dysfunction and reflex adrenergic activation, with an increase in heart rate and, possibly, coronary vasoconstriction. Paradoxical reduction of CBF was observed after intravenous and/or intracoronary short-acting nitrate administration in another study [27].

There are no data concerning the effects of chronic oral nitrate therapy in CSX patients, with the exception of a small study in which the administration of isosorbide-5-mononitrate (40 mg) failed to improve symptoms and quality of life over a period of 4 weeks [11].

In summary, short-acting nitrates are recommended to treat acute angina attacks in CSX patients, although a full benefit is achieved in only approximately 50 % of patients. Long-term nitrate formulations can be useful in a sizeable proportion of patients and are usually added, rather empirically, as second- or third-step therapy, to BB and CAs for prevention of symptoms.

Table 27.2 Main results of studies assessing the effects of alternative kinds of drugs with potential anti-ischaemic effects in patients with cardiac syndrome X

	Drug	Angina	QoL	EST	Holter	NTG use	Other
Xanthines							
Emdin et al. [31]	Aminophylline	↑		↑			
Yoshio et al. [32]	Aminophylline	↑		↑			↑ LVEF at rest but not at peak EST
Radice et al. [26]	Aminophylline	↑		↑			
Lanza et al. [33]	Aminophylline	↑		↔			
Lanza et al. [34]	Bamiphylline			↔			
Elliott et al. [35]	Aminophylline	↑		↑	↔		
ACE-inhibitors							
Kaski et al. [37]	Enalapril			↑			
Nalbantgil et al. [38]	Cilazapril			↑			
Ozcelik et al. [19]	Ramipril	↑		↑			
Pizzi et al. [39]	Ramipril		↑	↑			↓ oxidative stress
Chen et al. [40]	Enalapril			↑			↑ CFR and endothelial function
Alpha-antagonists							
Camici et al. [41]	Doxazosin	↑		↑			↑ CFR
Rosen et al. [42]	Doxazosin						↔ CFR, chest pain and ECG changes after dipyridamole.
Galassi et al. [43]	Prazosin			↔	↔		
Nicorandil							
Yamabe et al. [47]				↑			↑ perfusion defects at scintigraphy
Chen et al. [48]		↑		↑	↔		
Trimetazidine							
Leonardo et al. [12]		↔		↔			↔ diastolic function
Ranolazine							
Mehta et al. [52]		↑	↑				↑ perfusion defects at CMR
Statins							
Fábián et al. [53]	Simvastatin			↑			↑ FMD
Kayikcioglu et al. [54]	Pravastatin			↑			↑ FMD
Pizzi et al. [39]	Atorvastatin		↑	↑			↑ FMD; ↓ oxidative stress
Oestrogens							
Rosano et al. [61]	17-β-oestradiol	↑		↑			
Albertsson et al. [62]	17-β-oestradiol	↑		↑			

LVEF left ventricular ejection fraction, *CMR* cardiovascular magnetic resonance, *FMD* flow mediated dilation, Other abbreviations as in Table 27.1

Other Anti-ischaemic Drugs

Several other forms of therapy, shown to have anti-ischaemic effects, have been assessed in patients with CSX. Although data are limited in the context of CSX, they can be prescribed in addition to classical anti-ischaemic drugs. The main alternative anti-ischaemic medication tested in CSX patients and their main clinical results are summarized in Table 27.2.

Xanthine Derivatives

The beneficial effects reported with the use of xanthines in patients with CSX, and in MVA in particular, can be related to two different mechanisms [28, 29], firstly to their antagonistic effects on the adenosine receptor. Adenosine has arteriolar vasodilator effects (through stimulation of vascular smooth muscle cell A_2 receptors) [28]. Thus, the inhibitory effects of xanthines on the dilatory effects of adenosine in non dysfunctional microvessels may favour CBF redistribution towards myocardial areas with CMVD (where the release of adenosine is increased). This anti-steal effect can also be achieved by xanthines through stimulation of presynaptic alpha-1 adrenergic receptors; this results in enhanced noradrenaline release, which, again, causes a more significant microvascular constriction in non dysfunctional areas, thus favouring CBF towards dysfunctional microvessels. Xanthines may, in addition have "analgesic" effect, as adenosine is a major mediator of ischaemic cardiac pain through stimulation of cardiac nerve fibre A_1 receptors [29]. Adenosine antagonism at this level, therefore, may reduce pain transmission. This effect can be particularly important

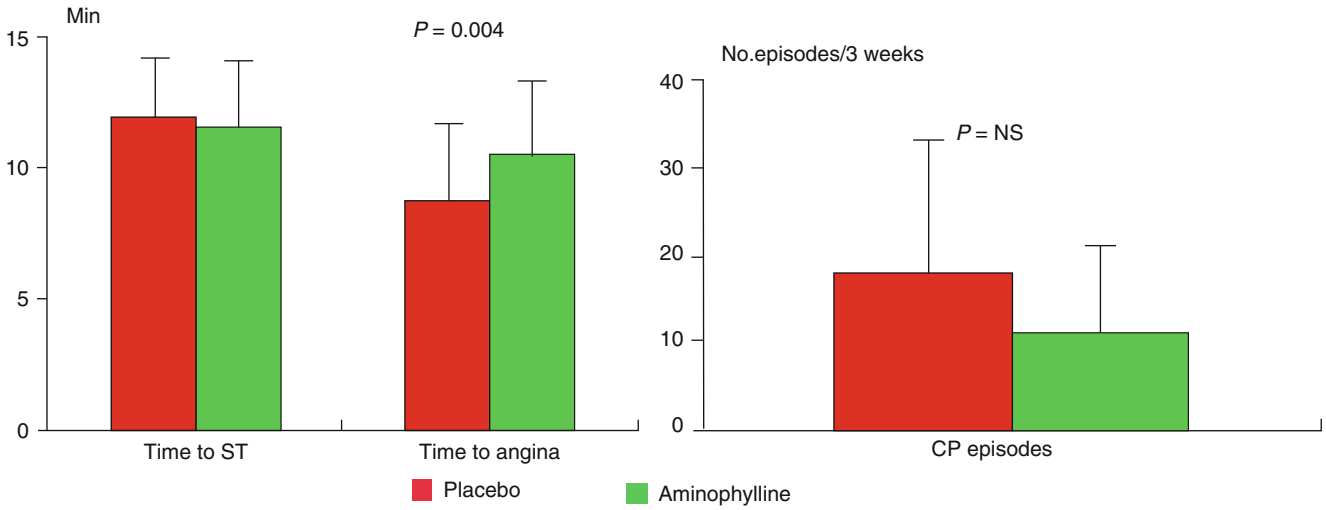

Fig. 27.3 Effect of aminophylline on exercise test (*left*) and episodes of angina (*right*) in patients with cardiac syndrome X (Based on data from Elliott et al. [35])

in patients with a reduced pain threshold, who also have been shown to have increased pain sensitivity to administration of adenosine [30].

Some studies have shown beneficial effects of aminophylline, a nonspecific A_1/A_2 adenosine receptor antagonist, on exercise-induced symptoms and/or ischaemic ECG changes in patients with CSX. In a controlled trial Edmin et al. [31] showed that intravenous aminophylline abolished ST-segment depression and angina induced by exercise in 100 and 50 % of just eight patients, respectively. Yoshio et al. [32], in a placebo-controlled trial, also found that aminophylline reduced average ST-segment depression and prevented EST-induced angina in 7 out of 12 patients.

Also a single oral dose of aminophylline (400 mg) [26] was reported to improve exercise test result in a study, in which the test was performed at baseline and 90 min after drug administration. At baseline all 20 patients included in this study had ST segment depression and 18 had anginal pain; after aminophylline, ST-segment depression and angina were induced in 11 and 10 patients, respectively.

In contrast with these reports, Lanza et al. in an uncontrolled trial, failed to find significant improvement of exercise induced angina and ST-segment changes after intravenous administration of aminophylline in nine CSX patients [33]. Furthermore, in a randomized placebo-controlled trial in 16 CSX patients with both angina and ST-segment changes induced during exercise testing [34], the same authors, showed no significant effects of the intravenous administration of the specific A1-receptor antagonist bamiphylline (300 mg) on exercise-induced ST segment changes, although there was a reduction of the severity of exercise-induced chest pain with the drug.

All previous studies, however, were focused on the acute effects of xanthines on exercise stress test results. The effects of chronic oral xanthine therapy on spontaneous angina attacks have only been assessed by Elliott et al. [35] who randomized 13 CSX patients to receive aminophylline (225–350 mg twice daily) or placebo for 3 weeks in a crossover trial. In the 10 patients who completed the trial, aminophylline improved angina, but not ST-segment depression induced by exercise stress testing; however, there was no significant improvement of spontaneous anginal episodes or episodes of ST segment depression on ECG Holter monitoring (Fig. 27.3).

Thus, although data suggest that xanthines may improve exercise-induced angina in patients with CSX and pharmacodynamics data suggest their utility in case of increased pain sensitivity, their effects on spontaneous angina episodes during continuous therapy needs further assessment.

ACE-Inhibitors

ACE-inhibitors have been proposed as therapeutic agents in this setting due to their lowering effects of serum and tissue angiotensin II. There is, in fact, no strong evidence that AT-II plays a role in CMVD in CSX patients. However, angiotensin II, in particular local tissue AT-II, is involved in the regulation of coronary microvascular structure and function, exerting, when increased, several potentially deleterious effects. It has direct vasoconstrictor effects and increases oxidative stress, favouring the degradation of the vasodilator agent nitric oxide and therefore causing endothelial dysfunction [36]. Furthermore, it enhances the effects of sympathetic nervous system on coronary vasomotor tone and may also induce structural microvascular changes by stimulating cell growth [36].

The favourable effects of ACE-inhibitors in CSX were suggested by a randomized placebo-controlled trial [37], where enalapril improved exercise tolerance and time to

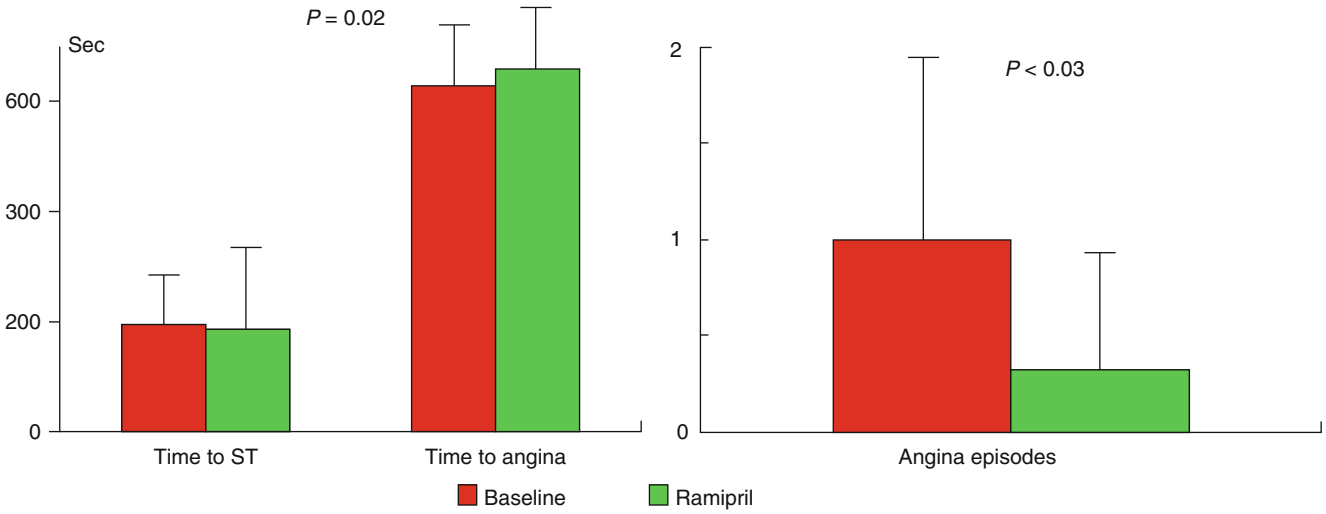

Fig. 27.4 Effect of ramipril on exercise test (*left*) and episodes of angina (*right*) in patients with cardiac syndrome X (Based on data from Pizzi et al. [39])

1 mm ST-segment depression. Similar results have subsequently been obtained with the use of cilazapril [38]. Moreover, an improvement of angina symptoms, as well as exercise capacity, has been reported with the use of ramipril [19, 39] (Fig. 27.4). Importantly, enalapril has been found to improve coronary microvascular function through increase of NO availability and reduction of oxidative stress in CSX patients [40].

According to these data, it is possible that some patients with CSX may benefit from ACE-inhibitors, in particular those with hypertension or evidence of endothelial dysfunction.

Alpha-Antagonist Drugs

The increased sympathetic activity shown in several patients with CSX might result in increased microvascular constriction through stimulation of vascular alpha-receptors. Accordingly alpha-blocking agents might have favourable effects in this condition.

Doxazosin, a post-synaptic alpha-1 receptor antagonist, has been reported to improve symptoms, as well as exercise tolerance, in an uncontrolled study [41], and was also found to improve CBF response to dipyridamole [42]. However, prazosin, which has similar effects of doxazosine, and clonidine, which instead reduces outflow alpha-stimulus through central effects, failed to improve exercise capacity and episodes of ST segment depression during Holter monitoring in other studies [43]. Furthermore, in two placebo-controlled trials, both clonidine and doxazosin did not have significant effects on exercise test results [44] and chest pain episodes [45], respectively.

The inconsistent results of peripheral alpha-blockers can, at least in part, reside in the development of tolerance. On the whole, the benefits and role of these drugs in CSX patients seem to be marginal.

Nicorandil

Nicorandil is an adenosine triphosphate (ATP) potassium channel opener, which also has nitrate-like effects. Nicorandil has been shown to have direct dilator effects on coronary resistance vessels, but might also modulate the response of small artery vessels to sympathetic stimulation [46]. In a non-controlled study of 11 patients with MVA, intravenous administration of nicorandil decreased the extension and severity of exercise-induced ST-segment depression at the ECG and myocardial perfusion defects on thallium myocardial scintigraphy [47].

Furthermore, in a randomized placebo-controlled trial in patients with MVA, oral nicorandil improved both symptoms and exercise ECG results over a 2-weeks treatment [48]. Accordingly, nicorandil should be taken into account in the treatment of CSX patients, in particular as an alternative to nitrates.

Trimetazidine

Trimetazidine has been suggested to improve tolerance to myocardial ischaemia during exercise and other forms of stress by switching cell metabolism from free fatty acid towards glucose oxidation, thus improving cardiac metabolism as well as reducing intracellular cell acidosis.

In a double-blind placebo-controlled study of 35 CSX patients [49] trimetazidine improved exercise capacity and time to 1 mm ST segment depression. In another placebo-controlled trial, however, trimetazidine failed to show significant effects on symptoms and exercise tolerance [12], thus questioning the place that this drug may have in the treatment of CSX patients.

Ranolazine

Ranolazine is a new anti-ischaemic drug which seems to act by inhibiting the inward late Na^+ current, thus reducing intracellular Ca^{2+} overload in cardiomyocytes during ischaemia and, therefore, improving myocardial relaxation and left ventricular diastolic function [50].

Ranolazine has been shown to be useful in patients with stable angina and obstructive CAD [51].

In a recent small randomized, double-blind, placebo-controlled, crossover trial 20 women with MVA showing >10 % of ischaemic myocardium on stress adenosine cardiovascular magnetic resonance (CMR) imaging, were treated with ranolazine or placebo for 4 weeks. Compared with placebo, ranolazine resulted in significantly higher Seattle Angina Questionnaire scores and showed a trend toward a higher mid-ventricular quantitative myocardial perfusion reserve index at CMR, which actually improved in the small subgroup with CBF reserve <3.0 [52]. Although these data seem promising, however, further studies are needed to establish the role of ranolazine in the treatment of CSX patients.

Statins

The usefulness of statins in CSX patients has its rationale in their powerful anti-oxidant and anti-inflammatory, as well as lipid-lowering, effects, all of which can result in an improvement of endothelial function.

In a randomized, placebo-controlled trial, simvastatin, 20 mg/day, significantly increased brachial artery flow-mediated dilation and time to 1 mm ST-segment depression on exercise stress testing in CSX patients with mild hypercholesterolemia [53]. Similar results were observed in a single-blind, placebo-controlled trial of pravastatin [54].

Furthermore, Pizzi et al. [39], in a randomized placebo-controlled trial of 45 CSX patients, showed that a combination of ramipril (10 mg) and atorvastatin (40 mg) for 6 months significantly reduced oxidative stress and improved endothelial function in CSX patients. At follow-up, patients taking ramipril and atorvastatin showed improved quality of life (as assessed by Seattle angina questionnaire) and exercise capacity. However, this study does not allow to identify the relative roles of these two drugs in the improved clinical variables.

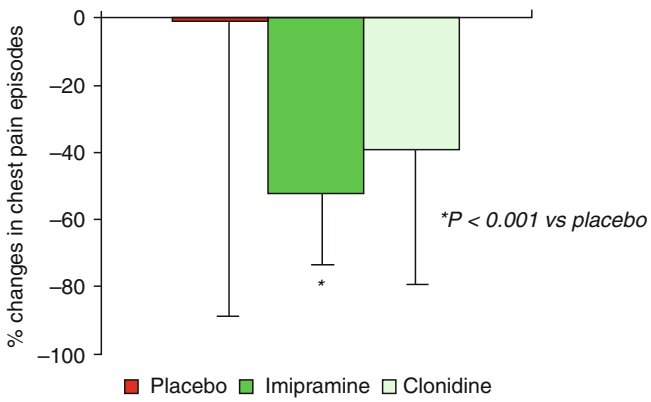

Fig. 27.5 Effect of imipramine and clonidine on episodes of chest pain in patients with angina and normal coronary arteries (Based on data from Cannon et al. [45])

In summary, some studies have recently suggested that statins improve vascular function and symptoms in CSX patients, and the use of these drugs might be of particular utility in patients with high cholesterol levels, evidence for inflammatory activity, and increased oxidative stress.

Oestrogens

Patients with CSX are predominantly women often in the peri-post-menopausal state [55], suggesting that a deficiency of oestrogens might constitute an important pathogenic factor.

Oestrogen deficiency is associated with vasomotor abnormalities, in particular an impairment of endothelium-dependent vasodilation [56]. Accordingly, oestrogen administration has been shown to improve endothelial function [57]. Of note, the hormonal changes typical of the peri-menopause period may also induce increased adrenergic activity [58], which can be reduced by oestrogen therapy [59]. Finally, oestrogens have been also shown to exert a modulatory effect on pain perception [60].

In a small placebo-controlled cross-over study [61], the transdermal administration of 17-β-estradiol (100 μg/24 h) reduced spontaneous episodes of chest pain (Fig. 27.5) in post-menopausal CSX women during 8 weeks of treatment, although no significant effects were observed on episodes of exercise induced ST-segment depression or Holter monitoring, and on stress-induced myocardial perfusion defects on thallium-201 myocardial scintigraphy.

Another randomized placebo-controlled trial, however, showed a significant improvement in time to angina and to ST segment depression during stress testing, together with exercise capacity, after 7 days of treatment with transdermal oestrogen [62].

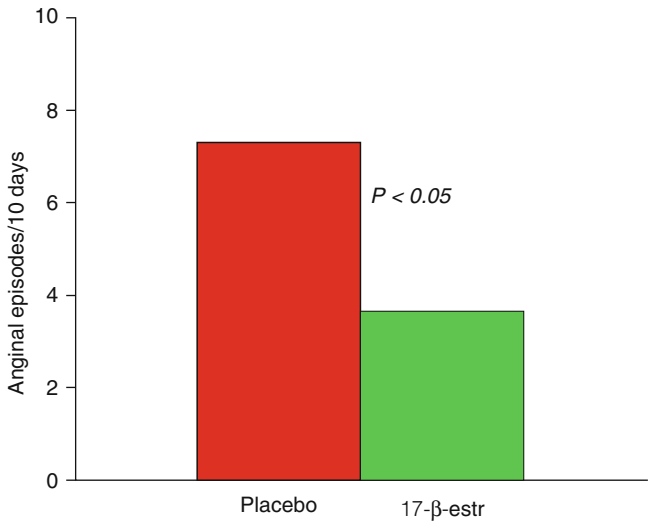

Fig. 27.6 Effect of 17-β-oestradiol on episodes of angina in patients with cardiac syndrome X (Based on data from Rosano et al. [61])

On the whole, these results suggest that oestrogens may be helpful for management of women with CSX who show clinical evidence of oestrogen deficiency. An issue, however, is that long-term therapy may portend some increased risk of serious adverse events [63]. Furthermore, some data suggest that the initial benefits of oestrogens may reduce or disappear over long term treatment [64].

Analgesic Agents

As mentioned above, an enhanced painful perception of cardiac stimuli is often present in CSX patients and can significantly contribute to impair their quality of life [8, 9]. Accordingly, the administration of drugs able to inhibit cardiac pain transmission and perception might be helpful in these patients.

As described above, xanthine derivatives can improve chest pain in these patients in part acting through inhibition of adenosine stimulated cardiac afferent pain fibres (see above).

In a randomized, double-blind, placebo-controlled trial, Cannon et al. assessed the effects of imipramine (50 mg), an antidepressive drug with inhibitor effects on visceral pain transmission, and clonidine (0.2 mg), an anti-hypertensive drug (see above) which also inhibits central perception of pain, in 60 patients with angina and normal coronary arteries during a period of 1 month (Fig. 27.6) [45]. Imipramine significantly reduced spontaneous chest pain episodes by 52 ± 25 %, whereas no significant effects were observed with placebo or clonidine. Of note, imipramine also reduced chest pain provoked by manipulation of a stimulation catheter in the right ventricular cavity [45].

In another placebo-controlled trial imipramine confirmed its efficacy in reducing the episodes of chest pain in CSX patients [65]; the latter study, however, failed to show an improvement of quality of life, as assessed by a validated health profile questionnaire. This disappointing result was probably related to significant occurrence of side effects caused by the drug.

Thus, although imipramine seems useful to prevent episodes of chest pain, and can therefore be taken into account in some patients, the frequent occurrence of side effects limits its use.

Non Pharmacological Therapies

In some CSX patients chest pain episodes are extremely frequent and severe, despite full administration of standard and alternative medical therapy. Some non pharmacological therapeutic measures have been suggested to be helpful in these patients (Table 27.3).

Spinal Cord Stimulation (SCS)

Some studies have shown beneficial effects with SCS in patients with refractory MVA. SCS consists in the electrical stimulation of the dorsal horns of the spinal cord at C7-T1 level through a quadripolar (or octopolar) electrode wire, introduced in the epidural space through an intervertebral puncture and connected through subcutaneous tunneling to a programmable generator, usually implanted in an abdominal pocket.

SCS has been reported to improve symptoms in patients with refractory angina with obstructive CAD [66, 67], and exerts its effects through modulation of cardiac pain transmission and processing and the improvement of myocardial ischaemia, likely mainly through modulatory actions on sympathetic tone [68].

Eliasson et al. [69] reported beneficial effects of SCS on exercise tolerance and on both ischemic and anginal threshold in 12 CSX patients. These data were confirmed in an uncontrolled study in 11 patients with CSX by Lanza et al. who also showed improvement of angina status over a period of 6 months [70].

The same group has subsequently published results on the long term clinical follow-up of 19 CSX patients with refractory MVA treated with SCS, showing a significant reduction of angina episodes and nitrate consumption, as well as improvement of quality of life, compared to control group of CSX patients with similarly severe angina symptoms who refused to undergo SCS device implantation (Fig. 27.7) [71].

Table 27.3 Main results of studies assessing alternative forms of therapy for patients with cardiac syndrome X with refractory chest pain episodes

	Angina	QoL	EST	Holter	NTG use	Other
Imipramine						
Cannon et al. [45]	↑					
Cox et al. [65]	↑	↔				
Spinal cord stimulation						
Eliasson et al. [69]	↑		↑			
Lanza et al. [70]	↑	↑			↓	
Sgueglia et al. [71]	↑	↑	↑		↓	
TENS						
Chauhan et al. [73]						↑ CBF
Sanderson et al. [74]						↓ CBF; ↑ coronary resistance
EECP						
Kronhaus and Lawson [77]	↑					↑ myocardial perfusion at scintigraphy
Psychological interventions						
Potts et al. [80]	↑					Improvement in anxiety and depression scores and EST tolerance.

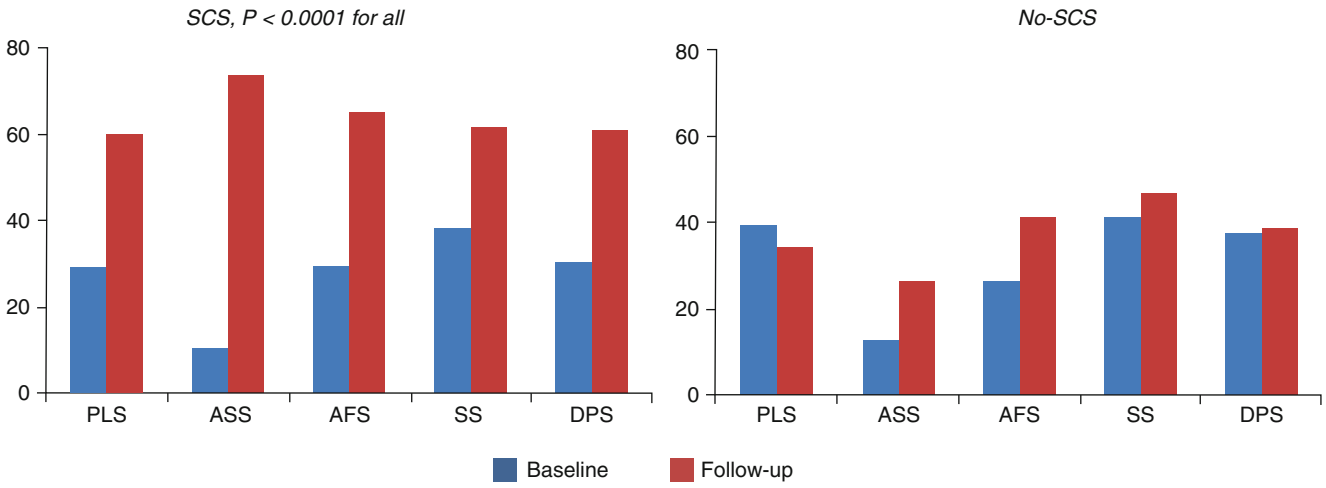

Fig. 27.7 Long-term effect of spinal cord stimulation (*SCS*) on Seattle Angina Questionnaire items in 19 patients with cardiac syndrome X and refractory angina episodes (*left*). Long-term follow-up of nine patients with similar characteristics who refused *SCS* is shown as a comparison group (*right*) (Based on data from Sgueglia et al. [71])

Transcutaneous Electrical Nerve Stimulation (TENS)

TENS consists in the electrical stimulation of cutaneous chest nerve terminations through multiple electrodes, and it is believed to have effects similar to SCS [72]. The effects of TENS in CSX patients were assessed in two studies. Chauhan et al. [73] found a significant increase in resting CBF velocity in response to TENS, suggesting microvascular coronary dilator effects. Sanderson et al. however [74], failed to find any improvement with TENS of CMVD in CSX patients, who, paradoxically, showed an increase in coronary resistance; a reduction of the rate-pressure product, however, was observed in this study, suggesting that a modulation in myocardial oxygen consumption consumption might be of more importance in the effects of TENS. Whether TENS improves symptoms and quality of life in CSX patients, however, remains unknown.

Enhanced External Counterpulsation (EECP)

EECP consists in the sequential beat-by-beat distal to proximal inflation (in diastole) and deflation (in systole) of three pneumatic cuffs applied to the patient's legs. This device increases cardiac preload, but also increases diastolic coronary perfusion pressure, which seems to improve coronary endothelial function [75]. Some studies have shown beneficial effects of EECP in obstructive CAD patients [76].

EECP has recently been tested in a study including 30 patients with refractory CSX. The treatment determined an improvement in CCS angina class and of regional myocardial ischaemia on myocardial scintigraphy; furthermore, at 12-month follow-up, 87 % of patients had sustained improvement in angina [77]. Despite these results, further controlled studies are required to confirm the usefulness of EECP in patients with

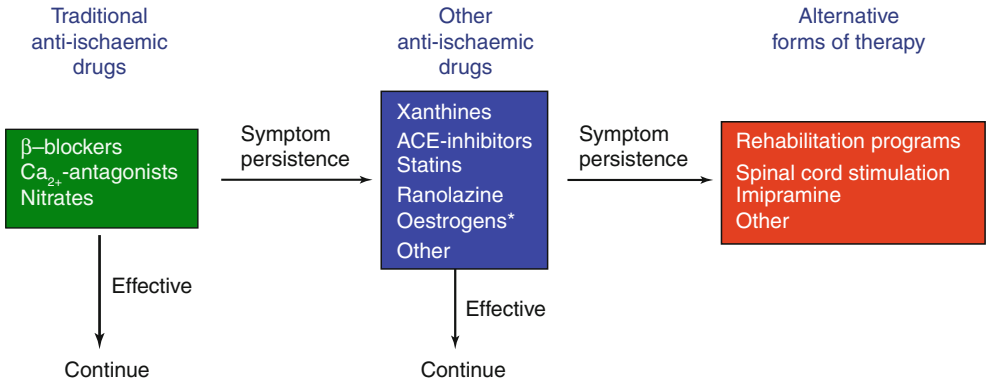

Fig. 27.8 Flow-chart for a rational approach to the management of patients with cardiac syndrome X. * In women, *ACE* angiotensin converting enzyme

refractory MVA and before it can be recommended as a valid and safe alternative for this type of patients.

Cardiovascular Rehabilitation

An exercise rehabilitation program, with progressive increase in workload, has been shown to be helpful in reducing chest pain symptoms and improving pain tolerance in CSX patients [78], and should be therefore recommended in CSX patients.

Psychologic Interventions

Psychologic disorders, both minor and severe, have been described in CSX patients and might, in fact, contribute to chronic chest pain and disability [79]. It is not clear, however, whether the prevalence of psychological disorders is actually increased in these patients and whether they constitute a causal factor for the syndrome or merely result from the clinical manifestations of the disease. Psychological interventions can be helpful in the management of CSX patients, independently of the mechanisms responsible for their occurrence and should be offered to suitable patients.

Various kinds of interventions have been proposed and assessed in small studies, including strategies for managing symptoms and for changing inappropriate beliefs and behaviour.

Improvement of angina symptoms and of psychologic morbidity has been reported using individual and group therapy approaches, with benefits maintained up to 6 months [80, 81].

Thus, psychological treatment might be helpful in CSX patients in whom appropriate medical and non pharmacologic therapies have failed and/or in those subjects with a clear psychologic disorder that can influence pain perception. Importantly, psychological treatment seems more likely to be effective if it is implemented early in these patients.

Conclusions

As shown in Fig. 27.8, it is our recommendation that beta-blockers or non dihydropiridine calcium-antagonists are administered as first line drugs in MVA patients.

A combination of a beta-blocker and a dihydropiridine calcium-antagonist can constitute the second step when monotherapy failed to control symptoms, and, long-acting nitrate or nicorandil can be added at any time.

The prescription of other drugs with potential anti-ischaemic effects, in addition to classical medication or in substitution of some of them, should be decided on an individual basis taking into account the clinical characteristics of patients.

Imipramine or equivalent medications should be considered in patients likely to have a reduced pain threshold, together with non pharmacological therapies such as SCS and TENS.

Implementation of rehabilitation exercise programs can help in improving physical performance. Psychological treatments are required in subgroups of patients.

Reassurance, a sympathetic approach by the treating physician and providing clear explanations of the possible pathogenic mechanisms are also crucial, albeit empirical, measures to improve patients symptoms and compliance with the treatment, as well as to obtain a more positive attitude towards their symptoms.

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Hormonal Changes in Cardiac Syndrome X – Role of Testosterone

28

Carolyn M. Webb and Peter Collins

Abstract

Cardiac Syndrome X occurs predominately in peri- or post-menopausal women. The onset of the chest pain associated with Cardiac Syndrome X coincides with the menopause or hysterectomy and the related decrease in circulating ovarian hormones. As well as estrogens and progestogens, testosterone is synthesized in the ovaries and adrenal glands of women, and has important physiological actions in women, either directly via androgen receptors or as precursors of estrogen production. Testosterone replacement can be given to menopausal women, with or without estrogen, to increase libido, relieve menopausal symptoms, increase bone density and improve quality of life. As well as chest pain, common symptoms of Cardiac Syndrome X include tiredness and lethargy, and it is feasible that reduced androgen concentrations may be involved in the pathophysiology of the syndrome. Relatively few studies have investigated the effects of testosterone replacement in women, and even fewer in women with Cardiac Syndrome X. Further studies are needed to better understand the role of testosterone in the pathophysiology and treatment of Cardiac Syndrome X.

Keywords

Cardiac Syndrome X • Testosterone • Androgens • Women

Hormonal Changes in Cardiac Syndrome X

Cardiac Syndrome X predominately occurs in women, and the majority of these women are peri- or post-menopausal with symptoms of ovarian failure [1, 2]. In addition, hysterectomy is four times more prevalent in Cardiac Syndrome X sufferers than that of an age-matched population [1]. There appears to be an association between age at onset of chest pain with age of the menopause in women with Cardiac Syndrome X [2]. Interestingly, chest pain in younger hysterectomized women (aged 30–40 years) commences sooner after hysterectomy than in older hysterectomized women with Cardiac Syndrome X (<3 years versus >10 years) [2]. This suggests that ovarian hormones play a causal role in the pathophysiology of the syndrome in a large percentage of female patients.

Studies to date have focussed on the association of Cardiac Syndrome X with estrogens [2–4], and although there does not appear to be a reduction in androgen concentrations associated with the menopause, there is an age-associated decline in androgen concentrations throughout adulthood [5–7]. The following discussion will consider the role of endogenous androgens, testosterone in particular, on the onset of symptoms of Cardiac Syndrome X, and the feasibility of testosterone as a treatment for some aspects of the complex syndrome, Cardiac Syndrome X.

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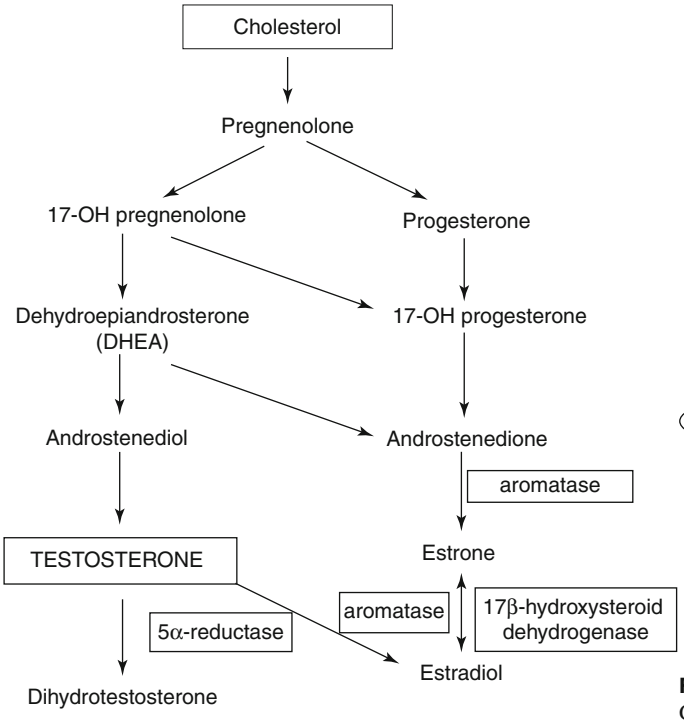

Fig. 28.1 Biosynthesis of testosterone and estradiol

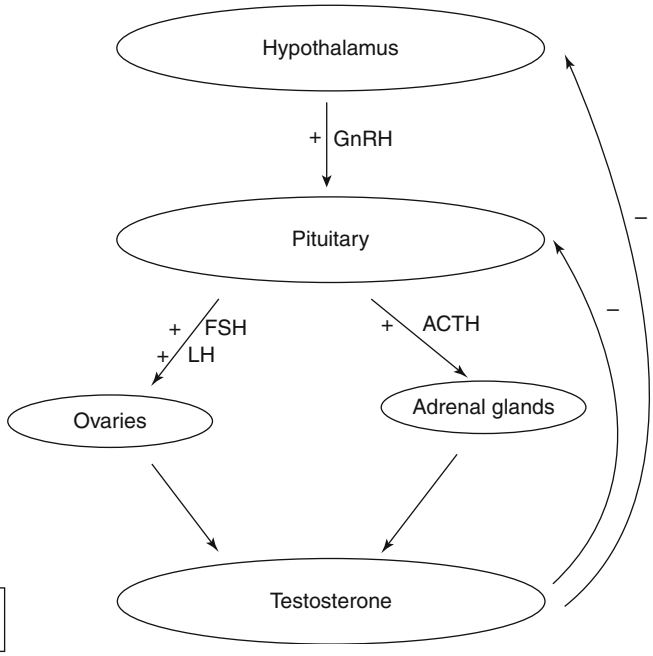

Fig. 28.2 Control of testosterone secretion in women. *GnRH* Gonadotrophin releasing hormone, *FSH* follicular stimulating hormone, *LH* lutenizing hormone, *ACTH* Adrenocorticotropic hormone

Physiological Role of Testosterone in Women

The biosynthesis of testosterone is presented in Fig. 28.1, and explained in detail elsewhere [5, 7]. Briefly, testosterone is synthesized in the adrenal glands and ovaries of women, and produced in the periphery from circulating androstenedione (Fig. 28.2) [5]. Testosterone is the most potent androgen which is carried in the blood largely bound to sex-steroid binding globulin (SHBG). It has important physiological actions, either directly via androgen receptors or as precursors of estrogen production. In particular in women, testosterone is involved in preservation of normal bone mass [8], psychological well-being [9], and regulation of sexual drive [10], therefore androgen insufficiency in women may manifest as impaired sexual function, lessened well being, energy loss and decreased bone density [11–14]. There are also some early data suggesting effects on blood vessels beyond the reproductive system [15].

Role of Testosterone in the Treatment of Cardiac Syndrome X

Symptoms

Androgen insufficiency in women may manifest as impaired sexual function, lessened well being, energy loss and decreased bone mass [11–14], and androgen treatment can help to alleviate at least some of these symptoms [16, 17]. Common symptoms of Cardiac Syndrome X include tiredness and lethargy as well as chest pain. It could be hypothesized that this fatigue may be associated, at least in part, with decreased androgen levels and if so, androgen treatment may relieve these symptoms.

There are no data describing the effects of androgen therapy on chest pain symptoms in women with or without obstructive coronary disease. Data from men show conflicting results. In men with coronary artery disease, some studies report a beneficial effect of testosterone treatment on angina pectoris frequency [18–20], whereas others do not [21–23]. Hormone studies to date have focussed on the treatment of Cardiac Syndrome X with postmenopausal estrogens or combination estrogens/progestogens [4, 24], showing a symptomatic benefit [4]. A study of combination esterified estrogens and testosterone in women with Cardiac Syndrome X showed no difference in time to onset of chest pain on exercise between treatment and placebo, but the effect of treatment on overall symptomology was not reported [25]. A possible association between endogenous testosterone concentrations and Cardiac Syndrome X symptomology is possible, however this requires further investigation. Only then would intervention studies be warranted.

Vascular Function

The increased incidence of coronary artery disease in men compared to women of a similar age might suggest a

detrimental role of androgens on the cardiovascular system. However, definitive evidence that testosterone increases cardiovascular morbidity and mortality does not exist. Results of non-randomized studies completed in the 1940s show a beneficial effect of testosterone therapy in men with angina [26–28]. Men with hypotestosteronemia may be at increased risk of developing coronary atherosclerosis [29–33]. These studies demonstrated a positive correlation between testosterone and high density lipoprotein cholesterol in men, suggesting that testosterone may be cardioprotective partly through a beneficial effect on lipoproteins.

These observational data led to interest in the effects of testosterone treatment on the heart and blood vessels beyond the reproductive system. In animal studies, testosterone relaxed precontracted isolated rabbit coronary artery and aorta [34], and increased coronary artery diameter and blood flow in vivo [35]. The addition of methyltestosterone to esterified estrogen therapy, given to atherosclerotic cynomolgus monkeys, had a null effect on the improvement in endothelium-dependent coronary vasodilatation shown with esterified estrogens alone [36]. Studies in men with coronary artery disease showed that single-dose testosterone can induce vasodilatation in the brachial artery [37] and coronary artery [38], can increase coronary blood flow [38], and prolong time to exercise-induced myocardial ischemia [39, 40]. Longer-term testosterone treatment can modestly enhance myocardial perfusion and decrease basal arterial stiffness in men with coronary artery disease [21].

Few studies have explored the effects of androgens in general, or testosterone in particular, on vascular function in women however. Vascular reactivity of the brachial artery is impaired in genetic women taking high-dose androgens [41], however physiological testosterone treatment, in addition to hormone replacement therapy, improved vascular reactivity in healthy postmenopausal women [15]. In postmenopausal women stabilized on estrogen or combination estrogen/progestin therapy, the addition of a testosterone implant to their treatment regimen improved flow-mediated dilatation (indicative of preserved endothelial function) and nitrate-mediated dilatation (vasodilatation independent of the endothelium) of the brachial artery [15]. This indicates that testosterone may indeed modulate vascular function beyond the reproductive system in women. Since the pathophysiology of Cardiac Syndrome X may include a generalized disorder of vascular function in some patients, testosterone may be beneficial to women with Cardiac Syndrome X. Again the data are scarce. A study of Estratest (Solvay pharmaceuticals) treatment for 8 weeks had no significant effect on exercise test parameters in postmenopausal women with Cardiac Syndrome X [25]. Nineteen patients were randomized and 16 patients (mean age 58 ± 2 years) completed the protocol. Plasma 17β-estradiol concentrations were significantly increased by Estratest however total testosterone levels were not (methyltestosterone has similar receptor binding activity to testosterone, but is not converted to testosterone). Three patients experienced androgenic side effects whilst taking Estratest, and two of these patients withdrew from the study because of these, indicating that there was an increase of androgen bioavailability despite the plasma testosterone concentrations. Estratest significantly increased systolic blood pressure and rate-pressure product at rest but had no effect on exercise parameters. Similar results were seen in patients with Syndrome X after treatment with 100 μg 17β-estradiol patches where no significant treatment effect was seen on either exercise duration or 48 h ambulatory ECG monitoring [4]. As discussed in the previous section of this article, estradiol decreased the incidence of chest pain in these patients [4], however Estratest did not affect time to onset of chest pain on exercise [25].

Estratest is no longer available, and still no studies have investigated the effects of androgens on vascular reactivity in women with Cardiac Syndrome X despite evidence that testosterone added to hormone therapy may be beneficial to vascular function in healthy postmenopausal women. Therefore there remains an opportunity to investigate this potentially beneficial treatment in women with Cardiac Syndrome X.

Psychological Morbidity

Androgens are currently prescribed to menopausal women, with or without estrogen, to improve libido and sexual function [16, 17]. The role of androgens in psychological well-being is controversial, however a number of studies support a positive role of androgen treatment in the general well-being of postmenopausal women. Androgen administration results in lower depression scores [42], increased energy levels and well-being [43]. Psychological general well-being improved in oophorectomized women treated with 300 μg transdermal testosterone, in addition to conjugated equine estrogens, for 12 weeks compared with placebo [44]. Within this mean composite score, positive well-being and depressed mood were also significantly improved [44]. In women with androgen deficiency secondary to hypopituitarism, 12 months treatment with 300 μg testosterone patch improved mood, sexual function, and some aspects of quality of life including energy/fatigue, general health and sleep [45].

We postulated that postmenopausal women with Cardiac Syndrome X may benefit from combination esterified estrogens and methyltestosterone hormonal supplementation by improving quality of life, and found that 8 weeks of Estratest treatment beneficially affected emotional well-being [25]. The mechanism was not identified but it could have been related to the addition of testosterone to esterified estrogen. Again, studies are required to investigate the possible beneficial effects of testosterone on psychological morbidity in women with Cardiac Syndrome X.

Side Effects and Safety

Clinical experience with androgen therapy in women is still limited, and there are few randomized controlled trials, therefore treatment must be commenced with caution [17]. The Princeton consensus recommends careful clinical evaluation of the indications for testosterone treatment before commencing therapy, and outlines a decision-making algorithm for doing so [17].

In practice a treatment is only effective if it is tolerated by the patient. There are a number of testosterone preparations available for testosterone treatment in women, delivering testosterone via a transdermal patch or an implanted pellet. Common side effects of physiological testosterone treatment in women include acne, hirsuitism, vulvo-vaginal swelling, and breast symptoms (tenderness and enlargement), and appear to be dose related. The safety of testosterone use in women has been presented in detail elsewhere [17, 46], however it must be remembered that there are few safety data beyond 1 year [7]. Current evidence indicates that testosterone given to postmenopausal women at doses that raise plasma concentrations to premenopausal levels, or slightly above this, does not appear to detrimentally affect behavior, breast cancer risk, the endometrium, cardiovascular risk factors, or liver function [16, 47]. The potential for virilization of a female fetus is a serious risk in premenopausal women [17]. Short-term studies of testosterone treatment that raises plasma testosterone levels to the upper concentration found in premenopausal women, given either with or without estrogen, indicate a small risk compared with the benefits. However, only long-term safety studies will provide evidence to inform us of the safety of testosterone use in women. In the meantime, as with all treatments, each individual must weigh the risks and benefits together with their physician.

Conclusions

The energy loss and fatigue associated with Cardiac Syndrome X is paralleled in women with testosterone insufficiency. The involvement of endogenous testosterone concentrations in the pathophysiology of Cardiac Syndrome X is unknown. Testosterone therapy is currently used in women to treat low sex drive and energy loss, and these treatment effects may translate into an effective treatment of some of the symptoms of Cardiac Syndrome X. However the data are meagre and so we require further studies to increase our fundamental understanding of the effects of androgens in general, and testosterone in particular, in women, and their potential effectiveness in treating the symptoms of Cardiac Syndrome X.

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Management of Estrogen Deficiency

29

Chrisandra Shufelt and Talya Waldman

Abstract

The estrogen deficiency of menopause is hypothesized to be a contributing impetus for the dramatic rise in cardiovascular disease mortality seen in postmenopausal women. An unfavorable shift in cardiovascular risk factors is common during this life transition and has been attributed to estrogen decline. Observational studies have consistently demonstrated a cardioprotective effect of menopausal hormone therapy, in direct contrast to the results of the Women's Health Initiative and other randomized controlled trials. Although questions still remain, this apparent contradiction has led to a better understanding of how estrogen influences the cardiovascular milieu. This chapter highlights the endogenous effect of estrogen on vasculature and cardiac biomarkers, as well as the current research regarding risks and benefits of exogenous hormone therapy in relation to coronary heart disease, venous thromboembolism, stroke, and diabetes. The latest evidence on timing of initiation, optimal route of delivery, dose, and duration of hormone therapy are discussed. The future of hormone therapy looks towards the development of new medications such as a tissue selective estrogen complex that may enhance the cardiovascular safety profile while simultaneously treating vasomotor symptoms.

Keywords

Hormone therapy • Estrogen • Progesterone • Transdermal estrogen

Background

In 2010, approximately 52 million US women reached the age of menopause, 50 years or older, and an expected 62 million women will reach this age in 2020. After the age of 50, cardiovascular disease (CVD) risk factors shift unfavorably for women. At the time of menopause, there is a dramatic increase in CVD mortality suggesting that the loss of estrogen at menopause contributes to this shift in CVD risk factors and rise in mortality. It has been shown that only 6 months after menopause, an adverse lipoprotein shift occurs resulting in increased low density lipoprotein cholesterol (LDL) and triglycerides and decreased high density lipoprotein cholesterol (HDL) [1]. With half of all women living more than a third of their life beyond the age of menopause, this transition is a vital time to assess CVD risk.

The connection between coronary heart disease (CHD) and menopause was first presented in a 1955 epidemiological report that showed the ratio of male to female death rates for coronary and hypertensive disease by age [2]. At age 50–55 years, the ratio of men dying of heart disease was eight times higher than females; however, this ratio declined dramatically after age 55 years. The results of this report were interpreted as an indication that women develop heart disease due to estrogen loss. With this knowledge, the Coronary Drug Project was the first double blinded randomized controlled

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trial (RCT) of estrogen effect on heart disease, done on men. Men with established CHD were randomized to 5 mg of conjugated estrogen or placebo. This study was stopped 18-months early due to the increased rates of myocardial infarction (MI), pulmonary embolism and death [3].

Despite these results, the relationship between CVD and menopause status continued to be demonstrated in observational studies of women. The Framingham cohort observed a trend of 2–4-times higher incidence of CVD in postmenopausal women compared with premenopausal women in the same age range [4]. Over 40 observational studies of hormone therapy (HT) and CVD suggested a 40–50 % cardioprotective effect among current or ever users of HT compared to never users [5–8]. Observational studies consistently demonstrated a lower risk of CVD in premenopausal women compared to age-matched men, and demonstrated an increased risk of CVD in women who undergo premature menopause, suggesting that CVD risk rises following menopause in women. And yet, RCTs of HT for both primary and secondary prevention of CVD have not demonstrated a reduced risk.

The first RCTs of HT and women were secondary prevention trials performed in women with established coronary artery disease (CAD). The Heart and Estrogen/Progestin Replacement Study (HERS) trial was designed to address whether estrogen and progestin would reduce ischemic heart disease events in women with CAD. Over the 4-year follow up, 2,700 women were randomized to HT or placebo and no differences in cardiovascular outcomes were found. It is important to note however, that during the first year, there was a 52 % increase in myocardial infarction (MI) in the women who received HT [9].

Subsequent secondary prevention RCTs all failed to demonstrate CVD risk reduction with HT compared to placebo. The Estrogen Replacement and Atherosclerosis Trial was an invasive angiographic study of 309 women with CAD (defined as stenosis >30 %) evaluating progression of disease over 3-years. The results revealed no change in luminal diameter and no change in atherosclerotic lesions with HT [10]. The Papworth HRT Atherosclerosis Study also randomized women with proven angiographic ischemic heart disease to transdermal HT or placebo. The primary end points of angina, MI or death also showed no difference, but during the first 2-years of follow up, a higher event rate was noted in the women randomized to estrogen [11]. The Estrogen in the Prevention of ReInfarction Trial randomized postmenopausal women who had survived an MI to estradiol or placebo, and also failed to demonstrate a reduced risk of reinfarction with HT [12]. Finally, the Women's Angiographic Vitamin and Estrogen (WAVE) Trial measured flow-mediated dilation in women with obstructive CAD and did not find improvement after 3-months in women randomized to hormones or placebo [13]. All the secondary prevention trials, despite different estrogen formulations and route of delivery, did not demonstrate a CVD risk reduction, and in some cases there was an increased risk in the first couple years of starting HT.

Estrogen has both positive and negative effects on the cardiovascular system. Positive effects include an improved lipid profile with higher HDL and lower LDL as well as flow-mediated vasodilation, a marker of endothelial function [14]. The presence of estrogen improves fibrinolysis, has antioxidant effects within a healthy endothelium [15], and reduces vascular reactivity thereby improving insulin sensitivity [16]. On the other hand, estrogen has a known procoagulant effect by inducing thrombin receptor expression [17]. Estrogen also increases production of triglycerides and inflammatory markers such as C-reactive protein and matrix metalloproteinases (MMP), an enzyme that degrades extracellular matrix proteins. Several important cardiovascular mechanisms are impacted by both estrogen and progestins including vasomotion, arrhythmogenesis, and the development of thrombosis and atherosclerosis (see Fig. 29.1) [68].

To understand the effects of estrogen on endothelium, it is important to consider the vascular age of the blood vessel and to note differences in estrogen activity on healthy endothelium compared to a vessel with atherosclerotic lesions present (see Fig. 29.2). In the presence of a healthy endothelium, estrogen acts as a potent vasodilator by binding to estrogen receptors within the vessel and producing nitric oxide [18]. In a healthy vessel, estrogen also decreases inflammatory markers and lesion progression by decreasing platelet activation, cell adhesion, and smooth muscle proliferation. When a preexisting atherosclerotic lesion is present however, there is decreased function of vascular estrogen receptors, resulting in decreased nitric oxide production. Plaque instability can also occur in the presence of estrogen via up-regulation of MMP-9 and increased neovascularization causing the fibrous cap of the atherosclerotic lesion to degrade and rupture.

Preliminary data in animal and human studies suggests that estrogen therapy may improve endothelial function [19–21]. Endothelial dysfunction is a marker of microvascular coronary disease characterized by open coronary arteries with signs and symptoms of ischemia. Small trials have studied the effects of estrogen therapy on myocardial ischemia and chest pain in postmenopausal women with microvascular disease. In one study of 11 women with exercise-induced ischemia, administration of sublingual estradiol 40 minutes prior to exercise increased exercise duration and time to 1 mm ST depression [22]. Another 8 week double-blind RCT demonstrated that transdermal estrogen therapy vs. placebo reduced the frequency of chest pain episodes (decreased 3.7 episodes/10 days) in postmenopausal women with Cardiac Syndrome X ($p<0.05$) [23]. In this same study, transdermal estrogen was not found to have an effect on exercise duration. A 12-week ancillary trial from the Women's Ischemia Syndrome Evaluation (WISE) evaluated the effects of low

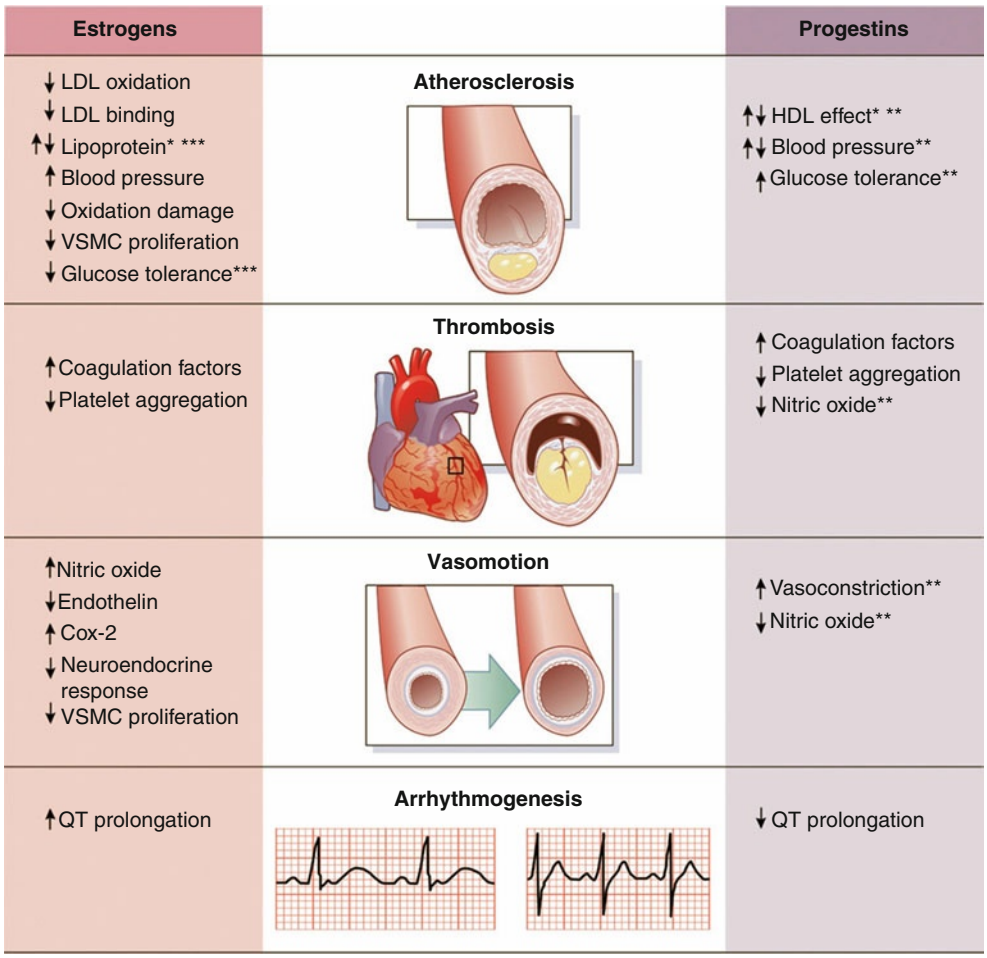

Fig. 29.1 Estrogens' and progestins' individual effects on atherosclerosis, thrombosis, vasomotion, and arrhythmogenesis. *Dependent on delivery route of estrogen, **dependent on type of progestin, ***dependent on the dose of estrogen. *Cox-2* cyclooxygenase-2, *HDL* high-density lipoprotein, *LDL* low-density lipoprotein, *VSMC* vascular smooth muscle cell. Figure illustration by Rob Flewell. Reprinted from Shufelt and Merz [68]

dose HT (1 mg norethindrone acetate/10 mcg ethinyl estradiol) vs. placebo in 36 postmenopausal women with microvascular coronary disease [24]. HT was shown to reduce chest pain symptoms ($p=0.02$), hot flashes ($p=0.003$), and improve quality of life. Although there was a trend for improved exercise performance, no significant improvement was found in myocardial ischemia or endothelial dysfunction, as assessed by cardiac magnetic resonance spectroscopy and brachial artery reactivity. These studies suggest that estrogen in women with coronary microvascular disease may improve chest pain symptoms but does not improve myocardial ischemia with short term administration. Long term studies are warranted to evaluate cardiovascular outcomes in women with microvascular coronary disease who use estrogen therapy

The Women's Health Initiative

The Women's Health Initiative (WHI) included a large, prospective, randomized primary prevention trial to assess the effect of HT on chronic disease. Within the WHI, there were two separate study arms. The first assigned participants to receive 0.625 mg of conjugated equine estrogen (CEE) plus 2.5 mg of medroxyprogesterone acetate (MPA) or placebo (EPT-arm), while the other arm randomized women with a hysterectomy to receive 0.625 mg of CEE alone or placebo (ET-arm). The EPT trial was stopped approximately 3-years early due to an unfavorable balance of risks and benefits when used for chronic disease prevention. These surprising results revealed that although HT lowered the risk of osteoporosis and colon cancer, a small but increased relative risk was seen for CHD events (37 vs. 30 per 10,000 women per year), stroke (29 vs. 21 per 10,000 women per year), venous thromboembolic events (VTE) (34 vs. 16 per 10,000 women per year) and breast cancer (38 vs. 30 per 10,000 women per year) [25].

The ET-arm was continued under close scrutiny, but was stopped 1-year prior to completion due to an increased risk of stroke (44 vs. 32 per 10,000 women per year, $p=0.007$) [26]. Overall, no change in CHD was observed (49 vs 54 per 10,000 women per year), and near significant protection from breast cancer was found (26 vs 33 per 10,000 women per year, $p=0.06$). Within the overall null effect for CHD, a lower relative risk was seen when analyzing the data by age group at study entry. Women age 50–59 years had a lower risk of CHD (RR 0.63 95 % CI, 0.36–1.09)

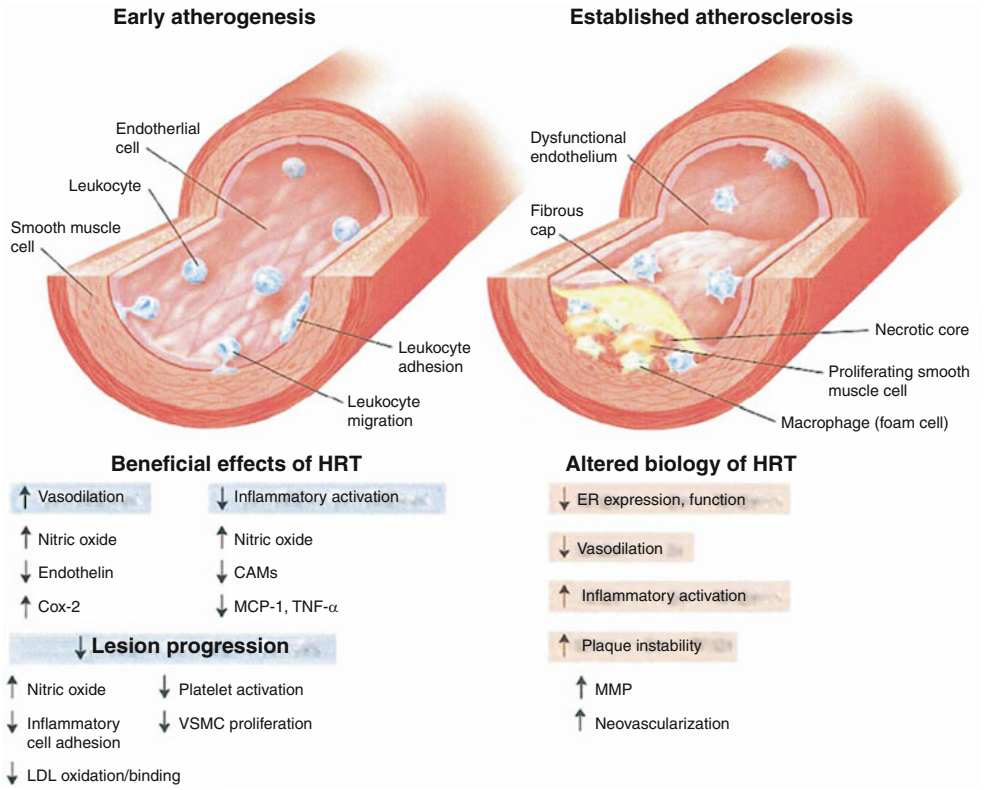

Fig. 29.2 Vascular effects of estrogen in early vs. established atherosclerosis. *CAM* cell adhesion molecule, *Cox-2* cycloxygenase 2, *ER* estrogen receptor, *HRT* hormone replacement therapy, *LDL* low-density lipoprotein, *MCP* monocyte chemoattractant protein, *MMP* matrix metalloproteinase, *TNF* tumor necrosis factor, *VSMC* vascular smooth muscle cell (Reprinted from Ouyang et al. [18]. With permission from Elsevier)

compared to the 60–69 year old and 70–79 year old women (RR 0.94, 95 % CI, 0.71–1.24 and RR 1.13, 95 % CI 0.82–1.54, respectively) [27].

HT and the Timing Hypothesis

The results of the WHI challenged the prior observed concept that HT provided cardioprotection. Subsequent analyses have led to the formulation of the "timing hypothesis," which suggests that HT initiated close to menopause may pose no increased CVD risk and may be cardioprotective, whereas HT initiated over a decade after menopause may incur increased CVD risk. In the WHI, the average age of women randomized to start HT was 63 years old, over a decade after menopause transition. In most observational studies, subjects were on average 52 years old, and initiated HT within 2 years of menopause [28]. In addition, women in observational studies were generally symptomatic with hot flashes compared to asymptomatic women in the WHI, and the HT formulations were diverse, not restricted to CEE.

Secondary analyses of the WHI have also shown that the risk of CHD increases with time since menopause in both the EPT and ET arm. Additionally, women who initiated HT > 10 years since menopause had increased CHD risk [27]. This timing concept has been further bolstered by a meta-analysis of 16,000 women with a mean age of 55 years, which showed decreased total mortality (RR 0.73, 95 % CI 0.52–0.96) with HT use in this younger population [29]. The Nurses' Health Study (NHS) also demonstrated CHD protection in women who initiated HT at or near menopause (RR = 0.66, 95 % CI 0.54–0.80 for ET; RR = 0.72, 95 % CI 0.56–0.92 for EPT) unlike those who initiated HT greater than a decade post-menopause [30].

In a sub-study of the WHI ET-arm, women 50–59 years receiving ET for an average of 7 years had lower coronary artery calcium scores compared to placebo (mean score 83.1 vs. 123.1, p = 0.02) [31]. In another RCT of young menopausal women, the rate of subclinical atherosclerosis progression was lower in those randomized to ET compared to placebo as measured by carotid intimal medial thickness (−0.0017 mm/year vs. 0.0036 mm/year, respectfully) [32]. Whether HT initiation close to menopause may slow the development of calcified atherosclerotic plaque and subsequently decrease risk of CHD, remains to be tested by RCT. Further investigations are underway to fully understand the biological implications of HT timing [33, 34].

The inherently opposing cardiovascular effects of exogenous estrogen provide further insight underlying the timing hypothesis. HT reduces LDL, increases HDL, lowers fibrinogen levels, and enhances endothelial vasodilation, which would all seem to exert cardioprotection [35]. In the short term however, first pass liver metabolism of oral estrogens increases thrombotic factors and decreases thrombolytic factor synthesis, which may accelerate thrombosis of pre-existing coronary plaque [35–37]. Plaque rupture may also

be induced by estrogen-mediated expression of MMP in the fibrous plaque caps, thereby placing women with pre-existing advanced plaques at increased short term risk of CHD [18, 38]. Older menopausal women, >10-years after menopause, are more likely to have pre-existing plaques, which may explain the finding of early increase in CVD in this cohort of the WHI, while perhaps younger women are more likely to benefit from the anti-atherosclerotic properties of HT.

Emerging data has shed light on predicting CHD outcomes with the use of HT using baseline lipoproteins, high sensitivity C-reactive protein (hs-CRP), and vasomotor symptom (VMS) assessment. In further analysis of the WHI ET-arm, women with baseline LDL < 127, hs-CRP < 1.30 or HDL > 58 had an overall lower hazard ratio for developing CHD [39]. In a nested case control study of the WHI trials, normal baseline lipoproteins resulted in more favorable CHD outcomes with the use of HT while women with an LDL/HDL ratio ≥2.5 had an increased risk of CHD (RR 1.73, 95 % CI 1.18–2.53) [40]. In another study, women with mild VMS who were placed on oral estradiol showed evidence of less compliant vasculature as measured by pulse-wave analysis and endothelial function testing with nitroglycerin and salbutamol challenges, compared to women with moderate to severe VMS on the same regimen [41]. These results may further explain the differences in CHD events seen in the observational studies and the WHI RCT since the majority of women in the WHI were asymptomatic for VMS. Interestingly, in the WHI observational study women with late onset VMS had a consistent increase in CVD risk and all-cause mortality compared to women with no VMS. This raises the question of whether late onset VMS may be a marker for vascular instability, suggesting a different mechanistic pathway for CHD development [42]. It appears that timing of HT initiation, healthy baseline lipid profiles, and characteristics of VMS are clinical predictors of more favorable CHD outcome; however, further data is needed to test these hypotheses.

HT and Venous Thromboembolism

Venous Thromboembolism (VTE) risk in HT users appears to be incurred by the acute hormone mediated production of clotting factors, rather than through a pathway of vascular damage [43, 44]. The presence of other risk factors such as obesity, prior history of VTE, and Factor V Leiden mutation, all lead to increased risk of VTE with hormone use [25, 26, 43, 44]. In a meta-analysis of 8 observational studies and 9 RCTs, a 2.5-fold increased risk of VTE was found in both oral ET and EPT use [45]. Risk of VTE was highest during the first 2 years of HT initiation and decreased slightly with longer HT duration. In the WHI studies an additional 18 VTEs per 10,000 women per year in the EPT-arm [25] and an additional 7 VTEs per 10,000 women per year in the ET-arm was seen compared to placebo [26].

Future direction of HT and VTE risk are focused on HT route of delivery. Canocico et al. evaluated VTE risk in a prospective, cohort study, and concluded that use of oral estrogen, but not transdermal estrogen, carries a substantially higher risk of VTE (HR, 1.7) [46]. Although observational studies alone do not provide irrevocable evidence that transdermal formulations are safer, these studies provide a foundation that calls for more research on optimal route of HT administration for menopausal management.

HT and Stroke

The NHS, a large prospective study on HT, demonstrated an increased relative risk of ischemic stroke with HT (RR 1.27, 95 % CI, 1.04–1.56), with a significantly higher risk for those using unopposed estrogen (RR 1.39, 95 % CI, 1.18–1.63). Although the relative risk was increased in women regardless of timing of hormone initiation, in younger women the absolute incidence of stroke was relatively low. Data from the NHS also suggest that stroke risk is minimized with lower dose and shorter duration of treatment; however results were limited by the small cohort on low dose estrogen [47].

The results of the NHS are consistent with the WHI findings. Both the EPT and ET arms of the WHI demonstrated an increased risk of ischemic stroke, with higher risk seen in the ET arm [25, 26]. Neither ET nor EPT seem to impact risk of hemorrhagic stroke, however there was not enough statistical power to evaluate this relationship.

HT and Diabetes

Diabetes (DM) is an independent risk factor for CVD and it is important to understand the impact of HT on DM. Both prospective cohort studies and RCTs show strong evidence that HT reduces new onset of Type II DM [48]. In the WHI EPT arm, women had a 21 % reduction in incident-treated DM [49] and in the WHI ET arm there was a 12 % reduction [50]. These results are statistically similar to those found in the HERS trial [51]. There are several hypothesized mechanisms of action that would explain why estrogen protects against DM. Estrogen mediates pancreatic insulin secretion, decreases hepatic glucose production, and reduces vascular reactivity thereby reducing insulin resistance [52–54]. Centripetal weight gain is believed to be a contributing risk factor for DM and women on HT also have less centripetal weight gain compared with never users [16].

Despite these results, HT is not recommended as primary prevention of DM; however, the data may begin to guide our approach to women with established DM who are on HT. Research suggests that perhaps lower doses of glycemic controlling medications may be used in postmenopausal women with type II DM who are on HT. Additionally, route of HT delivery may play an important role. Transdermal estrogen regimens may be more favorable in women with Type II DM since they appear to have no effect on blood pressure, and compared to oral regimens, cause less increase in triglycerides and thrombotic factors which may already be elevated in those with DM [55].

Treatment

Route of Delivery

Transdermal estrogen preparations (patch, spray, or gels) do not undergo first pass metabolism in the liver, resulting in lower production of coagulation factors and inflammatory markers such as C-reactive protein [56–58]. Oral regimens have been shown to have a more favorable effect on lipid profiles, generating greater reductions in total cholesterol and LDL and greater increases in HDL than transdermal [35]. However, oral preparations also result in higher triglycerides and greater production of clotting factors. A more physiologic ratio of estradiol to estrone is seen with transdermals and these regimens usually result in lower serum estradiol levels compared to oral estrogen [36]. Research is needed to determine whether the effects of estrogen on these biomarkers influence cardiovascular disease outcome.

Several studies, including the Estrogen and Thromboembolism Risk (ESTHER) trial have concluded that the risk of VTE appears lower with transdermal compared to oral hormone use [59]. Some data also demonstrates that the risk of stroke is lower with transdermal regimens compared to oral regimens [45, 60] and higher dose transdermal doses [60]. In a prospective cohort study of 80,000 women, users of oral estrogen were seen to have higher risk of VTE (irrespective of presence of concomitant progesterone) than those who used transdermal estrogen alone or with micronized progesterone [46]. These studies are limited by the use of varying hormone preparations and dosages, and the conclusions have yet to be tested in prospective randomized trials comparing equivalent doses of oral and transdermal therapy.

The Decision to Start HT

HT is the most effective therapy for the treatment of VMS, and it has also been shown to enhance sleep, increase bone mass, and improve QOL [61]. It is not indicated for the prevention of chronic disease and the decision to start HT should be made with an individualized risk-benefit analysis. Besides CVD risk, HT also poses an elevated risk of breast cancer (especially in women on EPT) and perhaps even lung and ovarian cancer [25]. In counseling patients about the use of HT for VMS treatment, it is important to note that the absolute risks of adverse CVD events and cancer, is low, especially in women who are recently menopausal. HT should not be initiated in women who are a decade post-menopause or in those who are at high risk for CVD or breast cancer [62].

HT and Dose

The WHI trial studied 0.625 mg of synthetic CEE with synthetic progestin, 2.5 mg MPA. At the time of the WHI, these were the most commonly prescribed HT and doses available. Today however, low and ultra-low doses are available as well as transdermal routes and the results of the WHI should not necessarily be extrapolated to all routes and dosages of HT [55].

Hypothetically, lower dose HT may be safer due to lower dose-related adverse CVD effects, and it is appealing to assume that there is a more favorable risk-benefit ratio with lower dose oral or transdermal delivery routes, however long-term RCTs are needed to provide more conclusive evidence. Current guidelines recommend using the "lowest effective dose of estrogen consistent with treatment goals, benefits, and risks for the individual woman… with a corresponding low dose of progestogen added to counter the adverse effects of systemic ET on the uterus" [55]. Low dose preparations include 0.3 mg CEE, 0.5 mg oral micronized 17B-estradiol, and 0.014–0.025 mg transdermal 17b-estradiol patches. Some women may require additional local ET for the treatment of vaginal atrophy. Local ET has minimal systemic absorption [63].

HT and Duration of Treatment

The initial findings of the WHI prompted the FDA to release a black box warning on ET stating that HT should be prescribed "at the lowest effective doses and for the shortest duration" [38]. Guidelines recommend extending HT only in those on the lowest effective dose, for whom benefits outweigh risk and who fail attempts to stop HT, or for those with decreased bone mineral density who cannot tolerate alternate bone therapies [55].

Interestingly, observational studies indicate that cardioprotection from HT may only become evident after several years of treatment [64]. A post-hoc analysis of data from the WHI EPT trial showed that women who initiated HT within a decade of menopause showed a late trend (after 5–6 years of treatment) toward greater event-free survival vs. placebo [65]. Secondary evaluation of the WHI ET trial found that

risk ratios for CVD were lower in years 7–8+ for all women ages 50–79 years, not just those who initiated ET close to menopause. These results were consistent with trends seen in the Nurses' Health Study as well as the HERS trial [9, 64].

The suggestion that longer duration of HT may have more favorable effects on CVD, questions the conclusion that HT should be initiated for shortest duration of time in all women, and further points to the need for more data on optimal timing, duration, dose, and route of HT [38]. Possible long term cardioprotective benefits must of course be weighed against the known risk of breast cancer which increases with longer duration of HT.

Future Developments in HT

Two upcoming HT studies will provide new insight into the timing hypothesis of HT initiation. Both studies address whether starting hormone therapy closer to menopause elicits a cardioprotective effect. In the Early versus Late Intervention Trial with Estradiol (ELITE), 504 women within 6 years (the early cohort) or greater than 10 years since menopause (the late cohort) will be randomized to receive estradiol or placebo [33]. In the 3 year follow-up period, outcome measures of this trial will include carotid intimal media thickness (C-IMT). The Kronos Early Estrogen Prevention Study (KEEPS) is a multicenter, randomized study over a 5-year period in which 720 women within 3 years of their final menstrual period will be randomized to pill and transdermal patch hormone therapy versus placebo, and also uses C-IMT as an outcome [34]. Results of these studies will test the hypothesis that early treatment with HT, in women close to menopause transition, may delay the onset of CVD.

In addition to these upcoming RCTs, new therapeutic modalities are in development that may decrease the risk associated with HT. Specifically a tissue-selective estrogen complex (TSEC) may preclude the use of a progestin in women with an intact uterus, possibly decreasing the CVD and breast cancer risk. These drugs will reduce menopausal symptoms, increase bone density, confer endometrial protection, and produce a favorable lipid profile, while not increasing risk of breast cancer. One such TSEC in development combines CEE and bazedoxifene [66, 67]. Further data and RCTs will be necessary prior to use of TSECs; however, the selective receptor mechanism is an appealing treatment option due to its potentially safer profile compared to conventional HT.

Conclusion

The North American Menopause Society, Endocrine Society, and the American College of Obstetricians and Gynecologists all concur that HT should be recommended for healthy symptomatic women, close to the age of menopause transition, using the lowest effective dose for the shortest duration of time. Hormone therapy should not be used for primary or secondary prevention of chronic diseases, including CVD. Estrogen exerts both positive and negative effects on the coronary vasculature, carries risks as well as benefits; therefore it is vital to determine an individual's CVD risk factors prior to HT initiation. While the results of the WHI clinical trial showed an increase risk for VTE, DVT, and stroke in both the EPT-arm and ET-arm, as well as an increased risk in the EPT-arm for CHD and breast cancer, observational data still suggests a more favorable safety profile when initiated close to menopause. RCTs underway are testing the hypothesis that low dose transdermal HT regimens given closer to the time of menopause may confer a more favorable safety profile. The future of HT research turns towards the development of tissue selective estrogen modalities that may provide full symptom benefits of HT with minimum patient risk.

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Progesterone Deficiency

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Ralph Kent Hermsmeyer and Theresa Lee Thompson

Abstract

Elusive pathophysiology of non-obstructive heart disease remains an unsolved problem, even after years of study by outstanding scientists. Analysis of potential etiologies of ischemia require a comprehensive overview approach. Here, the contemplation of physiological mechanisms that regulate coronary artery reactivity to endogenous vasoconstrictors has led to discovery of a gene regulation mechanism worthy of further investigation. A key role for low level, continuously present progesterone in the regulation of coronary artery reactivity by actions at the DNA (gene) translation level reviewed here suggests a medical approach that may potentially diagnose, treat, and medically manage myocardial ischemic causes. Microvascular ischemia has increasingly been recognized as a probable explanation for chest pain and related signs and symptoms of cardiac origin. Currently available strategies offer relief of coronary ischemia by nitrate dilators, beta-adrenergic receptor block, Ca^{2+} channel block, Na^{+} channel block, or other known vasodilators, but there remain patients who are not satisfactorily treated. When progesterone levels are correlated with the likelihood of prolonged ischemia in hormonally controlled primate coronary catheterization studies, there is a strong inverse correlation of systemic progesterone levels to ischemia. Determination of the progesterone threshold for cardiovascular (CV) protection against hyperreactivity and analysis of the most efficient means of diagnosing and medically managing progesterone deficiency has been the logical progression presented in this chapter. Route of administration and measurement of prolonged progesterone exposure are important aspects. Description of the consequences of the CV progesterone deficit, relationship to synthetic progestins, and patients that may particularly benefit from this approach are discussed. Open questions related to angina that does not have a structural basis are offered to stimulate further thought on this critical unsolved problem.

Keywords

Progesterone threshold • Microvascular dysfunction • Coronary hyperreactivity • Pregnanediol glucuronide • Heart disease in women

Progesterone Deficiency, A New Concept

This chapter will analyze the essential, ongoing importance of a threshold systemic production level of progesterone in the cardiovascular (CV) system. While progesterone deficiency in pregnancy is well-known, we have recently recognized that there are also important consequences of the fall

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of progesterone production in a far lower range, i.e., 1–2 nanomolar (nM), for the normal function of blood vessels, brain, bone, and other vital organs.

Progesterone is the quintessential reproductive hormone in women. It modulates the neuroendocrine effects of estrogen (estradiol) in regulating the mid-cycle surge in luteinizing hormone (LH) and prepares the endometrium for implantation [1]. In the absence of progesterone, the unopposed and prolonged action of estrogen is a harbinger of endometrial cancer [2]. Progesterone is also the maintenance hormone of pregnancy across mammalian species and comprises the principal hormonal change during the luteoplacental shift in human and nonhuman primates [3, 4]. That progesterone or its metabolites may have important peripheral or non-reproductive actions has long been intimated, but the nature and importance of these peripheral effects, especially in the cardiovascular realm has only recently been appreciated [5–8].

To the extent that progesterone is thought of only in a narrow context as a sex steroid hormone there had been little reason to consider the consequences of such a deficit. Progesterone plays vital beneficial roles for implantation, pregnancy, and continuing endometrial renewal [1]. But these familiar functions are far removed from the essential cardiovascular (CV) functions that must be ascribed to this ubiquitous precursor to all steroid hormones [5, 9, 10]. The one FDA recognized progesterone deficiency is infertility due to insufficient progesterone, particularly as determined in the third trimester. Progesterone normally reaches high levels (≥1,200 nM) during the final one-third of pregnancy. The lack of sufficient production of this steroid, essential embryologically for successful maturation and childbirth, is a recognized deficiency that is routinely monitored by obstetrical diagnostic tests [3, 4, 11, 12]. In comparison, monthly luteal progesterone peaks in the blood are 24–48 nM (8–16 ng/ml).

Evidence for the existence of a progesterone deficiency analogous to insulin, aldosterone, or other hormonal deficiencies [13, 14] has only been reported in the last few years. Combined primate (primarily rhesus macaque) and human evidence for the consequences of low physiologic level progesterone deficiency will establish the emerging biomedical concept of threshold progesterone requirements, analyze the settings in which progesterone deficiency is found, and describe the diagnosis, consequences, and medical management of progesterone deficiencies in clinical practice.

In order to understand the significance to CV function of maintaining a threshold level of progesterone, it is necessary to consider progesterone functions beyond its presence as a precursor steroid and principal importance for sustaining pregnancy. Only in exploring suspected actions of progesterone on the CV system has the discovery emerged that regulation of blood vessel function at the cellular level is beneficially modulated by progesterone. Molecular mechanisms recently recognized include that normal vascular reactivity (strength and duration of muscular artery contraction) depends upon a defined threshold of progesterone and that the threshold (≥1 nM) must be present over a major portion of 24 h [13, 15, 16]. The understanding that continuous progesterone release during a 24-h period, mimicking physiological release, is requisite for the progesterone mediated transactivational changes in receptor expression (DNA genome level effects) may represent a major insight [15–19]. Essentially, this homeostatic CV mechanism can occur even with sub-physiological progesterone, i.e., 1–2 nM [13]. The conclusion is that, for optimal effect, progesterone should be administered in a low-dose with slow-release to assure sustained blood threshold levels and total systemic exposure. A primary virtue of this concept is that potential side-effects of progesterone treatment are minimized or absent, making progesterone well-suited for treatment of angina pectoris or other ischemic presentations [13, 20].

Since blood levels during pregnancy climb to as high as 1,200 nM, and each luteal cycle normally include a peak of 16–24 nM, the search for the difference between <1 nM (deficient) and >3–10 nM (normal), the perimenopausal blood level experienced by the majority of women, easily might be (and has been) thought unimportant. However, recent evidence establishes that 1 nM (which is about 0.3 ng/ml) of circulating progesterone represents a threshold level for normal CV function in female primates [13, 20]. In all studies reported to date, 1 nM progesterone presence over a large part (33–100 %) of each 24 h appears sufficient to return normalized, non-ischemic function in progesterone-deficient individuals [13, 15, 16, 18, 21, 22]. In oral form (typically as 100 mg capsules), progesterone might be assumed to treat the deficiency. However, with single oral dosing of even 200 mg Prometrium, peak blood levels of 24–48 nM (8–16 ng/ml) occur for only 10s of minutes, falling precipitously to well below 1 nM within only a few hours [5, 10, 23]. This transient (high peak-valley) CV exposure is not sufficient to provide the levels of transactivational modulation needed to suppress coronary hyperreactivity and ischemic events. High peak-valley levels of steroids are also associated with higher rate of adverse side-effects [4, 5, 14, 23, 24].

Additional support for systemic continuous, low dose progesterone relies on established facts of progesterone pharmacology and metabolism. Hepatic enzymes rapidly convert the progesterone molecule to its excretion derivatives resulting in a short half-life for progesterone in circulation, only 15 min [9, 25, 26]. Glucuronide and the sulfate derivatives are rapidly removed from the blood by renal function [9, 23]. Progesterone supplied exogenously in oral forms is subject to the enterohepatic circulation, and thus is mostly metabolized to glucuronide or sulfate before reaching

the coronary circulation [12]. These derivatives of progesterone lack the beneficial actions that restore normal vascular reactivity at best, and at worst they may have adverse actions. Since approximately 93 % of orally administered progesterone is metabolized to these unwanted forms, only a small portion of any dose is available to provide the intended benefits and must function in spite of the potential adverse actions of metabolites [10, 23, 26]. This scenario highlights the difficulty of achieving sustained, therapeutic threshold levels (1 nM) of progesterone using current oral formulations. For clinical management, i.e., to prevent hyperreactivity, it is critical that there blood levels of at least 1 nM progesterone are present for at least 8 h/day [13, 15, 16] or as optimally determined by pregnanediol glucuronide excretion of >1 nmol/day.

Considering that the vast majority of the progesterone portion of "hormone replacement" in clinical medicine has been carried out with the decidedly xeno-progesterone synthetic derivative, medroxyprogesterone acetate, the scarcity of information, and erroneous presumptions, surrounding the cell and molecular actions of progesterone are of fundamental importance. A recent review that distinguishes progesterone from medroxyprogesterone acetate (MPA) on chemical, pharmacological, and medical bases provides a platform for understanding the roots of the wide-spread, but evidence-contradicting, confusion about progesterone actions [20].

In a following section, the fundamental chemical and medical distinctions between progesterone and synthetic progestins will be reviewed. To conclude, burning questions about the risks and consequences of progesterone deficiency will be highlighted to increase awareness of both the current status of scientific knowledge and elements that remain unknown.

The CV Threshold for Progesterone Deficiency

Angiographic and molecular evidence from a decade of primate studies will be presented in this section to establish the experimental basis for the existence and medical management of the threshold for progesterone deficiency as it applies to CV function. Combined heart and stroke data are unequivocally the leading cause of mortality that is declining as medical science progresses, which is probably contributing to increased life-expectancy [27].

Progesterone Deficiency and Myocardial Ischemia

The majority of investigations to determine significant direct actions of ovarian steroids on vascular muscle and endothelial cells have relied on pharmacological megadoses of estrogens and progesterone (between 10 and 50 μM, respectively) overwhelming natural hormone levels to achieve an effect [28–30], and thus led thought away from low dose investigations. Most of these studies used non-primates known to be highly insensitive to steroid hormones that are profoundly active in primates. Furthermore, none of the high dose progesterone non-primate studies used a transdermal route of administration, despite the pharmacokinetic superiority of parenteral forms of progesterone over the oral route [5, 10, 23, 26, 31].

When determined by vasoconstrictor challenges (using platelet release products or mimics) in the angiography (catheterization) laboratory, the differentiation of progesterone deficiency from the euprogesterone state is unmistakeable. Intracoronary injection of synergistic vasconstrictor substances, serotonin (100 μM) and thromboxane A_2, TxA_2 (mimicked by its nonmetabolizable surrogate, U46619 at 1 μM) induced a prolonged (>5 min), severe ischemic response in surgically menopausal (progesterone deficient) rhesus macaques [17]. The constrictor challenge was designed to plausible physiologic platelet release concentrations of Serotonin and TxA_2. In stark contrast, only a mild, transient (less than 3 min duration) vasoconstriction with subsequent relaxation was induced by S+U in ovariectomized (OVX) rhesus treated with subdermal (implant) progesterone providing blood levels of ≥1 nM for 2–4 weeks [16, 18, 21]. In these studies, treatment successfully normalized hyperreactivity responses in almost every instance (30 of 32) rhesus [13, 16–19].

The protection against hyperreactive (>3 min) ischemia could be investigated in the absence of structurally confounding influences because rhesus monkeys exhibit minimal incidence of coronary obstruction unless fed special atherogenic diets [32]. Surgically menopausal rhesus thus provide an experimental approach to distinguish dynamic dysfunction from structural causes of myocardial ischemia. For rhesus fed atherogenic diets daily application of transdermal, slow release progesterone over 4 weeks effectively protected against coronary hyperreactivity [13]. Furthermore, treatment with progesterone in the absence of estrogens (specifically excluding soy proteins and isoflavones typical in monkey chow) was beneficial.

Since 1 nM progesterone was protective against coronary hyperreactivity in >93 %, [13], we defined 1 nM as the CV protective threshold for progesterone. Both MRI and video analysis of contrast agent filling and emptying show that microvascular dysfunction (in the absence of structural occlusions) strongly evident in the progesterone deficient primates, is effectively relieved by transdermal progesterone treatment [13]. Therefore, it is reasonable to conclude that the coronary hyperreactivity consequence of progesterone deficit may act as an independent factor in non-atherogenic and also in pre-atherogenic scenarios.

As related to human coronary ischemia, salutary effects of threshold blood levels of progesterone may thus extend to the much larger progesterone deficient atherosclerotic

population, perhaps even those with significant obstructive coronary disease. Frequently, changes in vascular reactivity are discussed in terms of attenuation of endothelial dependent dilation, focusing only on inadequate vasodilator function. However, a dilator-only model of altered vascular reactivity ignores important vascular muscle contractility changes. The existence of hyperresponsiveness to endogenous vasoconstrictors, particularly to serotonin and TxA_2, provides a likely basis for observed, exaggerated vasoconstriction first observed in primates [13, 15, 16, 20–22]. Vascular function can be thought of as a two-part sequence, vasoconstriction and subsequent vasodilation. Vasconstriction is the first to occur and should be considered as a possible pathophysiological mechanism. The combination of constrictor and dilator mechanisms appears logical for a comprehensive analysis of the etiology of coronary ischemia.

The vasodilatory response to acetylcholine and low dose serotonin was the same in OVX placebo and progesterone, or estrogen plus progesterone, treated rhesus, but the response to serotonin and U46619 was enhanced and prolonged in the OVX placebo group. Therefore, in the absence of coronary structural occlusions rhesus can exhibit normal endothelial cell function, even in the absence of estradiol-17ß (E_2) and/or progesterone (progesterone).

In patients with angiographically detectable atherosclerosis and chronic stable angina, 100 μM ACh caused coronary constriction in non-stenotic segments of 21 patients, and both constriction and dilation in seven patients [33]. The explanation for the diversity in the ACh response was that the endothelium was not diffusely dysfunctional in 25 % of the patients, but rather showed marked segmental heterogeneity reflecting degrees of endothelial dysfunction. Endothelial dysfunction as an early marker of coronary atherosclerosis may be useful in combination with consideration of vascular muscle dysfunction to account for segmental heterogeneity as noted by El-Tamimi [33] and others.

To mechanistically understand how angina relates to coronary hyperreactivity, it appears important to clearly separate the arterial wall pathologies: atherosclerosis from medial coronary (vascular muscle cell) hyperreactivity. In surgically menopausal non-human primates, long duration coronary artery constrictions producing ischemia are reliably induced using S + U, which is effectively prevented when estradiol-17ß (E_2) and/or natural progesterone (progesterone) is continuously replaced (subdermally or via transdermal progesterone cream for ≤2 weeks [15, 21, 22]. At the cell level, agonist-stimulated Ca^{2+} and protein kinase C (PKC) responses of isolated coronary artery vascular muscle cells (VMC) in vitro [15, 17] were shortened to less than 3 min by continuous progesterone exposure, but showed abnormally prolonged responses of 15 min or more in the absence of progesterone [15, 18]. Based on these data, we proposed the hypothesis that, in hyperreactive VMC, PKC activation is required to maintain the pathophysiological sustained increase in intracellular Ca^{2+} [15–18]. Driven by this hypothesis, a definition of progesterone deficiency, based on cardiovascular endpoints was explored. Determining what, how, and when to sample for progesterone deficiency and efficient management was challenging.

Definition of Progesterone Deficiency by Demographic Group

Systemic exposure to progesterone as blood levels has shown great variability - explicable by pulsatile secretion, circadian variation, monthly cycle and variation in daily peak times [34] in addition to steroid binding, competition with glucocorticoids, rapid hepatic metabolism, and renal excretion\. Human laboratory normals have been inconsistently reported, have a wide range of values, and have sometimes been regarded as difficult to interpret. However, using the vasconstrictor challenge, prediction of ischemia occurrence during measured progesterone deficiency was greater then 90 % [13, 18]. Conversely, after at least 2 weeks of transdermal progesterone treatment (≥1 nM blood levels) prediction of lack of ischemia during vasoconstrictor challenge was >95 %. More importantly, urinary measures of systemic progesterone exposure in these studies defined that the much larger, more readily measured excretory levels of pregnanediol-3-glucuronide (PDG) that correlated with 1 nM continuous blood progesterone levels is 1 mM/day. The 24 h measure allows integration of progesterone exposure over time, less measurement variability, and is non-invasive. For clinical monitoring use, urinary PDG daily excretion is more practical than blood measures. For example, women with a BMI >30, there is a significant decline in PDG excretion [35] – it is tempting to correlate decreased PDG with increase CV risk. The Table that follows shows the laboratory normals averages and thresholds in cycling, menopausal, and menopausal progesterone deficient women, and for men. With these criteria and appropriate clinical laboratory determinations, clinical medical management of progesterone deficiency appears readily possible.

Several realities complicate compilation of progesterone blood and PDG urine values by demographic group for use in medical diagnosis and management of progesterone deficiency. Progesterone blood levels measured in serum are most frequently determined by radio-immunoassay (RIA), although there is growing utilization of high sensitive positive (un-confounded) measurement of progesterone by gas chromatography combined with mass spectrometry (GCMS), with the main disadvantage of increased cost [36]. The single time point blood progesterone assay is limited and can not provide a picture of systemic progesterone exposure.

Table 30.1 Values for the major progesterone excretory metabolite, pregnanediol-3-glucuronide (PDG) and coronary hyperreactivity (CH) as determined in rhesus and of blood progesterone and urine PDG groups of women and men, with CH observed (rhesus) or predicted (human)

Subject status	Peak blood progesterone, nM	PDG in urine, mmol/day	Severity	Coronary hyperreactivity
Rhesus OVX	0.6	0.2	+++	Demonstrated
Rhesus OVX + P	3	1.7	0	None
Rhesus OVX + P cream	3	1.6	0	None
Rhesus OVX + MPA	0.5	0.6	+++	Demonstrated
Cycling	20	2.2	0	None predicted
Pregnancy 3rd Tri	1,200	36	0	None predicted
Menopause	2	0.6	+	None predicted
Deficient	<1	0.2	+++	Predicted
Male	2	0.2	+	None predicted

The Table above is based on a single set of gas chromatography–mass spectrometry standards that pertain strictly to the reference laboratory; however, the relative values are important as they establish categorical differences that are expected to pertain in spite of differences in absolute value that are inherent in such measurements in different clinical laboratories

Table 30.2 Threshold for blood progesterone and urinary pregnanediol-3-glucuronide (PDG) for CV protection against coronary hyperreactivity

Condition	Average peak blood progesterone nM	Deficient peak blood progesterone nM	Average peak urine PDG, mmol/day	Deficient peak urine PDG, mmol/day
Normal cycling	36	1	12.5	3
Pregnant, 3rd Tri	1,200	450	500	140
Menopause	3	<1	2	<1
Obese cycling	20	<1	3	<1
Male	3	<1	2	<1

Progesterone and pregnandiol glucuronide (PDG) data are based upon data from the Study of Women Across the Nation (SWAN) project of the National Heart Lung and Blood Institute (NHLBI), for standardization [4, 39–41] as clinical laboratory methods and protocols determine variables that may make the absolute values shown vary from those of other clinical laboratories, Nonetheless, the concepts and relative comparisons shown are believed to be relevant indicators of progesterone and PDG averages and thresholds for risk of myocardial ischemia. Male and obese female threshold values in this Table have been imputed from implied data [4] and from method matched patient identity protected clinical lab data (Rhein Consulting Laboratories, Portland, Oregon GCMS data on file)

Alternatively, the urinary progesterone metabolite pregnandiol-3-glucuronide (PDG) easily allows a 24-h integration of systemic exposure, which is considerable less variable. However, most reported PDG measures are normalized on the basis of creatinine, itself an independent variable. Creatinine is well known to decline with age and to confound reported values from elderly people [37]. To allow combination of data that is not creatinine normalized, and to minimize variability due to creatinine measures, this analysis uses the latest available Center for Disease Control comprehensive compilation of creatinine by age and demographic [38]. The Table that follows shows the laboratory normals, averages, and thresholds in cycling, menopausal, and menopausal progesterone deficient women, and for men. With these criteria and appropriate clinical laboratory determinations, clinical medical management of progesterone deficiency appears readily possible.

The following two Tables provide a useful reference point for the diagnosis and medical management of progesterone deficiencies. These Tables and analysis, by their nature are a work in progress, that we suppose may prove useful (Tables 30.1 and 30.2).

Progesterone Deficiency CV Consequences

This section focuses on the important CV consequences of progesterone deficiency. The relief of ischemic events in the coronary circulations is pivotal to improving women's health. Although the current view assumes that coronary ischemia is due to structural narrowing by plaques, with the potential contribution of coronary flow reduction by blood clots, on close examination, the plaque and clot explanations for coronary dysfunction may account for as little as 25 % of observed illness and sudden death in women [2, 42].

Current coronary disease and dysfunction treatment is centered on known strategies for effective reduction of cardiovascular adverse events. Treatment is primarily based on identifiable epicardial coronary artery abnormalities, particularly those that are evident during coronary angiography or in postmortem pathological examinations [43]. Known structural reasons for ischemia include atherosclerotic plaques, thrombi from plaque rupture, blood clots, and similar anatomically evident elements, e.g., such as calcification, epicardial coronary vasospasm, or congenital vessel anomalies [2, 43–45]. Because they are not visible at post-mortem, functional causes – such

as abnormally persistent vasoconstrictions – are not readily appreciated. Non-structural reasons for ischemia are difficult to detect but may constitute an important additional mechanism, in effect, a separate form of coronary dysfunction. To this point, technology has been limiting in defining Non-Obstructive Coronary Disease (NO-CD). However, the rapidly developing field of CV magnetic resonance (CMR) technology seems promising to discover and analyze microvascular elements in coronary dysfunction [46–48].

Given the state of the knowledge of coronary disease and dysfunction, logic suggests that either: [1] there is only one etiology and women respond poorly to existing treatments, or [2] there is at least one other etiology occuring predominantly in women that is not diagnosed or treated by existing strategies. Assuming the latter, progesterone deficiency, resulting in coronary artery hyperreactivity, offers a compelling possibility, given the observations of the previous section.

Microvascular Ischemia Contribution to Angina

The paradigm of atherosclerotic obstructive coronary disease in the pathophysiology of myocardial ischemia and the clinical manifestation of reversible myocardial ischemia as angina is well established [49]. Although the mechanisms of angina pectoris have been extensively explored since William Heberden's first description of left-sided chest pain [50], the contributions of vascular structure, vasoconstriction, vasodilation, thrombosis, and other possible pathogenetic mechanisms of angina are becoming better identified [43, 45, 51–53]. In particular, the contribution of vasomotor dysfunction (both in the forms of lack of vasodilation and increased vasoconstriction) to both flow-dependent and flow-independent forms of myocardial ischemia should present as microvascular dysfunction. One recognized example of microvascular dysfunction is the special case of cardiac syndrome X (CSX) patients, who present an enigma thought to depend on localized perfusion deficits [44, 45, 51, 52].

Prognostic implications of myocardial ischemia can vary depending upon the pathophysiology and clinical presentation [54]. There is a growing recognition of important differences in coronary dysfunction pathophysiology and clinical presentation in women. Foremost among these gender differences – women presenting with chest pain suggestive of myocardial ischemia frequently have either insignificant obstruction or Non-Obstructive Coronary Disease (NO-CD). Despite normal angiograms, these patients experience debilitating symptoms and undergo repeated diagnostic tests and hospitalizations [55]. Such subjects with chest pain and NO-CD have been generally considered to have a good prognosis [45] until reports from the NIH WISE study showed the hidden increased risks [6, 7, 43, 54, 56, 57]. Unequivocal evidence of ischemia in these NO-CD patients experiencing microvascular angina does indicate a statistically increased risk of infarction or sudden cardiac death [43, 54, 57–59]. The innocence of NO-CD has not, however, been substantiated by rigorous clinical and epidemiological research. Un-presaged fatal myocardial infarction occurs in a substantial number of women [2, 56–59]. The contribution of NO-CD to the much more prevalent non-CSX cases of coronary dysfunction, particularly in the form of flow-dependent microvascular ischemia, is only beginning to be appreciated. Follow up studies suggest a 2 % risk of death or acute MI in subjects with unstable angina and non-obstructive coronary disease at 30 days [6, 55, 60]. Furthermore, 30 % of the NO-CD women in the WISE study showed significantly increased rates of hospitalization (up to 40 % patients) and repeat invasive angiographic investigation over a 1–5 year follow up period [2, 7, 55, 61]. It is important to note that women in the WISE study were at or near menopause, with predicted lower steroid hormone levels that prevail in the perimenopause [4, 40]. These data suggest that coronary microvascular dysfunction should be considered as a possible cause in both CSX and more generally in women with chest pain (of cardiac origin) lacking obstructive coronary disease [62, 63]. Certain groups of women may be particularly appropriate to benefit from medical microvascular dysfunction therapy [64]. Prevention of hyperreactivity can be predicted to be time-sensitive [7].

Microvascular Ischemia as an Underlying Contributor to All Coronary Dysfunction

During effort-induced ischemia, angina can precede the occurrence of ECG changes in some patients [44, 45, 51]. One possible mechanistic explanation is a subendocardial perfusion deficit, which would not be detectable during angiography [45, 65]. Another possibility is flow-dependent microvascular dysfunction that would likely be undetected during angiography or by adenosine or dobutamine dilator strategies.

The subendocardium appears to be more severely impaired than the more epicardial aspects in patients with the most severe deficiency in coronary vasodilator reserve [66]. Abnormal subendocardial perfusion, correlated with incidence of angina, was reported in NO-CD patients provoked with adenosine using Gadolinium (Gd) enhanced first-pass MR in a highly influential report by Panting [46]. Careful validation of the Gd enhanced magnetic resonance imaging coronary flow measurement in beagles with gold stand microspheres [67] established the correlation to be better than 0.9, and sufficiently accurate for localized studies of subendocardial, transmural, and subepicardial segmental flow. Muehling [68] used magnetic resonance Gd first pass perfusion imaging to demonstrate regional perfusion heterogeneity exists even in the normal myocardium of healthy

Table 30.3 "Progesterone" clinical studies where progesterone (CAS#57-83-0, unique molecule identifier assigned by the Chemical Abstracts Service) was not used in the study, according to the authors

Acronym of trial or primary endpoint	First author	Year	Reference	Progestin
WAVE[a]	Waters [72]	2002	*JAMA* 288:2432–2440	MPA
Unstable Angina	Schulman [73]	2002	*J Am Coll Cardiol* 39:231–237	MPA
Brachial Flow Med Dil	Faludi [74]	2004	*Atherosclerosis* 177:89–96	Norethisterone acetate
Breast perfusion	Delille [75]	2005	*Radiology* 235:36–41	MPA
Killer cells (WBC)	Stopinska-Gluszak [76]	2006	*J Reprod Immunol* 69:65–75	MPA
Lupus Erythrematosis	Buyon [77]	2005	*Ann Int Med* 142:953–962	MPA
Tear function	Uncu [78]	2006	*Gynecol Endocrinol* 22:501–505	MPA
Bone loss	Popp [79]	2006	*Maturitas* 53:191–200	Norethisterone acetate

References to progesterone are based on either the clinical trials database (http://www.clinicaltrials.gov/) or the referenced abstracts cited
[a]WAVE (Women's Angiographic Vitamin and Estrogen trial) is official trial acronym supplied by trial authors, other names are impromptu. MPA is medroxyprogesterone acetate, the C24 synthetic progestin used in major prospective CV clinical trials

volunteers at the University of Minnesota. Non-ST-segment elevation acute coronary syndrome patients were successfully diagnosed with cardiac magnetic resonance (CMR) imaging, achieving a sensitivity of 96 % and specificity of 83 % in 68 patients, which result was significantly more sensitive and accurate than the TIMI risk score at $p < 0.001$ [69]. Thus, evidence is mounting that CMR provides a definitive noninvasive diagnostic determination of even hard to detect microvascular and subendocardial ischemic factors contributing to NO-CD.

For NO-CD patients, currently available anti-anginal therapeutic agents (nitrates, calcium antagonists, and beta blockers) may be unsatisfactory, and if so, the substantially impaired QOL will progressively deteriorate [44, 45, 70]. This supports the premise that different underlying mechanisms, including microvascular dysfunction, are likely to be important in NO versus obstructive CD.

Progesterone Distinguished from Synthetic Progestins

Evaluation of the distinct effects of progesterone on the cardiovascular system has been complicated by semantics and by continuing failures to appreciate the essential distinctions between progesterone and progestins. While the term "estrogens" is a valid class name, there can be no "progesterones" because progesterone is a specific chemical. The class name analogous to estrogens is progestins, or alternatively progestogens [5]. In clinical studies, essential statistical subgroup analysis (by chemical entity) is missing, particularly by specific progestin [2, 71]. This discrepancy has led to a case of mistaken identity: MPA is not progesterone! A contributing confounder is the ongoing confusion in classifying MPA studies as "progesterone" studies (Table 30.3.)

MPA CV Effects Contrasted with Progesterone

Differing progestin CV effects are predicted by chemical structure. Progesterone has 21-carbon atoms in its ring structure and is chemically distinct from synthetic progestins such as MPA, norethindrone acetate (NETA), levonogestrel, or norgestimate. For example, MPA has 24 carbons and was first derived as an androgen. Based on the evidence, progesterone improves CV function [80, 81]. In contrast, MPA and other widely used synthetic progestins do not improve CV measures [71, 81–83]. Canonico [84] reported that norpregnane synthetics–but not progesterone–increased venous thromboembolism VTE risk. The absence of serious adverse events due to strokes, blood clots, or renal disease from both clinical trials and pre-clinical studies are strong evidence for the safety of progesterone [13, 20, 31, 71]. Several studies have evaluated cardiovascular effects of progestins in women, among them the Women's Health Initiative (WHI, [85]), but those conclusions do not (and can not be) generalized to reflect (or predict) risks due to progestins other than the specific progestin used in the study (most commonly MPA).

Steroid progestin hormones, like MPA, are infamously promiscuous [5], binding to and affecting (i.e., may stimulate or block) multiple steroid receptors. Actions of MPA on vascular muscle and endothelial cell receptors must be characterized by a multiplicity of affinities for steroid receptors other than the progesterone receptor. Molecular actions of MPA are similar to those of dihydrotestosterone [86]. For example, MPA significantly stimulates mineralocorticoid and androgen receptors, while progesterone blocks instead of stimulating both [81, 87]. Each progestin may have a different CV actions, with progesterone and nomegestrol acetate apparently most beneficial [5, 20, 88].

Multiple comparative published studies of MPA and progesterone reveal the following facts distinguishing progesterone from MPA. (1) The direct effect of MPA on blood vessels,

as distinct from intended actions on the endometrium, consistently includes adverse actions on menopausal coronary arteries. This fact is in contrast to progesterone, which provides substantial benefits [13, 16, 19, 21]. (2) The dose of MPA used in menopausal therapy equates to pre-menopausal circulating luteal phase levels of progesterone, even though MPA is about 50 times as potent as progesterone [89]. (3) Effects of MPA on mitogen-activated kinase in neurons reported after WHI [90, 91] corroborate findings that Ca^{2+} cellular signals in coronaries are adverse [15], rather than beneficial as they are in response to progesterone treatment [13, 16, 17]. This knowledge was the basis for our predictions that the MPA (contained in Prempro™) treatment might have a negative outcome in the WHI study [15, 21]. Based on the evidence presented, skepticism expressed about CV effects of progesterone should be directed specifically to progestins and, in particular, should not be generalized to progesterone [20].

Critical Missing Information and New Technology

Progesterone *per se* has never been tested as a treatment–alone or combined with estrogen–to relieve angina pectoris, treat heart disease, prevent sudden heart death, or prevent thromboembolic events. While current clinical trials, as evidenced by the NIH clinical trial site, are now studying CV actions of progesterone [92, 93], they neglect a critical aspect of progesterone activity, i.e., the requirement for a maintained threshold blood level. There are, currently, no data from clinical trials that allow the evaluation of human CV effects of continuously supplied progesterone at threshold levels.

Coronary arteries from ovariectomized (OVX) primates (progesterone deficient) become hyperreactive, as compared to non-OVX primate controls. In response to constrictor challenge during angiographic examination, the arteries of the OVX primates constrict to a greater degree and remain constricted longer before relaxing [13, 15–18, 21]. Carefully controlled pre-clinical menopausal studies show remarkable (>90 %) protection against excess coronary constriction and hyperreactivity in the menopausal state by subphysiological blood levels of progesterone delivered continuously (at least 8 h/day for >2 weeks) to achieve gene regulated receptor expression [13]. Continuous release dosing with progesterone achieves clear CV benefits in primates [13].

The PEPI study showed that progesterone with estrogen had a more favorable effect on HDL-cholesterol than MPA with estrogen in women [2, 94]. Retrospective analysis of human clinical trial treadmill exercise test (combined estrogen and progestin) studies substantiates the benefits of progesterone–in marked contrast to adverse effects on TET reported with MPA [95]. Elective oophorectomy (with consequent loss of progesterone and estrogen production) at the time of hysterectomy carried an increased risk of death due to cancer, heart disease, hip fracture, or stroke [96]. Special populations such as women with systemic lupus erythmatosus have recently been found as a subset in WISE who may be expected to benefit preferentially from prevention of coronary hyperreactivity [64]. Obese women show a profound deficiency of systemic progesterone [35]. In general, women with fatal myocardial infarctions have less severe obstructions than men [97]. The ProTECT prospective study of traumatic brain injury showed that intravenous progesterone (without estrogen) in human patients caused no discernible harm–and showed possible benefits including lower a 30-day mortality rate [98]. In contrast, the neuroprotective effects of progesterone against kainic acid are totally absent with MPA [99].

A primary concern when administering hormone treatments is the potential increased risk of cancer in the patient. Several studies, including WISE, have found increased risk of breast cancer in women treated with hormone replacement therapies [100]. However, it should be noted that MPA, not progesterone, was included in WISE [57]. Progesterone itself is cited as the hormone that does not increase risk of breast cancer [101, 102]. Further, using progesterone in combination with estrogens may decrease the risk [103]. A secondary issue for clinicians is loss of bone density. Studies of bone mineral density with progesterone treatment show increased levels of bone turnover markers. Based on a review of nine studies Seifert-Klaus and Prior suggest combining progesterone and anti-bone resorptive agents as a single treatment for osteoporosis [104].

For steroid hormones, the effects within the body are mediated by receptor binding. Progesterone receptor A (PRA) and Progesterone receptor B (PRB) are found in both the human vascular endothelium and vascular muscle cells [105]. As a key point, there is a distinct difference between the distribution and abundance of progesterone receptors in vascular muscle cells from the aorta when comparing men and women [106]. PRA was significantly more abundant in female aorta, with the highest levels found in postmenopausal women. It is interesting that PRA is known to suppress the transcriptional activities of other receptors including PRB and estrogen receptor in rat uterine cells [107]. PRA acts as a strong ligand-dependent, cofactor binding-dependent, transdominant repressor of human steroid hormone receptor trancriptional activity [108]. Since evidence suggests that transcriptional regulation by progesterone can occur through a PKC mediated pathway in rats [109], it is interesting to note that the human thromboxane receptor (TP) gene has PKC responsive sites in the 5′ controlling region [110].

Primary cell culture explants of vascular muscle cells observed for Ca^{+2} indicators of muscle cell constriction and relaxation in response to constrictor stimulation (serotonin and a thromboxane analog) showed explicit differences between progesterone and progestins. Incubation with progesterone (1 nM, 3–7days) decreased reactivity in response constrictor challenge. Incubation with MPA increased reactivity [18]. The requirement for time suggests that changes in gene expression are necessary to alter the response to constrictor challenge.

In coronary arteries taken from OVX rhesus macaques the abundance of the TP in the vascular muscle varied in response to hormone treatment. Treatments including progesterone decreased the abundance of TP. Treatments including MPA increased the abundance of TP. This response remains true for pre-atherogenic primates, OVX female primates, male primates, and with either subdermal hormone implants, or transdermal administration of progesterone versus MPA [13, 18, 19]. While initial progesterone measurements were from blood, the measures required an invasive procedure and were complicated by measuring low threshold levels. In this case, a primary diagnostic for progesterone deficit and replacement levels is based on total daily progesterone (as pregnanediol-3-glucuronide) levels that are readily and non-invasively available from urine.

The main urinary metabolite of progesterone is pregnanediol-3-glucuronide (PDG). Concentration of PDG in the 24 h urine samples reflects the daily patient exposure to progesterone. These levels can be used to monitor fertility [111], and the menopausal transition [12, 112], as well as the effects of parenteral progesterone treatment. Samples from serum or saliva are subject to wide cyclic variations and sampling time effects, making it difficult to track progesterone levels . Threshold blood progesterone levels of ~1 nM translate to 1,250 mg PDG/24 h as detected by GCMS. Therefore, 24-h urine monitoring represents the best choice for assessing progesterone levels and treatment effects during progesterone therapy.

Taken together these data, studies and observations support a view of an angina type resulting from progesterone deficiency. Increased thromboxane receptor expression as a consequence of progesteorne deficit, may play a pivotal role in a type of angina etiology. Endogenous Thromboxane A_2 resulting from cyclooxygenase activity acts as a constrictor *in vivo* [113]. The mechanism of MPA-induced coronary hyperreactivity in intact male rhesus could be correlated with increased expression of TP receptors and androgen receptor expression in a pattern similar to dihydrotestosterone (DHT), suggesting adverse coronary actions of MPA are mediated via actions at androgen receptors [19]. However, proof of coronary hyperreactivity has until recently only been demonstrated unequivocally in the catheterization laboratory—and therefore underestimated [43, 51, 114]. CMR investigation of ischemic myocardium that reveals microvascular dysfunction [8, 47, 48, 115, 116] holds the promise of revealing the underlying pathophysiology.

Concluding Comments That Highlight Open Questions

Etiology of CV disease, the unequivocal leading cause of death on planet Earth, remains among the most elusive of problems facing scientists. Since the remarkable insights of Leonardo Da Vinci, including recognition of concepts such as turbulent blood flow, relationship of form and function, and vasomotion, progress has been limited by concepts as well as technology. The majority of known causes of death in women must be attributed ultimately to myocardial ischemia and related dysfunctions [117]. Incremental understanding of heart disease has been dominated by plaques and clots that are structurally identifiable and stable during pathological analysis. This focus on measurement of coronary obstructions by angiography, treatment with cholesterol synthesis inhibitors such as statins, ratios of low to high density lipoproteins, and vasodilation (medically, by coronary bypass grafts, or by catheter revascularization) has allowed reduction of mortality due to myocardial ischemia to decrease to less than one half in incidence between 1970 and 2010. However, the structural analysis appears to offer only part of the picture. The part of the puzzle attributable to obstructive vascular disease is clearly a productive approach to the problem, and yet may represent only about 50 % of the solution.

Progress in CV medicine appears most likely by concentration on non-structural elements, particularly to address questions such as NO-CD, silent ischemia, and atypical anginal presentations. To quote a favorite thought leader, "… prevailing paradigm was that ischemic heart disease was caused by athereosclerotic coronary obstructions severe enough to determine 'coronary insufficiency' with a consequent reduction of myocardial blood flow that resulted in angina when mild, and in infarction when severe. This paradigm, which originated from a widely accepted, exaggerated extrapolation of post-mortem findings and offered an apparently plausible explanation, had a profound, long-lasting influence in three major areas. It conditioned for a long time clinical practice, pharmacological development, and clinical research" [43].

Non-structural elements components that may initiate or exacerbate coronary ischemia, myocardial infarction, sudden heart death, and heart failure may be logically examined as an approach to treatment of the unexplained part of heart disease. For example, a significant proportion of pathological analyses of fatal myocardial infarctions raises these eight questions. (1) Why did the infarct area not occur in a region of the heart attributable to an obstruction, rather occurring in an apparently "normal" region? (2) Why did threatening coronary obstructions that existed in some patients for over 70 years (before the availability of coronary revascularization) not apparently contribute to the cause of death? (3) What is the explanation for fatal myocardial infarctions in which there is no evidence of significant coronary obstructions? (4) What is the underlying cause of coronary ischemia symptoms in patients with normal coronary angiograms? (5) What is the cause of microvascular ischemia (that can only be unequivocally detected by MRI dynamic perfusion techniques)? (6) What triggers non-exercise angina pectoris events, e.g., awaking from sleep due to cardiac or oxygen insufficiency symptoms that are more common in women? (7) Why is the combined vasoconstrictor-pressor- increased heart rate

challenge posed by the cold pressor test more efficacious for diagnosis of myocardial ischemia than adenosine or dipyridamole pharmacological vasodilator challenges? (8) Why does non-obstructive angina increase with age?

Determining non-structural causes of myocardial ischemia represents a challenge that is orders of magnitude greater than finding structural occlusions that are persistent, even through tissue fixation. To determine dynamic vasoconstrictor events that can produce ischemia, it is necessary not only to reliably assess regional myocardial blood flow, but also to sufficiently challenge the coronary circulation with a perturbation that redistributes myocardial blood flow but is not dependent on exercise (at least to investigate non-obstructive, non-exercise induced ischemia). Imposition of a timing constraint, a useful challenge, and optimized visualization of epicardial vessels (as occurs during coronary catheterization angiography) is much more stringent, and thus likely to show false negative tests. Furthermore, angiographic resolution is insufficient to reveal local microvascular areas of insufficient perfusion, as may occur in subendocardial and septal areas. Only with powerful, high resolution imaging approaches, such as CMR (CV magnetic resonance with first pass perfusion protocols) have such microvascular areas of non-structural (prolonged vasoconstriction) ischemia been documented [48, 116, 118]. The transient nature of functional (non-structural) microvascular ischemia furthermore demands an intervention other than exercise that triggers vasoconstriction, e.g., cold pressor test protocol (hand in ice water), ergonovine intracoronary injection, mental arithmetic, or lower body negative pressure, during high resolution coronary blood flow monitoring. First pass perfusion, the CMR specialty of MRI, appears to offer definitive technology that reveals subendocardial and septal perfusion deficits that are most likely to appear in such protocols.

Given the promised insights, a solution for the unsolved half of fatal heart disease etiology may be emerging at last—as explained by molecular changes in blood vessels. The focus is logically drawn to developmental changes in the second 50 years of life – and beyond. When both functional and structural myocardial ischemia etiologies are considered together, there is a renaissance of belief among medical scientists that major quality of life advances in the diagnosis and medical management of heart disease is imminent in coming years.

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Management of Pain

31

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Abstract

Management of patients with persistent angina and no obstructive coronary artery disease continues to be a challenging area. Currently, pharmacotherapy used in patients with microvascular coronary dysfunction (MCD) is targeted at their underlying mechanism for pain. Therapies used in patients with coronary artery disease such as nitrates, β-blockers, calcium channel blockers, and statins have also been found to be beneficial in those with MCD. Other agents found to have promising effects on anginal symptoms includes ranolazine and angiotensin converting enzyme inhibitors. Hormone therapy in women with MCD improves quality of life, although improvement in myocardial ischemia remains to be determined. In patients with cardiac syndrome X, small trials have been performed showing either beneficial or indeterminate results with the use of other pharmacologic agents such as tricyclic medications, L-arginine, xanthine derivatives, n-3 polyunsaturated fatty acids, nicorandil, and trimetazidine. Non-pharmacologic therapies in the management of chronic angina also play an important role. Lifestyle modification, exercise, and cognitive behavioral therapy have shown to improve angina and exercise capacity in those with MCD. The use of neurostimulation, including transcutaneous electrical nerve stimulation and spinal cord stimulation, can also improve symptoms in those with chronic angina. Incorporating both pharmacologic and non-pharmacological therapies can lead to the effective management of chronic angina in patients with MCD.

Keywords

Microvascular coronary dysfunction • Endothelial dysfunction • Normal or nonobstructive coronary arteries • Management of chest pain • Chronic angina • Cognitive behavioral therapy Enhanced external counterpulsation • Transcutaneous electrical nerve stimulation Anti-anginals • Pharmacotherapy and chest pain • Nitrates • Beta blockers • Calcium channel antagonists • Angiotensin converting enzyme inhibitors • Ranolazine • Hormone therapy

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Introduction

Management of patients with chest pain, objective evidence of myocardial ischemia, and no obstructive epicardial coronary artery disease (CAD) continues to be a challenging area. A proportion of these patients include those with Cardiac Syndrome X (CSX), which the American College of Cardiology (ACC) and the American Heart Association (AHA) have defined as patients with angina or angina-like discomfort with exercise, ST-segment

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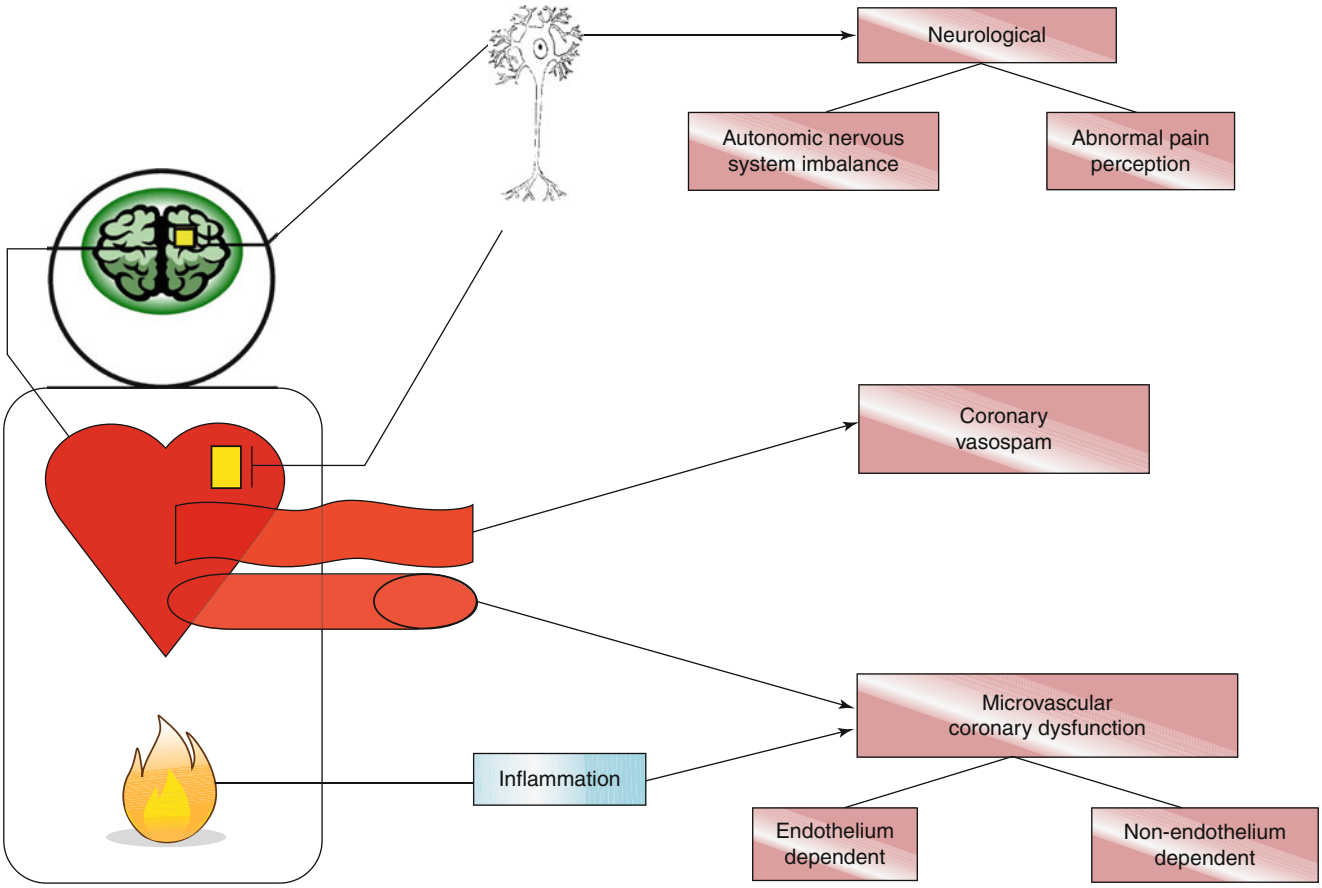

Fig. 31.1 Mechanisms of cardiac chest pain in those with normal coronary arteries. Etiologies include; neurological causes with autonomic nervous system imbalance and abnormal pain perception, coronary vasospam, and coronary microvascular dysfunction with endothelial dependent and independent mechanisms

depression on exercise testing, and normal or nonobstructive coronary arteries on arteriography [1]. The pathophysiology contributing to angina in those with cardiac chest pain and no obstructive CAD is in part due to the coronary microvasculature and vascular endothelial dysfunction leading to microvascular coronary dysfunction (MCD) and myocardial ischemia. Functional changes in the endothelium, with both endothelium-dependent and endothelium-independent mechanisms have played a role in decreasing coronary blood flow [2]. Other mechanisms including sympathetic tone [3, 4] and altered or heightened pain perception [5, 6] are also thought to influence angina in this population. Potential mechanisms of chest pain in this population are depicted in Fig. 31.1.

Therapeutic options for those with microvascular angina and no obstructive CAD are focused on the use therapies that alter endothelial-dependent and non-endothelial dependent arterial function, as well as modalities influencing pain perception since these patients are not candidates for revascularization. Treatment modalities incorporating current guidelines from the ACC and the AHA for CSX including more recent trials on patients with angina and no obstructive CAD, suggests a treatment approach based on mechanism of pain; microvascular coronary dysfunction, abnormal smooth muscle function, and abnormal cardiac nociception [7]. A summary of the treatment modalities incorporating current trials is depicted in Table 31.1.

Pharmacotherapy

Anti-Anginal Agents

Anti-anginals used in the treatment of patients with obstructive CAD can also have beneficial effects in patients with chest pain and no obstructive CAD. Patients with MCD have imbalances in the regulation of coronary blood flow to the myocardium leading to myocardial ischemia. This mechanism of angina can be alleviated with anti-ischemics such as nitrates, β-blockers, and calcium channel blockers, which all have a Class I indication for patients with CSX [1].

Table 31.1 Treatment of subjects with angina, evidence of myocardial ischemia, and no obstructive CAD

Microvascular coronary dysfunction (MCD)
Abnormal endothelial function
Angiotensin converting enzyme inhibitors (ACE-I)
HMG CoA reductase inhibitors (statins)
L-arginine supplementation
Aerobic exercise
Enhanced external counterpulsation (ECP)
Abnormal non-endothelial function
Beta-blockers/alpha-beta blockers
Nitrates
Anti-anginal -anti-ischemic
Ranolazine
Xanthine derivatives
Abnormal smooth muscle function (Prinzmetal's angina)
Calcium channel blockers
Nitrates
Abnormal cardiac nociception
Low dose tricyclic medication
Spinal cord stimulation
Cognitive behavioral therapy

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Nitrates

Nitrates act through a mechanism of dilation of arterial and venous walls by production of cyclic guanosine monophosphate. Currently, no large randomized placebo controlled trials have been performed to investigate the effects of nitroglycerin in patients with MCD. In contrast to those with obstructive CAD, the limited trials performed on patients with CSX suggest that nitrates as monotherapy are inadequate in treatment of clinical symptoms [8–10]. Observational studies have demonstrated that sublingual nitroglycerin in patients with angina and normal coronary arteries provided symptomatic relief in only 42 % of patients, with the same percentage of patients experiencing symptomatic relief even when oral nitrates, such as isosorbide dinitrate or mononitrate, were used in combination with calcium channel blockers [8]. Sublingual nitrates during exercise did not improve time to electrocardiographic ischemic changes or exercise duration in CSX, and additionally may possibly worsen exercise duration [9, 11]. The use of nitrates as monotherapy in the treatment of angina in patients with MCD is likely not to be adequate [10, 12].

β-Adrenoceptor Antagonists

The mechanism of action for β-blockers involves competitive blockade of catecholamines on cell membrane β-1-adrenergic receptors. Through these effects patients with CAD are known to derive benefits with decrease myocardial oxygen consumption and reduction of cardiac work load. Ischemia in these patients is also reduced with lower heart rates leading to increased diastolic time and coronary blood flow. The pathophysiology of angina in patients with chest pain and normal coronary arteries appears to be related to increased cardiac adrenergic activity as well as abnormal vasoconstriction and vasodilatory responses [12], leading to compromised coronary blood flow. These mechanisms the use of β-blockers as an anti-anginal agent through its anti-adrenergic properties.

β-adrenoceptor antagonists studied in CSX include propranolol, atenolol, and nebivolol. Both atenolol and propranolol significantly decrease the frequency of ischemic episodes in CSX patients [10, 13–15]. Atenolol also has the ability to prevent or delay ST-segment changes during exercise [14, 15]. In addition to increased cardiac adrenergic activity which can contribute to angina in patients with MCD, endothelial dysfunction also plays a significant role in the alteration of coronary blood flow and microvascular angina, a mechanism which can be altered with the use of certain β-blockers. Third generation β-adrenoceptor antagonists such as carvedilol and nebivolol, unlike first and second generation β-blockers, have vasodilatory effects that can improve coronary blood flow through endothelium dependent vasodilation and by nitric oxide (NO) mediated effects and alpha-adrenergic blockade [16–18].

Compared to other β-blockers, nebivolol is a highly cardioselective β-1-adrenoceptor antagonist. Nebivolol also possess NO potentiating vasodilatory effects [19–21], and in the CSX population has improve endothelial functioning and is associated with increased markers of endothelial function such as NO and L-arginine [21, 22]. Similar to other β-blockers, nebivolol improves exercise duration and time to ischemic changes on electrocardiography in patients with CSX [21]. β-adrenoceptor antagonists with α-blocking effects, such as carvedilol, influence coronary flow reserve [23] and endothelium dependent vasodilation [24] that may provide additional benefits to patients with MCD by alleviating microvascular ischemia.

In addition to having symptomatic and functional improvements with the use of β-blockers in patients with MCD, other potential beneficial mechanisms of actions of β-adrenoceptor antagonists include their antioxidant effects [24, 25] and anti-inflammatory properties [22] that can influence endothelial functioning. The use of β-adrenoceptor antagonists in some instances may be superior in controlling chest pain in patients with microvascular angina when compared to nitrates and calcium channel blockers [10, 13], and have been found to provide clinical improvement in 75 % of CSX patients [26].

Calcium Channel Antagonists

Calcium channel antagonists act through mediation of calcium ion influx in arterial smooth muscles leading to vasodilation and decreased myocardial contractility. Calcium

channel antagonists have been well accepted in the treatment of patients with vasospastic angina along with nitrates [1, 27, 28]. The use of amlodipine in patients with chest pain due to Prinzmetal's angina has shown significant decrease in chest pain episodes [29]. In contrast, results from studies using calcium channel antagonists for the treatment of chest pain in patients with MCD are variable. Calcium channel antagonists such as nifedipine and verapamil have demonstrated improvement in exercise duration and decrease in frequency of symptoms [30]. Other calcium channel antagonists such as diltiazem did not improve coronary flow reserve in microvascular angina [31]. Several randomized trials comparing the effects of calcium channel antagonists to other agents on ischemic episodes in patients with microvascular angina, did not find them to be as effective as β-blockers [10, 13].

Ranolazine

In 2006 the Food and Drug Administration approved ranolazine for the treatment of chronic angina, becoming first line therapy in 2008. Ranolazine possesses anti-anginal effects, although its mechanism of action has not yet been fully determined. Both anti-anginal and anti-ischemic effects of ranolazine are not related to reductions in heart rate and blood pressure [32], which can be perceived as a benefit in treatment of patients when compared to other anti-anginals such as β-blockers and calcium channel antagonists, allowing for increase in medication dosage without the constraints of hemodynamic influence.

Patients with MCD may find beneficial effects with ranolazine from its selective inhibition of late sodium current, which plays a role in the alteration of intracellular sodium levels following myocardial ischemia [33], as well as its role in the inhibition of fatty acid oxidation, shifting the metabolism toward carbohydrate oxidation, and therefore increasing efficiency of oxygen usage [34]. Patients with no obstructive CAD, objective evidence of ischemia, and chest pain are also thought to have abnormal pain perception, and may find benefit in this drug's ability to target neuronal voltage gated sodium channels which are implicated in neuropathic pain [35]. In patients with chronic angina, ranolazine decreases episodes of chest pain, and increases exercise capacity and performance, both with monotherapy and in combination with other anti-anginals such as atenolol, amlodipine, and diltiazem [34, 36]. The use of ranolazine specifically in women with microvascular angina has shown to significantly improve physical functioning, angina stability, and quality of life [37].

Angiotensin Converting Enzyme Inhibitors and Angiotensin II Receptor Blockers

Although, the ACC and AHA guidelines do not include the use of angiotensin converting enzyme inhibitors (ACE-I) or angiotensin-II-receptor blockers (ARBs) in the management of patients with CSX [1], ACE-I in the treatment of microvascular angina may provide some beneficial symptomatic control. ACE-I or ARBs can be considered in patients with chest pain, positive stress test and normal coronary arteries on appropriate anti-ischemic therapy in the setting of continued chest pain.

Endothelial dysfunction is thought to play a large role in the pathophysiology of MCD, a mechanism which can be altered through the use of ACE-I. ACE-I influences endothelium mediated vasodilation [38, 39] and increase vasodilation in response to acetylcholine [40] leading to improvement in coronary blood flow [41]. The use of ACE-I in the treatment of patients with CSX improves both exercise duration and coronary flow reserve, through a mechanism related to increase NO availability [42]. In a small randomized double-blind crossover placebo-controlled trial on cilazapril in CSX, it was found that the magnitude of ST-segment depression was significantly decreased during treatment, and time to ischemic ST-segment changes during exercise was increased, leading to improved exercise time [43].

In a small randomized, single-blind, crossover, placebo controlled trial on the effects of enalapril in patients with chest pain, positive stress test and normal coronary arteries, enalapril significantly increased exercise duration prior to ST-segment changes and decreased magnitude of ST-segment changes during exercise when compared to placebo [44]. Quinapril was also found to be effective in women with MCD in the Women's Ischemia Syndrome Evaluation [45]. ACE-I can also have potentiating effects when used in combination with other agents, such as calcium channel blockers, leading to more effective angina status than calcium channel antagonists used alone [46]. ACE-I in combination with statins have also shown to not only improve endothelial functioning but quality of life in CSX [39].

The use of ARBs in microvascular angina has not been as well studied as ACE-I. ARBs have been shown to improve microvascular flow reserve [47], although in a small trial on CSX patients the use of irbesartan did not significantly change exercise duration, there was a trend towards decreased number of ST-segment depression during 24 h holter monitoring [48].

HMG-CoA Reductase Inhibitors

The use of HMG-CoA reductase inhibitors or statin therapy has been well established in those with CAD, although its role in the treatment of those with MCD is not as well defined. Aside from the cholesterol lowering effects of statins, various studies have demonstrated their potential pleiotropic effects, including anti-inflammatory and anti-oxidant effects, as well as influences on NO availability and endothelin-1

synthesis, all of which can influence endothelial functioning in patients with MCD [49].

Statins have been shown to cause improvement in endothelial-dependent vasodilation [50]. Patients with CSX treated with statin for a period of 3 months had a decrease in their lipid levels, as well as an increase in their exercise duration and time to ischemic signs on electrocardiography independent of cholesterol level [51, 52]. Part of the beneficial effects of statins in this population is thought to be contributed by statin effects on endothelial functioning and coronary flow reserve [51–53].

Tricyclic Medications

Guidelines recommend the use of imipramine in the management of CSX patient who do not respond to the conventional therapy with nitrates, β-blockers, and calcium channel antagonists [1]. Thus far, all trials performed on imipramine in patients with chest pain and normal coronaries have been relatively small. One of the mechanisms for chest pain in patients with normal coronary arteries includes abnormal pain perception or increased sensitivity to cardiac pain. Imipramine is a visceral pain inhibitor which has been demonstrated to decrease frequency of angina in those with normal coronary arteries and chest pain, with a 52 % reduction in chest pain episodes [54]. Although imipramine provided symptomatic relief in those already on treatment with conventional anti-anginals, these patients did experience side effects and no significant change in their quality of life [55].

α-Adrenoceptor Antagonists

Theoretically, α-adrenoceptor antagonists could have beneficial effects in the treatment of chest pain through their vasodilatory and anti-adrenergic properties, especially in the MCD population who have increased sympathetic activity leading to heightened vasoconstriction. A small trial performed measuring myocardial blood flow in CSX patients found a significant increase in coronary flow reserve after treatment with doxazosin, an α1-adrenoceptor antagonist [56], although this has not translated to improvements in clinical symptoms [57, 58]. The use of doxazosin in patients with CSX showed no significant change in their perception of chest pain [58]. In addition, a double blind, placebo controlled, cross over study on doxazosin in patients with CSX did not find any significant effect on duration of exercise, time to angina, or improvement in ischemic changes on electrocardiography during exercise despite its vasodilatory effects [57]. Trials using α-adrenoceptor antagonists in patients with chest pain and normal coronary arteries has therefore largely been abandoned after the late 1990s.

Other Agents

L-Arginine

As the pathophysiology of microvascular ischemia is thought to be secondary to endothelial dysfunction leading to a decrease in NO availability, trials have been performed to investigate the effects of L-arginine, a precursor of endothelium derived NO. In small trials, L-arginine increased coronary blood flow through the improvement of endothelium dependent vasodilation in patients with angina and normal coronary arteries [59]. Functionally, women with microvascular angina treated with L-arginine were found to have significant improvement in exercise capacity, functional class, quality of life, and angina [60, 61]. In contrast, the use of L-arginine in patients after myocardial infarction may be associated with increased mortality. A double blind, placebo controlled trial performed by Schulman and colleagues on the use of L-arginine post infarction demonstrated that it did not improve vascular stiffness or ejection fraction, in addition, enrollment was closed due to safety concerns [62].

Aminophylline

Xanthine derivatives, such as aminophylline, are adenosine receptor antagonists that have been employed in treatment of chest pain in patients with CSX. Mediators of cardiac pain include adenosine, which has been implicated in causing chest pain in those with CSX. A small double-blind, crossover trial using aminophylline in patients with CSX resulted in a decrease of chest pain episodes and frequency [63]. Aminophylline has also been found to increase exercise tolerance and improve ischemic changes on electrocardiography during exercise [11, 64, 65]. Bamiphylline, in contrast, another specific A1-receptor antagonist, was found to have little effect on anginal pain, and had no change in exercise duration or ischemic changes on electrocardiograms during exercise in CSX [66].

n-3 Polyunsaturated Fatty Acids

A small study performed by Gaibazzi et al. found that patients with normal epicardial coronary arteries, chest pain, and endothelial dysfunction treated with oral supplementations of n-3 polyunsaturated fatty acids normalized their endothelial function, with resolution of ischemic changes on electrocardiogram during stress test [67]. Effects on endothelial functioning are hypothesized to be due to favorable influences on mediators that can impact vascular reactivity and changes in vascular tone.

Nicorandil

Nicorandil is a vasodilator with effects on potassium channels that has been investigated in patients with CSX. Small studies demonstrated that treatment of these patients with nicorandil did not have an effect on heart rate or blood

pressure, but improved chest pain and signs of ischemia on electrocardiogram during stress testing, possibly from improvement in coronary flow reserve [68, 69]. Its effects on microvascular dysfunction are thought to be due to direct effects on microvascular vasodilation and possibly alteration of cardiac autonomic activity [68].

Trimetazidine

Trials performed using trimetazidine, which has intracellular metabolic effects on coronary ischemia, have been ambiguous. Some trials showed beneficial effects of trimetazidine in patients who had microvascular angina by increasing exercise duration and time to ST-segment depression during exercise [70, 71]. Other studies demonstrated that this drug did not have a significant effect on electrocardiographic evidence of ischemia during exercise and diastolic function in patients with CSX [15].

Hormone Therapy

Women appear to have relatively less CVD compared to men, suggesting an important role of hormones in heart disease [8, 72]. Estrogen deficiency has been suggested to contribute to the pathophysiology of MCD [72, 73]. Estrogens have vasoactive properties, and their use as anti-anginal agents has been shown to be effective through improvement in endothelial function and dilation of coronary arteries [74, 75]. Administration of estrogen in postmenopausal women with cardiovascular disease improves exercise duration, time to ischemic ST-segment changes, number of ischemic events and has a beneficial effect on myocardial ischemia [76]. Its effects on postmenopausal women with CSX are similar with decreased frequency of chest pain and improvement in exercise tolerance [77, 78]. The mechanism of effect of estrogen in postmenopausal women with coronary endothelial dysfunction appears to involve potentiation of endothelium dependent and independent vasodilation [74, 79]. In a multicenter, randomized, placebo controlled trial on postmenopausal women with normal coronary arteries and chest pain, the Women's Ischemia Syndrome Evaluation results suggested that low dose hormone therapy improved quality of life scores, however did not improve myocardial ischemia [80].

Non-Pharmacological Treatment

Exercise

Exercise is an integral part of treatment in patients with MCD. It is well documented that routine physical activity has beneficial effects on overall cardiovascular health and risk factors [81–83]. Often patients who have had persistent chest pain are afraid to exercise, due to increased pain sensitivity as well as fear of precipitating angina. Those who have objective evidence of ischemia despite normal coronary arteries by angiography may qualify to participate in a cardiac rehabilitation program, where they can exercise in a monitored setting. Eriksson and colleagues demonstrated that female patients with CSX have a low pain threshold to exercise and impaired exercise tolerance despite normal skeletal muscle [84]. One study in CSX patients showed that 8 weeks of endurance exercise training for 30 min, three times per week on a bicycle ergometer, resulted in improvement in exercise capacity, oxygen uptake, and peak heart rate and systolic blood pressure compared to gender- and age-matched normal controls [85]. Exercise training also significantly delayed the onset of pain in this group from 3 ± 2 to 6 ± 3 min ($p < 0.05$), although maximum pain did not change [85]. Brachial artery endothelial-dependent blood flow also trended to increase following exercise training ($p < 0.06$) [85]. Exercise increases sheer stress as well as increases NO bioavailability [86], and chronic increases in shear stress have been shown to improve endothelium-dependent vasodilation [87]. Varying intensities of exercise have not been compared in patients with MCD, but it is likely that moderate intensity exercise as is usually recommended for cardiovascular health is of benefit and should be included as part of a comprehensive treatment plan in MCD.

Cognitive Behavioral Therapy

Patients with chronic refractory angina despite optimal medical therapy often benefit from non-pharmacologic approaches to treatment of pain. Psychological interventions, including cognitive behavioral therapy (CBT) have been shown to be an effective modality for some patients with chronic angina [1]. CBT is also beneficial in patients with angina who have open coronary arteries [88–91]. In a randomized trial from United Kingdom of 142 patients newly diagnosed with angina who were randomized to CBT versus routine secondary prevention educational session, those who practiced CBT had a greater reduction in anxiety ($p = 0.05$), depression ($p = 0.01$), the frequency of angina (reduced by three episodes per week, versus a reduction of 0.4 per week, $p = 0.016$), the use of nitroglycerin (reduced by 4.19 fewer doses per week versus a reduction of 0.59 per week, $p = 0.018$), and physical limitations ($p < 0.001$: Seattle Angina Questionnaire) [92]. Another study from the United Kingdom also showed that an outpatient-CBT program helped improve angina, quality of life, and reduced hospitalizations in 271 patients with chronic stable angina [93]. Those who practiced CBT were more likely to change their diet and increased daily walking [92]. A recent study showed that an 8 week program of autogenic training decreased symptom frequency and severity in women with ischemia

and non-obstructive coronary arteries [94]. An analysis of ten randomized trials by Kisley et al. [95] that tested psychological interventions in subjects with chest pain in the setting of normal coronary arteries (484 participants) showed a modest to moderate benefit restricted to the first 3 months after the intervention.

Enhanced External Counterpulsation

Enhanced external counterpulsation (ECP) is a non-invasive, USA Food and Drug Administration-approved adjunct therapy for treatment of chronic stable angina; it is based on counterpulsation, and mimics the hemodynamics of intra-aortic balloon pump [96, 97]. During ECP, ECG-triggered sequential pneumatic inflation of cuffs placed on the lower extremities (upper and lower thighs and calves) during diastole increases venous return, increasing preload and cardiac output, and improves coronary blood flow. In addition to its hemodynamic effects, ECP may also improve angina due to its effect on endothelial function; vascular pathways involved in angiogenesis are induced by sheer stress that occurs during chronic ECP therapy [98–100]. ECP is well tolerated, with minimal side effects in most patients, and is a Class IIb indication per ACC/AHA chronic stable angina guidelines [101]. A recent report showed that in 30 patients with CSX and persistent angina, ECP therapy reduced angina and improved regional ischemia [102]. This improvement was sustained in 87 % of patients at almost 12 months [102]. In a randomized, controlled, blinded, multicenter trial of 184 patients with angina, positive treadmill test and documented CAD, ECP treatment led to reduced angina and nitroglycerin use, and increased time to exercise-induced ischemia [103]. Interestingly, in 450 patients with refractory angina and left ventricular dysfunction (ejection fraction < 40 %) who received adjuvant ECP therapy, there was a significant reduction in emergency department visits and hospitalizations at 6-month follow up [104].

Transcutaneous Electrical Nerve Stimulation

There have been some trials evaluating the use of transcutaneous electrical nerve stimulation (TENS) units in patients with refractory angina, which consists of cutaneous nerve stimulation to modulate pain pathways. TENS treatment has been shown to reduce frequency of angina, time to ST-segment depression, and increase work capacity [105–107]. The mechanism by which neurostimulation leads to improved angina remains unclear, but Chauhan et al. [108] have reported that while coronary artery diameter does not change with TENS, resting coronary blood flow velocity can increase with electrical stimulation. In patients with coronary artery disease, TENS has also been shown to reduce systemic vascular resistance and blood pressure, likely related to a decreased sympathetic activity due to pain inhibition [106].

Invasive Non-pharmacological Treatment

Spinal Cord Stimulation

Unlike TENS, spinal cord stimulation (SCS) directly delivers current to stimulate the spinal cord, via an electrode in the epidural space. In patients with normal coronary angiograms who underwent SCS, Eliasson et al. [109] reported a significant improvement in time to angina, improvement in ST-segment depression, and improved exercise tolerance on stress testing. More recently, Lanza et al. [110] studied SCS in ten patients with CSX with severe angina refractory to multiple medications and found that SCS reduced the number, duration, and intensity of anginal episodes; patients with SCS had less use of nitrates, and improvement in Seattle Angina Questionnaire and Visual Analogue Scale.

Conclusion

Management of patients with persistent chest pain, objective evidence of ischemia, but no obstructive CAD remains a challenge for the treating physician. A subgroup of these patients, who are predominantly women, have MCD, which is associated with adverse cardiovascular outcomes. Treatment of persistent angina and no obstructive CAD focuses on therapeutic lifestyle counseling and use of pharmacotherapy aimed at improving endothelial function as well as use of modalities that alter pain perception. While there is evidence from clinical trials that provide guidance in the treatment of angina with no obstructive CAD, much mechanistic work regarding the pathophysiology of angina and adverse outcomes in patients with ischemia remains, and a better understanding would contribute to better use of our current therapeutic strategies as well as the design of novel therapeutics.

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Chest Pain with Normal Coronary Arteries: Future Directions

32

C. Noel Bairey Merz, Guy D. Eslick, and Juan Carlos Kaski

Abstract

A significant proportion of symptomatic patients (e.g. angina) with suspected chronic ischemic coronary syndromes presenting to coronary angiography have no obstructive coronary artery disease (CAD). These patients most often receive no specific therapy and are dismissed from sub-specialty care. Epidemiological and clinical evidence demonstrates that a subgroup of these patients are at higher risk of adverse cardiac events and poor quality of life. Available evidence now exists that identifies elevated risk as well as mechanistic pathways of coronary vascular dysfunction. Large clinical outcome trials testing traditional anti-atherosclerosis and anti-anginal as well as novel strategies in this population are needed. Existing guidelines for diagnosis and treatment of patients with chest pain and normal coronary arteries need to be updated, based on this existing body of evidence, as well as from results of ongoing and future investigation.

Keywords

Angina • Microvascular • Normal coronary arteries

Epidemiology and Pathogenesis

More than 40 % of symptomatic patients (e.g. angina) with suspected chronic ischemic coronary syndromes presenting to coronary angiography have no obstructive coronary artery disease (CAD). Such patients have historically been considered "low risk" and typically receive no specific therapy and are dismissed from sub-specialty care. Yet the epidemiological and clinical evidence reviewed in this book demonstrates that despite exclusion of non-cardiac causes of chest pain, this heterogeneous group includes a substantial proportion of patients at higher risk of adverse cardiac events and poor quality of life [1]. Recent studies with coronary computed tomographic angiography further confirm these findings of a relatively higher prevalence in women, and extend the findings of an adverse mortality in men [2, 3]. Many knowledge gaps remain. While a relatively high prevalence of coronary vascular function is apparent among symptomatic subjects, the prevalence of coronary vascular disorders among asymptomatic subjects is not well understood. Given our understanding of silent ischemia in the obstructive CAD, the prevalence of this should be explored in other populations. Initial findings from the MESA [4] linking traditional risk factors with myocardial perfusion reserve should be extended in order to understand etiologies and potential prevention and treatment targets. Identifying the different phathogenic subgroups that are encompassed by

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the term "angina with normal coronary arteries" is of paramount importance and one of the challenges that need to be addressed without further delay. Well designed multicenter multinational studies and ad hoc registries are needed.

Microvascular Angina

Pathogenesis studies reviewed in the book document the frequent occurrence of coronary endothelial dysfunction (e.g. constriction to acetylcholine) in patients with angina despite "normal coronary arteries", who often have more coronary atherosclerosis than appreciated at angiography, coronary vasomotor abnormalities that include microvascular coronary dysfunction, coronary vasospasm and coronary slow flow. Coronary vascular dysfunction, ischemia on stress testing and chest pain persisting at 1 year of follow-up identify a subgroup at higher risk for adverse clinical outcomes, linking outcomes with mechanistic pathways. Estimates from the ACC-NCDR and WISE databases, indicate that there are at least three to four million patients in the US alone with signs and symptoms of ischemia but no obstructive CAD [5–7], with associated poor quality of life, psychological distress and health-care costs that approximate those of obstructive CAD patients. Developing strategies to provide effective prevention and treatment of microvascular angina is an urgent need given the benefits that both patients and health services would derive from successful programs in this area.

Diagnosis

A growing body of evidence questions the utility of current algorithms for detection and treatment of obstructive CAD based on detection of ischemia in cohorts composed mostly of men. Specifically, diagnostic algorithms aimed at detection of obstructive CAD have a limited sensitivity and specificity for diagnosis of ischemia related to coronary vascular dysfunction. Studies reviewed in the preceding chapters suggest that advanced diagnostics, including newer imaging modalities, offer promise for improved detection of ischemia in subjects with no obstructive CAD. Techniques which can measure relative and absolute myocardial blood flow should be further investigated with regard to diagnostic utility in this population. At present, however, invasive coronary vasomotor testing remains the gold standard for diagnosis, yet existing guidelines do not adequately address this fact [8, 9]. While an initial publication has reported the risks and safety of coronary vasomotor testing [10], further work is needed to fully understand the relative risks and benefits of invasive testing in this population.

Prognosis

Contemporary studies suggest that the prognosis of "normal" coronary arteries in the setting of signs and symptoms of myocardial ischemia is not as benign as historically reported or as commonly assumed by physicians. As reviewed in these chapters, short-term prognosis of patients with unstable angina and non-obstructive coronary artery disease is not consistent with the Cardiac Syndrome X historical low-risk studies, while investigation in stable subjects with chest pain, "normal" angiograms, and ischemia on stress imaging suggests increased event rates at longer term follow-up. While these initial reports suggest an adverse prognosis, many knowledge gaps remain. The specific prognosis of ischemia and no obstructive CAD in stable patients has not been determined in an adequate sample size and in the different subgroups of patients among the heterogeneous Cardiac Syndrome X population. Additional studies are needed. Accurate risk stratification is necessary to both avoid overtreatment of subjects without ischemia, as well as inappropriate reassurance and under-treatment of subjects with microvascular angina.

Treatment

Relatively small and short term studies in predominantly heterogeneous Cardiac Syndrome X populations suggest effectiveness in terms of symptom and functional improvement with reduction in ischemia for various therapeutic strategies. More recent reports in more specifically characterized cohorts with microvascular angina have suggested potentially beneficial effects on coronary vascular dysfunction (within the macro and/or microcirculation). However, appropriately powered, randomized, outcome trials testing management strategies have not been performed in this population. Existing guidelines focus on symptom management and current clinical practice typically is "reassurance" [8, 9]. This is inappropriate because ischemia-related symptoms frequently recur and these patients incur relatively large health care costs, as well as adverse cardiac events. Large-scale, practical, outcome trials testing efficacy of currently available traditional anti-atherothrombotic and anti-ischemic therapy, as well as novel therapies in this population are warranted.

Summary

Taken together, the findings reviewed in these chapters emphasize the need for a better understanding of the epidemiology, pathophysiology, diagnosis, prognosis and

treatment of chest pain with normal coronary arteries. Future steps should include investigation regarding shifting from reliance on tools to assess disease burden and diagnosis of obstructive luminal disease to the characterization of functional abnormalities and clinical outcomes. As evolving strategies change, investigation should evaluate new stress imaging modalities, symptom burden, functional assessment and quality of life as markers of the global burden of risk in these patients. Strategies aimed at providing an accurate diagnosis of microvascular angina are needed. Further study of traditional and novel markers among subjects with chest pain and normal coronary arteries, stratified by the presence of absence of sensitive and specific markers of ischemia is needed. A sufficient body of evidence exists that identifies elevated risk as well as mechanistic pathways of coronary vascular dysfunction, such that large clinical outcome trials testing traditional anti-atherosclerosis and anti-anginal as well as novel strategies in this population are needed. Existing guidelines for diagnosis and treatment of patients with chest pain and normal coronary arteries need to be updated, based on this existing body of evidence, as well as from results of ongoing and future investigation.

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