Chapter 5
Epidemiology of Coronary Microvascular Dysfunction

Peter Ong and Hiroaki Shimokawa

Abstract Coronary microvascular dysfunction (CMD) is a frequent clinical condition leading to angina pectoris and/or shortness of breath in various forms of cardiovascular disease. Several invasive and non-invasive assessments are available for a comprehensive evaluation of the underlying microvascular abnormalities (e.g. coronary flow velocity reserve (CFR) via transthoracic Doppler echocardiography, cardiac magnetic resonance imaging or positron emission tomography, invasive assessment of CFR and microvascular resistance using adenosine as well as the assessment of microvascular coronary spasm using acetylcholine). It is consensus that impaired microvascular vasodilatory function, but also enhanced microvascular vasoconstriction/spasm represent important mechanisms for CMD. The clinical presentation as well as the methods applied for investigation of CMD is associated with the prevalence of CMD. Overall, in patients with signs and symptoms of myocardial ischemia yet unobstructed coronary arteries, CMD can be found in approximately 50–60% of cases. However, the epidemiology of CMD is still difficult to assess. Novel diagnostic techniques involving smartphone-based ECG recordings offer a direct assessment of ischemic ECG shifts during a chest pain attack. The broad applicability of this technology may also influence the epidemiology of CMD. This chapter reviews the available epidemiological data on CMD in patients with angina and unobstructed coronary arteries.

Keywords Coronary microvascular dysfunction · Epidemiology · Prevalence · Acetylcholine · Coronary flow reserve

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Abbreviations

ACh	Acetylcholine
ACS	Acute coronary syndrome
APV	Average peak velocity
CAD	Coronary artery disease
CFR	Coronary flow reserve
CMD	Coronary microvascular dysfunction
CSX	Cardiac syndrome X
CTCA	Computed tomography coronary angiography
ECG	Electrocardiogram
FFR	Fractional flow reserve
IDP	Interventional diagnostic procedure
LCA	Left coronary artery
MINOCA	Myocardial infarction with non-obstructive coronary arteries
NOCAD	Non-obstructive coronary artery disease
NSTEMI	Non-ST-elevation myocardial infarction
PET	Positron emission tomography
RCA	Right coronary artery
STEMI	ST-elevation myocardial infarction

5.1 Introduction

Coronary microcirculation plays a pivotal role in coronary blood flow regulation in various forms of cardiovascular disease [1]. Commonly, microvessels are defined as vessels with a diameter of <500 μm. Remodelling of the coronary microcirculation in response to various stimuli may result in structural and functional alterations [2]. Various clinical conditions, such as hypertension, diabetes, hypercholesterolemia, smoking, obesity and others, have been shown to adversely affect the coronary microcirculation [3]. Clinically, coronary microvascular dysfunction (CMD) can be associated with epicardial atherosclerotic disease, myocardial disease, iatrogenic causes and in the absence of the latter conditions. This allows classification into four different groups as suggested by Crea and Camici [1]. Diagnosing CMD in patients without myocardial or epicardial coronary disease represents a special challenge for the clinical cardiologist. Studies have shown that the prevalence of CMD in patients with unobstructed coronary arteries is high and that their prognosis is not benign. Thus, assessment of the integrity of the coronary microcirculation is important because of its prognostic impact [4]. Depending on the clinical presentation of the patient and the co-existing comorbidities, the clinical cardiologist has to decide which assessments (non-invasive and/or

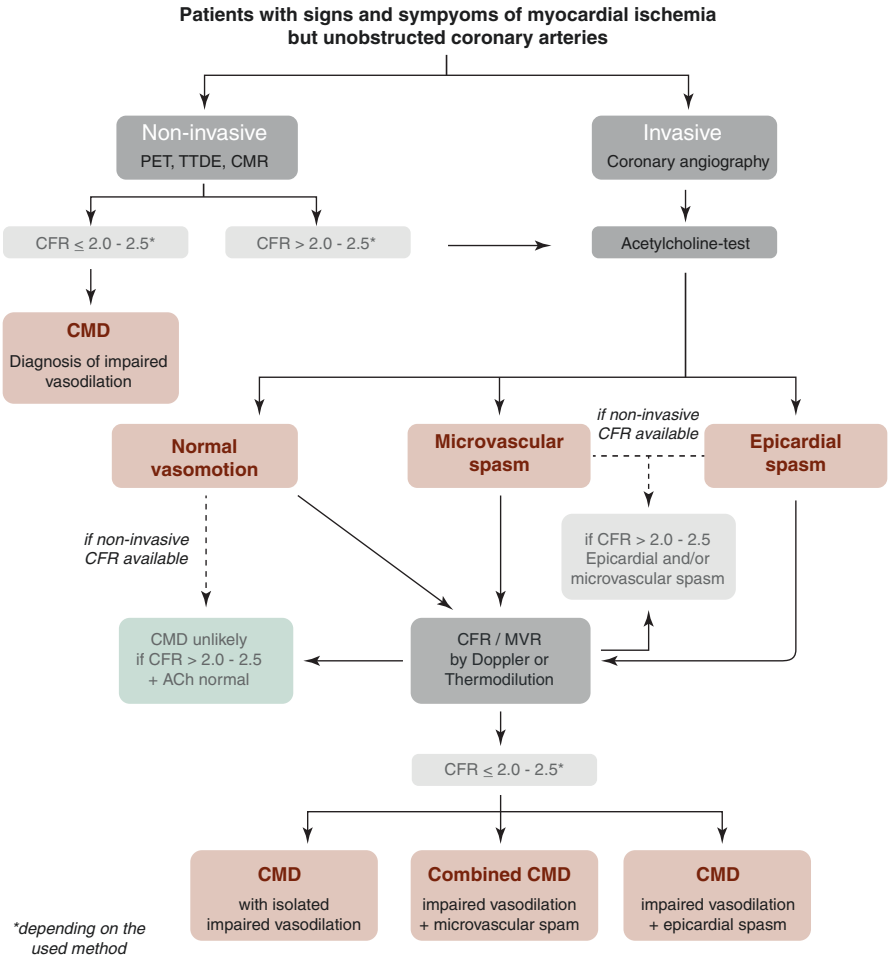

Fig. 5.1 Interventional diagnostic procedure (IDP), proposed by Ong et al. [5], including both non-invasive and invasive techniques in symptomatic patients with unobstructed coronary arteries and suspected CMD. *CFR* coronary flow reserve, *CMR* cardiovascular magnetic resonance, *MVR* microvascular resistance, *PET* positron emission tomography, *TTDE* transthoracic Doppler echocardiography. (Reproduced from Ong et al. [5])

invasive) are appropriate. A proposed diagnostic workup including both non-invasive and invasive techniques is shown in Fig. 5.1. Depending on the diagnostic methods applied for the investigation of CMD, there is a variation in the prevalence of CMD. This chapter gives a contemporary overview of the epidemiology of CMD in patients with signs and symptoms of myocardial ischemia yet unobstructed coronary arteries.

5.2 Historical Background

Long before the discovery of coronary angiography and the advent of invasive cardiology, physicians all over the world have treated patients with chest pain. In the absence of any detailed information about structural or functional heart disease, they could only speculate about the origin of the patient's symptoms. However, the description of the patient's symptoms was one of the most important tasks in which many of these physicians were masters. One of them was William Heberden, a British physician who lived from 1710 until 1801. He was one of the first physicians to describe chest pain as "angina pectoris" a term that has survived until today. Traditionally, the term "angina" arose from about two centuries before his time and was used to describe throat pain, accompanied by a feeling of anxiety. In Heberden's description, angina pectoris was a thoracic discomfort, frequently retrosternal pain, with radiation to the left arm. The symptoms usually occurred during exertion and subsided at rest [6].

With the discovery of the ECG in 1903 by Eindhoven, physicians were able to correlate chest pain symptoms with ischemic ECG changes. Based on the initial description by Heberden [6], it was found that patients with exertional chest pain frequently showed ischemic ECG changes during exercise leading to the term "typical angina". In contrast, others made the observation that patients with resting chest pain could have transient ST-segment elevation on the 12-lead ECG while their exercise capacity was preserved which led to the term "variant angina" by Prinzmetal in 1959 [7]. Prinzmetal assumed that this phenomenon was based on transient spasms of the coronary arteries, and only later it was found out that a substantial proportion of his patients suffered from additional stenosing epicardial disease on autopsy. The description of patients with variant angina and unobstructed coronary arteries was made shortly after and termed "variant of the variant". Although this only fostered the confusion of terminology in this area of cardiology, it should be acknowledged that with the advent of coronary angiography it became apparent that many patients with angina pectoris had unobstructed coronary arteries. In an early study by Proudfit in 1978, it was documented that the prognosis of patients with angina pectoris correlated with the severity of their symptoms, the arteries affected and with an impaired left ventricular function [8]. Moreover, it was previously shown in 1966 that 37% of all patients had unobstructed coronary arteries (<30% luminal obstruction) [9]. Comprehensive research was carried out and Arbogast and Bourassa showed that rapid pacing paradoxically resulted in enhanced left ventricular function in patients with angina but normal coronary arteries, called "group X" [10]. This phenomenon led to the introduction of the term "syndrome X", a label that was commonly used to describe these patients at the time (i.e. chest pain and unobstructed coronary arteries). In 1988, Cannon and Epstein showed that a substantial percentage of patients with angina and unobstructed coronaries exhibited a coronary microvascular disorder and thus introduced the term "microvascular angina" [11]. Subsequently, the concept of coronary microvascular spasm was introduced by Mohri et al. suggesting that an increased vasoconstrictive potential of the coronary microvascular system may be another form of microvascular dysfunction [12].

Despite these seminal studies, the focus of research in clinical cardiology shifted towards epicardial coronary artery disease (CAD) with the introduction of percutaneous coronary interventions in the 1980s by Puel and Sigwart [13]. Thus, the

pivotal role of the microcirculation in regulating myocardial perfusion [14] and its clinical importance in patients with angina and unobstructed coronary arteries received less attention. In recent times, the topic has gained more and more attention. This is due to an important review article in the *New England Journal of Medicine* in 2007 [1], the improvement of diagnostic assessments and therapeutic pathways in these patients [15, 16] and the body of evidence confirming an unfavourable prognosis in various cohorts of patients with CMD [4, 17].

5.3 Epidemiological Considerations

Epidemiology is defined as "the study and analysis of the distribution (who, when and where), patterns and determinants of health and disease conditions in defined populations" [18] with two important measures, incidence and prevalence. Whereas incidence refers to the frequency of events correlating with time and does thus reflect morbidity in a population [19], prevalence is a measure for the frequency of a disease, by defining a specific part of a defined population at a time that carries either a certain disease or a risk factor [20]. The epidemiology of CMD is difficult to assess as it can be present in various forms of cardiovascular disease. This chapter will focus on the epidemiology of patients with type 1 CMD according to Crea and Camici (i.e. CMD in the absence of coronary and myocardial disease) [1]. Moreover, there are several different tools available to assess CMD, each with a different definition and yield of establishing the diagnosis. On average, the prevalence of CMD in observational studies in patients with NOCAD ranges from 22% to 63% (Table 5.1) [2].

Table 5.1 Prevalence of CMD in observational studies with various testing modalities

Author	Number of patients (*n*)	Diagnostic approach	Prevalence of CMD %()	Ref.
Cassar et al.	376	Coronary reactivity testing	63	[21]
Hasdai et al.	203	Coronary reactivity testing	59	[22]
Murthy et al.	1218	PET (CFR < 2.0)	53	[4]
Mygind et al.	919	TTDE (CFR < 2.0)	26	[23]
Reis et al.	159	Coronary reactivity testing	47	[24]
Sade et al.	68	TTDE (CFR < 2.0)	40	[25]
Sara et al.	1439	Coronary reactivity testing	64	[26]
Sicari et al.	394	TTDE (CFR < 2.0)	22	[27]
Wei et al.	293	Coronary reactivity testing	49	[28]

A comprehensive analysis of the prevalence of CMD, reported by multiple studies using various testing approaches, revealed an overall prevalence ranging from 22% to 63%

In addition, various taxonomic definitions and descriptions for CMD have been used inconsistently in the literature complicating this aspect even more. A meta-analysis looking at 57 studies in patients with chest pain and unobstructed coronary arteries previously labelled as cardiac syndrome X revealed very heterogeneous inclusion and exclusion criteria. The authors found as many as 9 inclusion and 43 exclusion criteria limiting the comparability of the studies. Moreover, these different criteria had an impact on the estimated incidence of the disease over 1 year treated in a general hospital ranging from 3% to 11%. Interestingly, the meta-analysis revealed a pooled proportion of females of 0.56 (n = 1934 patients, with 95% confidence interval: 0.54–0.59) (Fig. 5.2) [29].

5.4 Definition of Unobstructed Coronary Arteries

Patients with angina and unobstructed coronary arteries are frequently encountered in daily clinical practice. However, the interpretation of epicardial disease regarding its severity has many pitfalls. As previously shown by Bertrand et al., visual assessments of epicardial stenoses by experienced cardiologist are somewhat inaccurate compared to computerized assessments [30]. The authors demonstrated that the degree of epicardial stenosis pre-PCI differed between the cardiologists and the computerized quantitative analysis (80.6 ± 9.7 vs. 73.4 ± 11.1). Interestingly, the assessment after PCI was 18.8% ± 12.3 by the cardiologists and 37.4 ± 14 by the computer system [30]. Moreover, there is no international consensus regarding the definition of unobstructed coronary arteries. A frequently applied criterion is a <50% stenosis based on visual assessment. However, other studies have applied a 30% criterion or even a 70% criterion [9]. With the introduction of invasively available pressure-wire measurements for assessment of hemodynamic relevance of epicardial stenoses, it is recommended to refrain from a percental classification of epicardial stenoses. It is rather advisable to perform pressure-wire assessments of any intermediate epicardial lesion as even epicardial lesions with a 30% stenosis may be hemodynamically relevant as shown by Toth et al. [31]. Thus, contemporary study protocols for the evaluation of CMD should include such pressure-wire measurements in order to not overlook any relevant epicardial stenosis amenable for coronary revascularization.

The improvement of the CTCA technology and its broader applicability has led to several large studies, showing that an initial CTCA approach in patients with suspected CAD is feasible [32]. However, such an approach is limited by the fact that CTCA only delivers information about coronary anatomy but neither on any functional coronary disorders nor on the hemodynamic relevance of any intermediate epicardial lesion. These limitations can be overcome by the CT-FFR technique, where not only anatomic information about epicardial stenoses but also functional information about the hemodynamic relevance of a given lesion is assessed [33, 34]. In addition, a combined assessment of not only CTCA and CT-FFR but also CT-perfusion has been shown to be feasible in clinical studies [35]. The

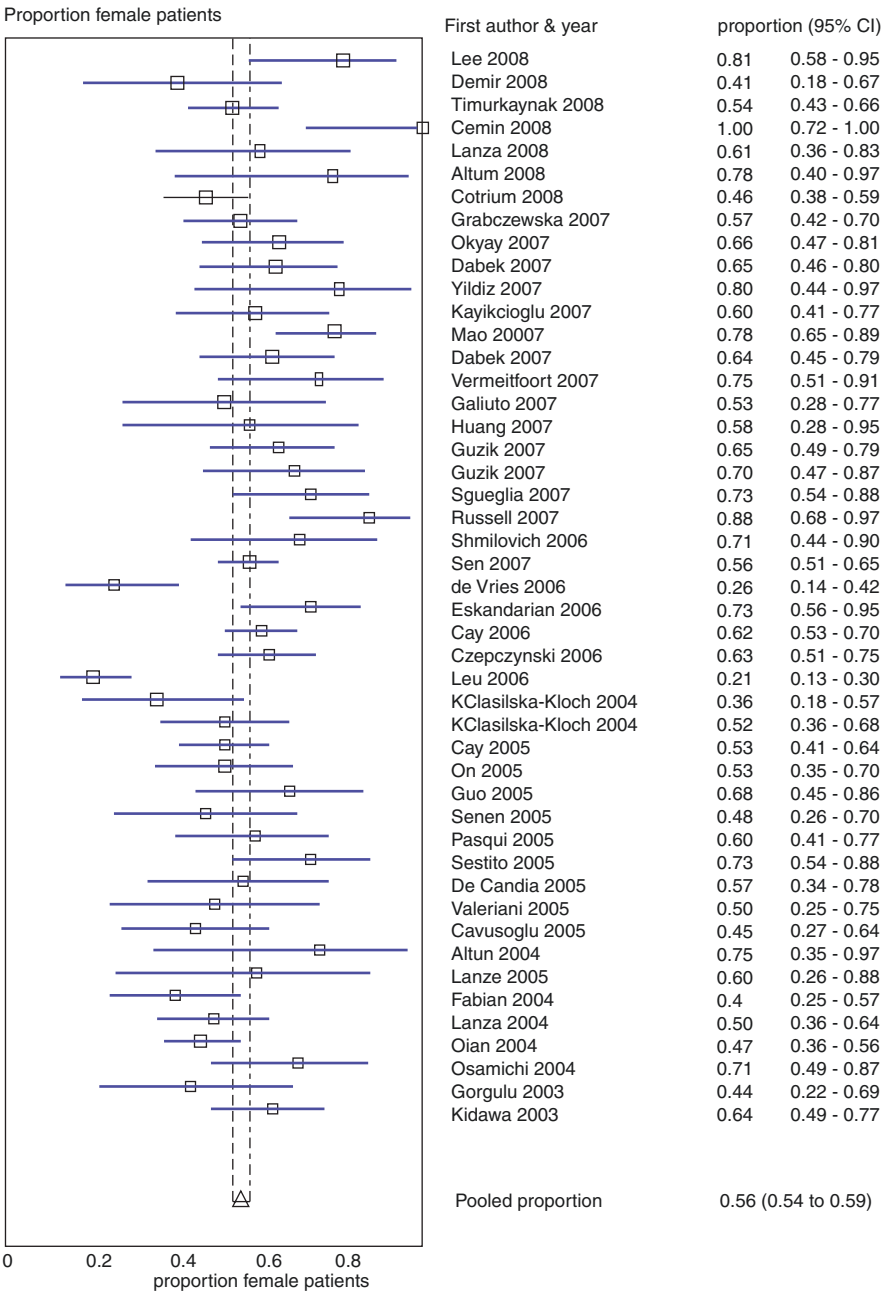

Fig. 5.2 The proportion of women of individual studies regarding cardiac syndrome X (CSD), including 95% confidence intervals. A considerable variation in 47 studies regarding the proportion of women with CSX could be seen with values ranging from 0.21 to 1.0 and a pooled estimate of 0.56 (95% confidence interval: 0.54–0.59). Thus, women suffer significantly more often from CSX compared to men. (Reproduced from Vermeltfoort et al. [29])

development of such imaging techniques represents an attractive and innovative approach for future assessments of such patients in whom a “one stop shop” may be able to provide information about epicardial plaques/stenoses (CTCA), hemodynamic relevance (CT-FFR) as well as impairment of the coronary microcirculation (CT-Perfusion-CFR).

5.5 Prevalence of CMD Depends on Diagnostic Assessments Used

The fact that the coronary microvasculature cannot be visualized in vivo patients makes its assessment a true challenge. Over the past years, multiple non-invasive and invasive methods have been established for the assessment of CMD and their specific use depends not only on the clinical state of the patient, but also on local availability, expertise and cost as well. Non-invasive methods to evaluate the coronary microvasculature include the assessment of coronary flow velocity reserve (CFVR) via transthoracic Doppler echocardiography, cardiac magnetic resonance imaging or positron emission tomography. Invasive methods, on the other hand, comprise the assessment of CFR and microvascular resistance using adenosine as well as the assessment of microvascular coronary spasm using acetylcholine (ACh). The COVADIS (Coronary Vasomotion Disorders International Study) Group has assembled the diagnostic criteria for CMD as shown in Table 5.2 [36]. It has been acknowledged that impaired microvascular vasodilatation as well as enhanced microvascular vasoconstriction/spasm represent mechanisms for microvascular dysfunction. Recently, a new innovative approach titled “interventional diagnostic procedure” (IDP), which allows the invasive assessment of coronary vasoconstrictor and vasodilator abnormalities in combination, has been established (Fig. 5.1) [5].

5.6 Prevalence of Chest Pain and Unobstructed Coronary Arteries and Prevalence of CMD in Acute Coronary Syndrome

Early studies have shown that a substantial proportion of patients with acute coronary syndrome have unobstructed coronary arteries [37]. Hochman et al. showed that ~30% of women and ~14% of men with ACS had no culprit lesion [37]. The frequency of NOCAD was greater in patients with unstable angina compared to those with STEMI or NSTEMI. A more recent meta-analysis of 27 large studies involving a total of 176,502 patients with myocardial infarction showed frequencies of ACS patients without culprit lesion ranging from 1% to 14% (overall prevalence 6%) [38]. Furthermore, patients with ACS and non-obstructive coronary arteries are more likely to be younger, female and it could be observed that they were less likely

Table 5.2 Clinical criteria for suspecting coronary microvascular dysfunction

1.	Symptoms of myocardial ischemia
	(a) Effort and/or rest angina
	(b) Angina equivalents (i.e. shortness of breath)
2.	Absence of obstructive CAD (<50% diameter reduction or FFR > 0.80) by
	(a) Coronary CTA
	(b) Invasive coronary angiography
3.	Objective evidence of myocardial ischemia
	(a) Ischemic ECG changes during an episode of chest pain
	(b) Stress-induced chest pain and/or ischemic ECG changes in the presence or absence of transient/reversible abnormal myocardial perfusion and/or wall motion abnormality
4.	Evidence of impaired coronary microvascular function
	(a) Impaired coronary flow reserve (cut-off values depending on methodology use between ≤2.0 and ≤2.5)
	(b) Coronary microvascular spasm, defined as reproduction of symptoms, ischemic ECG shills but no epicardial spasm during acetylcholine testing
	(c) Abnormal coronary microvascular resistance indices (e.g. IMR > 25)
	(d) Coronary slow flow phenomenon, defined as TIMI frame count >25

The following criteria should lead to the suspicion of CMD
ECG electrocardiogram, *CAD* coronary artery disease, *CTA* computed tomographic angiography, *FFR* fractional flow reserve, *IMR* index of microcirculatory resistance, *TIMI* thrombolysis in myocardial infarction. (Reproduced from Ong et al. [36])

to have hyperlipidemia compared to those with myocardial infarction and obstructive CAD. Nowadays such patients should be labelled with a working diagnosis of MINOCA (myocardial infarction with non-obstructive coronary arteries) and possible ischemic causes in the setting of ACS without culprit lesion should be investigated according to the so-called "traffic light approach" [39]. This should also involve assessments for CMD. The feasibility to determine a diagnosis of CMD in an ACS setting has been described using non-invasive as well as invasive techniques. A study by Safdar et al. using PET-CFR (cut-off CFR > 2.0 for rate-pressure product corrected values and CFR < 2.5 for uncorrected values) in 195 emergency room patients showed that in nearly half of the patients with chest pain and without MI or CAD, CMD could be diagnosed [40]. A great amount of these patients were females and obese, highlighting the important role of cardiovascular risk factors [40]. Other studies reported the usefulness of investigations for CMD in ACS patients undergoing invasive angiography. Sato et al. [41] showed that ACS patients without culprit lesion may also suffer from microvascular spasm on ACh testing, a finding that was predominantly seen in female patients. In addition, Pirozzolo et al. showed that coronary microvascular spasm, a subtype of CMD, can be frequently found in patients with MINOCA. Indeed, while epicardial spasm could be induced with ACh in 27% of the 96 patients, coronary microvascular spasm was seen in 31% [42]. Furthermore, the prevalence of epicardial spasm could be associated with smoking, a finding, which has been previously described [41].

5.7 Chronic Coronary Syndrome

From the beginning of coronary angiography, patients with angina and unobstructed coronary arteries were not infrequently encountered. Until today, they represent one of the most challenging groups of patients in clinical cardiology. The study by Proudfit et al. in 1966 revealed that 37% of 1000 patients undergoing coronary angiography had unobstructed coronary arteries (<30% diameter obstruction) [9]. Such numbers were confirmed in several large registry studies. In more recent times, a seminal publication from the USA by Patel et al. revealed that more than 50% of patients with suspected CAD had NOCAD [43]. This led to speculations as to whether or not the inclusion criteria and the indication for invasive angiography should be optimized. Moreover, these findings also fostered prospective studies for the investigation of coronary vasomotor disorders as an explanation for the patient's symptoms in this setting [44]. A study by Jespersen et al. confirmed previous observations that a diagnosis of NOCAD is not benign with an event rate of 1.7%/year [45]. Frequently, cardiovascular risk factors lead to the pathophysiologic sequelae of CMD and ultimately a clinical presentation with either shortness of breath, angina or both. Established causes for CMD in this setting are either an impaired coronary flow reserve/elevated microvascular resistance or coronary microvascular spasm [36]. Recently, detailed recommendations for the diagnosis of CMD in the clinic have been published [5], and a comprehensive assessment of both impaired vasodilatory capacity and assessment of enhanced vasoconstrictor responses to ACh has been recommended (so-called interventional diagnostic procedure, IDP) (Fig. 5.1).

Non-invasive assessments have revealed a prevalence of CMD between 26% and 54%. In the iPower study, 26% of 963 symptomatic women with no obstructive CAD had coronary flow velocity reserve <2 when assessed by transthoracic Doppler echo [23]. Furthermore, Murthy et al. [4] could show that PET-CFR was not only a powerful tool to diagnose CMD (prevalence ~50%), but that it can also be used as a powerful predictor of MACE since patients with a reduced CFR exhibited a higher likelihood of cardiovascular events.

Invasive assessment revealed that approximately 34% of patients with angina and unobstructed coronary arteries in the ACOVA study suffered from microvascular spasm (Fig. 5.3) [44] and approximately 50% of patients suffered from impaired CFR (Fig. 5.4) in another cohort as shown by Reis et al. [24]. The high prevalence of CMD in the setting of NOCAD has been recently confirmed in a study from the WISE cohort. The investigators compared their findings from coronary reactivity testing in an older patient cohort (1997–2001) with a more recent patient cohort (2009–2011) and endothelial and microvascular dysfunction prevalence and severity was similar to that found in the earlier original WISE cohort (overall approx. 40%) [46]. More recent data from Suda et al. have shown that when the IDP is applied in patients with angina and non-obstructive coronary arteries, 12% suffer from microvascular spasm, 35.3% suffer from impaired CFR, 40.1% suffer from a high IMR and 15% suffer from a combination of low CFR and high IMR [47]. These various forms of CMD are called endotypes and have been described in more

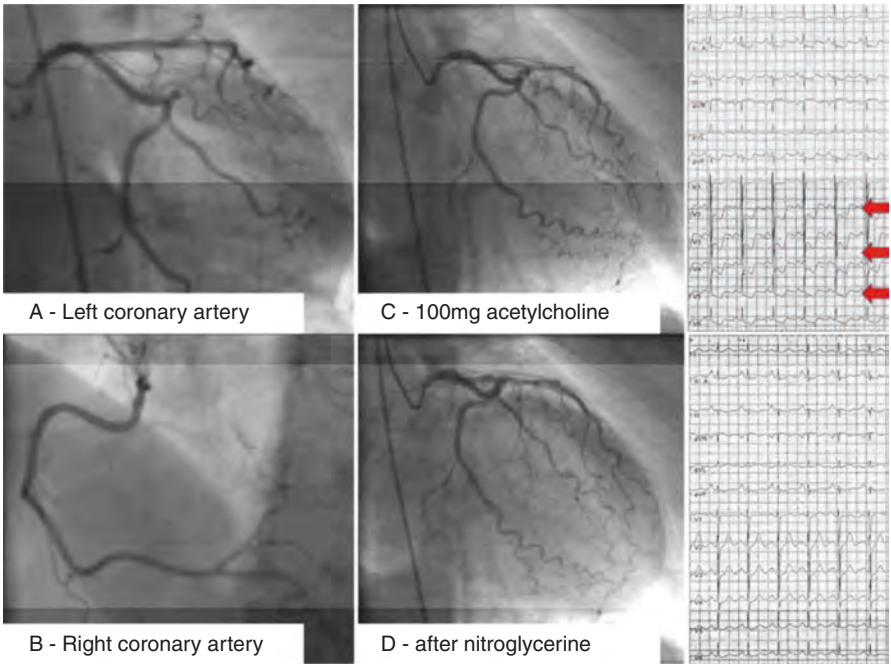

Fig. 5.3 Representative example of a patient with CMD, diagnosed with ACh provocation testing, as part of the IDP. This case presents a 73-year-old woman with hypercholesterolemia and recurrent attacks of resting angina pectoris associated with nausea and palpitations. Coronary angiography showed unobstructed but curly LCA (**a**). No relevant epicardial stenosis could be found in the RCA either (**b**). Additional intracoronary ACh testing to assess vasomotion in this patient revealed coronary microvascular spasm. The patient reported a reproduction of her usual symptoms and ST-segment depression in leads V2–V6 occurring at a dose of 100 mg of ACh (red arrows), without relevant epicardial vasoconstriction of the arteries (**c**). After intracoronary administration of nitroglycerine, her symptoms and ECG shifts quickly resolved (**d**). ACh, acetylcholine. (Reproduced from Ong et al. [5])

detail elsewhere [15]. A methodological limitation of the IDP is that CFR and microvascular resistance are often only measured in a single coronary artery (e.g. left anterior descending coronary artery) and not all three coronary arteries. This may be an important factor for the prevalence of CMD as studies could show that invasive evaluation of all three coronary arteries in 93 patients revealed 1-vessel CMD in 23.7% of cases, 2-vessel CMD in 14.0% and 3-vessel CMD in 3.2%. CMD was observed at a similar rate in the territories supplied by all three major coronary vessels (left anterior descending coronary artery 28.0%, left circumflex artery 19.4% and right coronary artery 23.7%; $P = 0.39$) [48].

Overall, the prevalence of CMD in patients with angina and unobstructed coronary arteries is not negligible and prospective randomized trials are on the way for the development of targeted treatments based on these different endotypes [16, 49]. Due to the high prevalence of CMD, additional assessments during invasive coronary angiography are highly recommended when epicardial disease is ruled out.

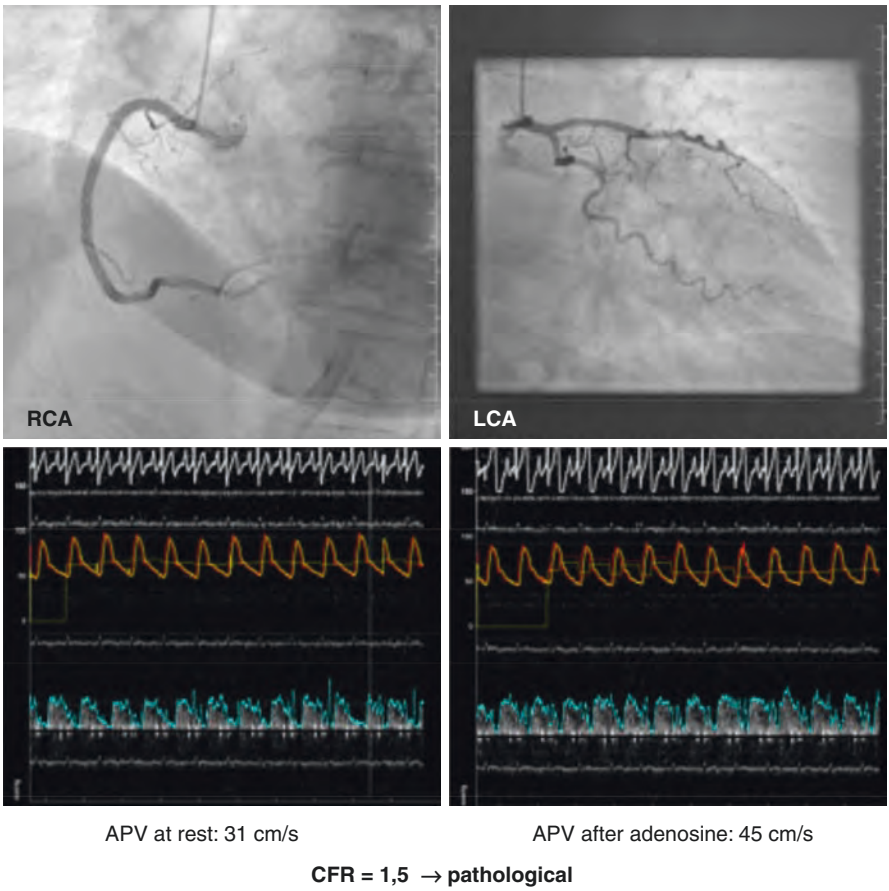

Fig. 5.4 Representative example of a patient with CMD, diagnosed with CFR measurement during IDP. This figure presents a case of a 74-year-old female patient with diabetes type 2, hypercholesterolemia, increased lipoprotein(a) and hypertension. She suffered from effort-related dyspnoea and chest tightness for several months. During coronary angiography, unobstructed coronary arteries could be seen (RCA and LCA). Additional CFR measurement in the left anterior descending coronary artery revealed a pathologically reduced CFR (1.5), indicating an impaired microvascular dilator capacity, which is known to be a typical long-term complication of diabetes affecting the coronary microvasculature. APV, average peak flow velocity. (Reproduced from Ong et al. [5])

5.8 Outlook

In times of personalized and individualized medicine, patients with angina and unobstructed coronary arteries should be comprehensively investigated (e.g. by an IDP). This is warranted because of the guarded prognosis of these patients in whom frequently the quality of life is severely impaired with loss of workforce in many cases. Indeed, studies by Jespersen et al. could show that the prevalence of

persistent angina in patients with diffuse non-obstructive CAD or normal coronary arteries was higher compared to those with obstructive CAD [50, 51]. Moreover, patients with persistent angina were likely to suffer from long-term anxiety, depression, decrease in physical function and impairment of quality of life. Consequently, patients with angina symptoms and both obstructed or non-obstructed coronary arteries have a significantly higher likelihood of disability pension and premature workforce compared to the reference population [50, 51].

In patients with chest pain of unknown origin, novel smartphone-based ECG technologies offer a direct assessment of ischemic ECG changes during a chest pain attack [52]. This may reduce diagnostic uncertainty and prompt further diagnostic assessments. The broad applicability of this technology may also influence the epidemiology of CMD as many patients with chest pain of unknown origin may suffer from undetected CMD. Further studies are needed to provide robust data in this emerging field of digitalized medicine where artificial intelligence may also be involved.

Another important aspect is the female preponderance of patients with angina and unobstructed coronary arteries in general and those with CMD in particular [53]. Basic science as well as clinical research projects should focus on such sex differences and ensure equally distributed numbers of male and female study participants. It seems likely that individualized pharmacotherapy may also be different in male and female patients with CMD as recently shown in other cardiology drug studies [54]. Finally, research projects aiming at the discovery of systemic microvascular dysfunction and its associated conditions such as Raynaud's disease, cerebral microvascular dysfunction and microvascular renal impairment may revolutionize our understanding of CMD and put the condition in a new light [55].

5.9 Conclusion

CMD is an important condition often responsible for the clinical presentation of patients with angina and unobstructed coronary arteries. It can be comprehensively assessed by e.g. an interventional diagnostic procedure. The prevalence of CMD in patients with angina and unobstructed coronary arteries is high with approx. 50–60%. The unfavourable prognosis should prompt proper assessments enabling the treating physician to prescribe the most appropriate pharmacological treatment.

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