CMD in the Absence of Myocardial Diseases and Obstructive CAD

4

Camici and Crea have proposed a clinical classification of CMD into four main types on the basis of the clinical setting in which it occurs [1]: (1) CMD in the absence of myocardial diseases and obstructive CAD, (2) CMD in myocardial diseases, (3) CMD in obstructive CAD, and (4) iatrogenic CMD (Table 4.1).

As outlined in Chap. 2, CMD can be determined by several pathogenetic mechanisms. The importance of these mechanisms is different in different clinical conditions, but several of them may coexist in the same condition.

This chapter will describe the first type of CMD characterized by the lack of myocardial diseases and obstructive CAD.

4.1 Cardiovascular Risk Factors and CMD

4.1.1 Smoking

Cigarette smoking is a well-established risk factor for cardiovascular disease [2], affecting both the coronary and the peripheral circulation [3]. Endothelial dysfunction in brachial [4] and large coronary [5] arteries has been demonstrated in long-term smokers and even in passive smokers [6, 7].

The findings of a PET study by Kaufmann et al. [8] extend these observations and demonstrate that the noxious pro-oxidant effects of smoking go beyond the epicardial arteries and also involve the coronary microcirculation, affecting the regulation of MBF. In smokers, adenosine-induced hyperemia was reduced by 17 % and CFR by 21 % compared with nonsmoking controls ($p < 0.05$) (Fig. 4.1). Although the mechanisms of smoking-associated vascular damage are not fully established, several factors may be involved. Nicotine has been shown to produce structural damage in aortic endothelial cells of animals [9], and smoking has been associated with a direct toxic effect on human endothelial cells [10]. The gas phase of cigarette smoke contains large amounts of free radicals and pro-oxidant lipophilic quinones [11], which can form the highly reactive

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Table 4.1 Clinical classification of CMD. Modified from Camici and Crea [1]

CMD in the absence of myocardial diseases and obstructive CAD	This type represents the functional counterpart of traditional coronary risk factors (smoking, hypertension, hyperlipidemia, diabetes and insulin-resistant states). It can be identified by noninvasive assessment of coronary flow reserve. This type is at least partly reversible, and CFR can also be used as a surrogate end point to assess efficacy of treatments aimed at reducing the burden of risk factors. It may be severe enough to cause angina and myocardial ischemia
CMD in 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 CFR 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 cardiomyopathies (e.g., dilated and hypertrophic) and secondary cardiomyopathies (e.g., hypertensive and valvular)
CMD in 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 CMD	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 CFR, which seems to revert spontaneously in the weeks after revascularization. Pharmacologic treatment has been shown to promptly restore CFR, 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

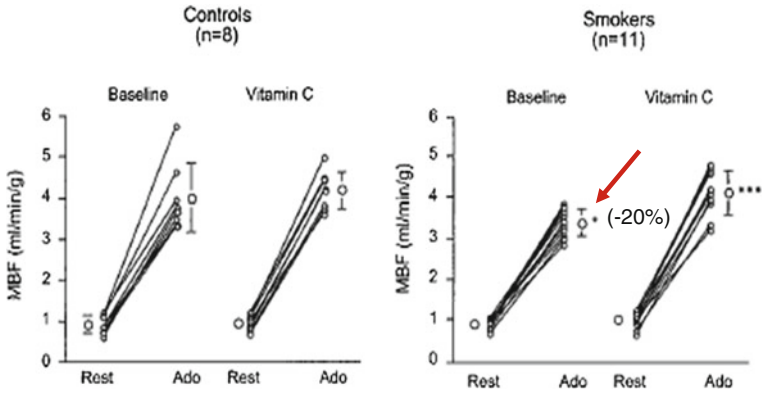

Fig. 4.1 Baseline and hyperemic (adenosine) MBF was measured with PET in two groups of healthy subjects: nonsmoking controls (*left panel*) and smokers (*right panel*). There were no differences in baseline MBF between the two groups. However, compared to nonsmokers, maximum hyperemic MBF was reduced by 20 % in smokers. Antioxidant therapy with vitamin C (3 grams i.v.) led to normalization of hyperemic MBF in smokers, suggesting a significant role of oxidative stress in the mechanisms responsible for CMD in these subjects. Adapted from Kaufmann et al. [8]

hydroxyperoxide radicals. These oxidants may increase the amount of oxidized LDL, which is markedly more effective than native LDL in impairing eNOS [12].

Notably, short-term administration of the antioxidant vitamin C restored coronary microcirculatory responsiveness and normalized CFR in smokers without any significant effect in nonsmoking controls, lending support to the hypothesis [13] that the damaging effect of smoking is at least in part explained by an increased oxidative stress (Fig. 4.1). This is in line with the results of a previous investigation in which another antioxidant, reduced glutathione [14], was shown to improve endothelial dysfunction in patients with cardiovascular risk factors, but had no effect in subjects without risk factors. Of note, vitamin C has been reported to attenuate abnormal coronary vasomotor reactivity in smoking patients with vasospastic angina by scavenging oxygen free radicals [15].

4.1.2 Hypercholesterolemia

In subjects with angiographically normal coronary arteries, hypercholesterolemia has been shown to impair endothelium-mediated coronary dilatation [16, 17]. This is, at least in part, reversed by L-arginine infusion [18, 19] and by therapy with lipid-lowering drugs [20–23] or with calcium channel blockers [24]. A reduction of CFR in asymptomatic hypercholesterolemic subjects with angiographically normal coronary arteries, as well as its reversibility with the use of cholesterol-lowering strategies [25–27], has been documented by PET [28, 29]. Notably, results from in vitro studies suggest that endothelial dysfunction is due to reduced

NO release or increased production of superoxide anion by oxidized LDL [12], or both, rather than by an increase in total cholesterol. In fact, LDL apheresis in humans has been shown to improve endothelium-dependent vasodilatation in hypercholesterolemic patients [30].

In a recent study, in a population which included asymptomatic subjects with normal or elevated total cholesterol [31], no difference in either resting or hyperemic MBF was found in relation to total cholesterol levels. When all subjects (i.e., with normal and abnormal total cholesterol) were considered, a weak correlation between CFR and HDL cholesterol, but not between CFR and LDL cholesterol, was observed. However, when the subjects with high total cholesterol only were considered, CFR was inversely related to the LDL subfraction.

Similarly, previous studies demonstrated a significant inverse correlation between CFR and lipid subfractions, including LDL cholesterol [28, 29, 32]. The latter studies, however, found also a correlation between CFR and total cholesterol. Some of these discrepancies can be explained by differences in patient selection criteria, sample size of the study cohorts, reference cholesterol levels, and concomitant medications.

Furthermore, although Yokoyama et al. [32] found a significantly reduced CFR in patients with familial hypercholesterolemia, it seems that isolated and familial hypercholesterolemias do not necessarily have the same impact on endothelial dysfunction. This is supported by the results of Pitkänen et al. [33] who found a correlation between total cholesterol and CFR in patients with familial combined hyperlipidemia and the phenotype IIB, but not in those with the phenotype IIA, despite comparably increased total cholesterol levels in the two phenotypes. The same group provided evidence of linkage to a sub-chromosomal region (1q21-23) in familial combined hyperlipidemia [34], and therefore suggested that genetic factors behind familial combined hyperlipidemia may cause endothelial or SMC dysfunction, or both, by mechanisms unrelated to lipid metabolism.

As noticed above, in the study by Kaufmann et al. [31] no relation between total cholesterol and MBF or CFR could be demonstrated, although LDL cholesterol subfraction correlated inversely with CFR in those with high total cholesterol, thus supporting a direct pathogenic role of this subfraction in the development of CMD (Fig. 4.2). These in vivo results are in agreement with the previous observations identifying the LDL subfraction as a cause of endothelial dysfunction, and extend these findings to the coronary microcirculation in humans. Furthermore, this provides pathophysiologic support for a clinical strategy [35] aimed at the treatment of the entire lipid profile rather than targeting total cholesterol reduction alone. In fact, risk assessment without taking LDL subfraction into account seems to provide unreliable results [36]. It is important to remember that the benefits of treating any risk factor depend not only on the absolute risk of future disease but also on the degree to which the index risk factor contributes to the risk [37].

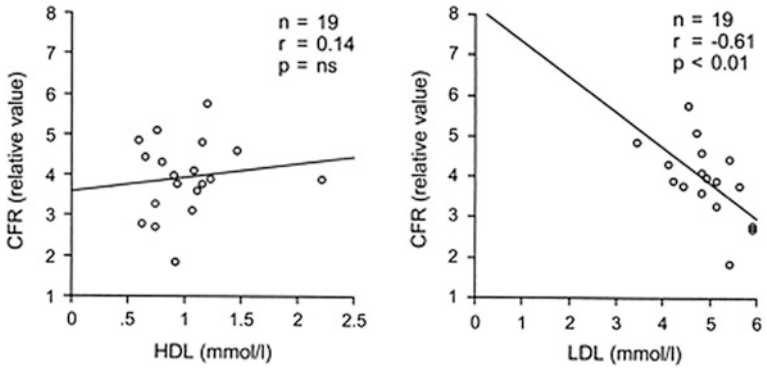

Fig. 4.2 Evidence for a significant inverse relationship between CFR, measured with PET, and LDL cholesterol (*right panel)*, in asymptomatic subjects. By contrast, no relation between CFR and HDL cholesterol (*left panel)* could be demonstrated. Adapted from Kaufmann et al. [31]

4.1.3 Hypertension

Arterial hypertension is a major independent risk factor for adverse cardiovascular events and concurrence of LVH further increases cardiovascular morbidity and mortality [38, 39]. Randomized studies have demonstrated that treatment of hypertension has beneficial effects on cardiovascular outcome [40]. In a recent meta-analysis, however, the better cardiovascular prognosis achieved with some anti-hypertensive drugs, such as ACE-inhibitors, exceeded that predicted on the basis of the reduction of blood pressure and LVH [41].

Patients with hypertension have evidence of CMD and may present signs and symptoms suggestive of myocardial ischemia, despite normal coronary angiograms [42, 43].

Abnormal CFR, despite angiographically normal coronary arteries, has been demonstrated in several studies in patients with essential hypertension (Fig. 4.3) [42, 44–46]. This observation has often been attributed to the effects of LVH secondary to hypertension, which include increased extravascular compressive forces, with elevated systolic/diastolic wall stress and impaired relaxation, and structural alterations such as myocyte hypertrophy, interstitial fibrosis, and rarefaction of coronary microvasculature [45] (see Chap. 2). However, the impairment of CFR in hypertensive patients is not necessarily related to the presence or degree of LVH [47], but is rather caused by remodeling of intramural coronary arterioles due, at least in part, to excessive activation of the renin-angiotensin-aldosterone system [48, 49]. Treatment with ACE-inhibitors may indeed revert microvascular remodeling and improve rarefaction of the microvascular bed in experimental hypertension [50, 51].

Duration and severity of hypertension may have an important effect on CFR [52]. A recent PET study has provided new insights into the complex interactions among hypertension, LVH, and impaired CFR [53]. In this study, the authors

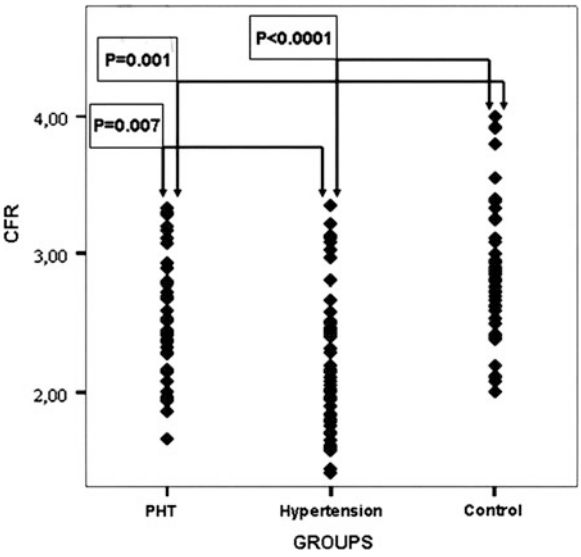

Fig. 4.3 Reduced CFR assessed by TTDE in patients with hypertension and with pre-hypertension (PHT), compared to normotensive controls. Adapted from Erdogan et al. [46]

found a significantly impaired CFR in hypertensive patients compared to normotensive controls. The global impairment, however, was not directly linked to the presence or degree of LVH, as assessed by echocardiography thus supporting the importance of primary vascular involvement in the genesis of CMD and regional perfusion abnormalities. However, the reduction of hyperhemic MBF during pharmacological stress test was often found to be regionally heterogeneous, and the degree of heterogeneity increased in presence of LVH.

These findings [53] may also shed some light on the evidence of increased incidence of sudden cardiac death and ventricular arrhythmias in hypertensive patients with LVH. It is indeed possible that regional heterogeneity in impaired vasodilating response and myocardial ischemia may predispose to local patterns of abnormal myocardial depolarization and repolarization during high flow demand conditions, which can form a substrate for induction of clinically relevant arrhythmias. Thus, spatial flow heterogeneity during pharmacologic coronary vasodilatation as shown by PET, most often observed in hypertrophic hearts, might be a pathophysiologic mechanism for malignant arrhythmias.

Some insights into the mechanisms of CMD in hypertension also come from pharmacological studies. Thus, reversal of microvascular remodeling by ACE-inhibitors has been demonstrated in subcutaneous small arteries [54–57], which was associated with improvement of CFR [58]. Schwarztkopff et al. [59] have demonstrated that ACE-inhibitors can significantly improve maximum CBF in hypertensive patients, but they could not provide definitive evidence of reverse microvascular remodeling using endomyocardial biopsies obtained from the right side of the interventricular septum. Tissue specimens obtained with this procedure, however, are minute and limited to the inner surface of the ventricular cavity. As a

consequence, only arterioles with a diameter approximately $\leq$20 μm can be assessed, whereas CMD might involve larger arterioles or pre-arterioles [60].

In an exploratory study, Mourad et al. [61] demonstrated that perindopril and indapamide increased CFR measured by PET. Neglia et al. [62] expanded these findings showing, in the experimental model of spontaneously hypertensive rat, that maximum MBF and minimal coronary resistance improved significantly after treatment with these drugs, but that the changes were not correlated with the reduction in blood pressure or LVH, thus suggesting that the favorable effects of treatment were more related to reverse remodeling of coronary arterioles and reduction of vessel rarefaction than to changes in hemodynamic parameters or cardiomyocyte mass (Fig. 4.4).

An improvement of endothelial function might also contribute to the improvement of CMD with ACE-inhibitors (in agreement with the known effects on systemic endothelial function) [63], suggesting a significant role for endothelial dysfunction in hypertensive CMD. In the study by Neglia et al., indeed, animals treated with perindopril (alone or in combination with indapamide) had a significant inverse relationship between hyperaemic MBF and the reduction of arteriolar medial area, whereas indapamide alone had no effect on CBF despite a similar reduction in arteriolar medial area, thus supporting the hypothesis that perindopril may increase MBF not only by promoting reverse arteriolar remodeling, but also by improving endothelial function [62].

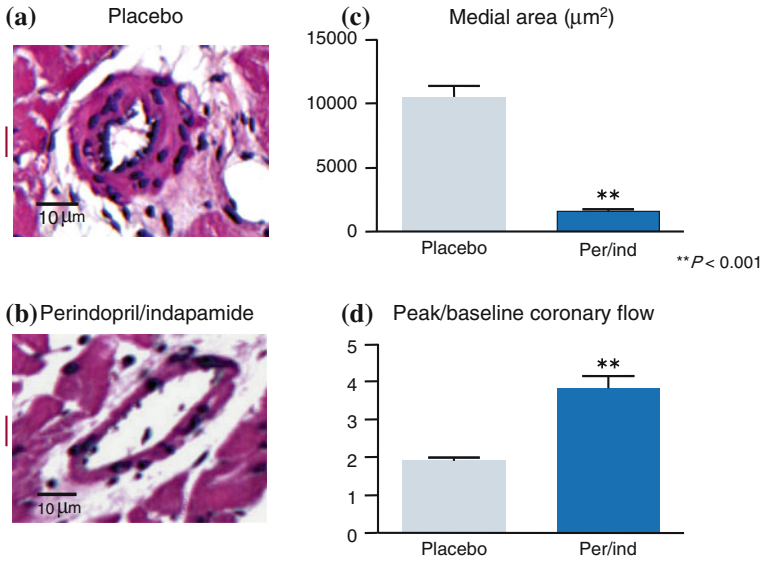

Fig. 4.4 Histological sections (hematoxylin-eosin) of intramural coronary arterioles of spontaneous hypertensive rats (SHR) treated with placebo (**a**) or perindopril + indapamide (**b**). Active treatment led to a decrease in medial wall thickness (**c**) and to an improvement of peak to baseline coronary flow ratio (**d**). ** = $p < 0.001$. Adapted from Neglia et al. [62]

4.1.4 Diabetes and Insulin Resistance

The Framingham study clearly showed that patients with diabetes mellitus have an increased risk for the development of micro- and macro-angiopathy and cardiac disease [64]. Diabetic microangiopathy is probably the best known clinical expression of microvascular disease. The microvascular disease can variably involve different districts and organs leading to specific clinical manifestations, such as diabetic retinopathy, nephropathy, and neuropathy, which can cause highly invalidating complications [65]. These dramatic evolutions are due to functional and structural modifications of arterioles, capillaries, and venules. In contrast to large vessel disease, which is largely glycemia-independent, microvascular complications are almost linearly linked to hyperglycemia and can be detected even in the presence of marginally elevated blood glucose levels [66]. Indeed, abnormalities are found long before macrovascular disease is observable, as illustrated by retinal microcirculatory defects before diabetes is diagnosed [67].

Several biochemical pathways have been well described whereby hyperglycemia can exert its deleterious effects on microvessels, two of which should be particularly emphasized, i.e., oxidative stress and protein and lipid glycation [68]. The latter, in particular, results in the formation of so-called advanced glycation endproducts or "AGEs" [69]. Glycation modifies microvessel structure, severely impairing their function [70].

Although much of the excess CAD risk can be accounted for by the presence of diabetes-associated coronary risk factors, such as obesity, dyslipidemia, and hypertension, a significant proportion of the risk remains unexplained [71]. A direct deleterious effect of diabetes on vascular and, in particular, on endothelial function has been suggested, thereby increasing the potential for vasoconstriction and thrombosis. There is indeed consistent evidence that patients with diabetes exhibit CMD and that this may be an early marker of atherosclerosis that precedes clinically overt CAD [72–75].

Of note, vascular abnormalities can be found before diabetes becomes evident. Caballero et al. have indeed demonstrated that vascular reactivity in micro- and macrocirculation is reduced in subjects with impaired glucose tolerance and in normoglycemic individuals with a parental history of diabetes, when compared with healthy controls without any individual or familial evidence of glucose intolerance [76]. Similar alterations are observed in patients with overt diabetes (Fig. 4.5) [77]. Pre-diabetes represents an elevation of plasma glucose above the normal range but below that of clinical diabetes, and can be identified as either increased fasting glucose or impaired glucose tolerance. Pre-diabetes, however, seems to induce only functional abnormalities on microcirculation, in contrast to the visible, structural microvascular modifications occurring when diabetes is established [66]. Glucose-lowering drugs can delay conversion from pre-diabetes to diabetes, but whether they will in the long run delay the development of microvascular disease is in dispute. To date, indeed, the drug approach for the prevention of microvascular disease starting with pre-diabetes is still debated [78].

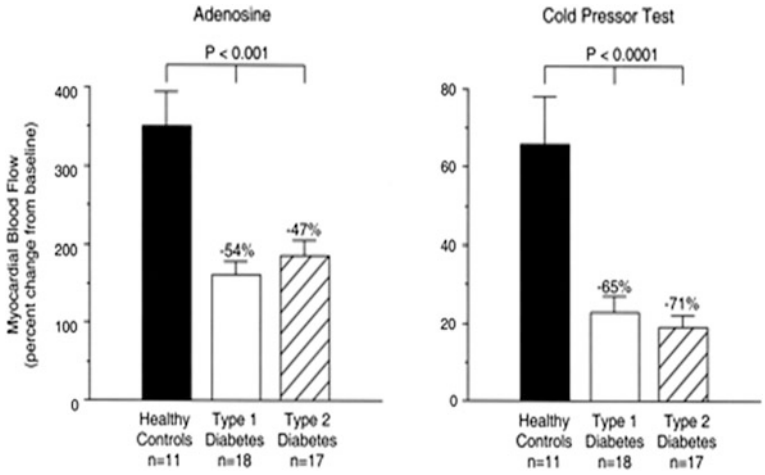

Fig. 4.5 Evidence of reduced CFR in asymptomatic patients with either type 1 or type 2 diabetes mellitus as compared with matched healthy controls in response to adenosine and CPT. Adapted from Di Carli et al. [77]

Using PET, Di Carli et al. [77] have demonstrated marked CMD in response to adenosine (reflecting partly endothelium-independent vasodilatation) and to CPT (reflecting primarily endothelium-dependent vasodilatation) in young subjects with uncomplicated diabetes. The findings were very similar in type 1 and type 2 diabetes, although patients with type 1 diabetes were insulin-deficient (rather than insulin-resistant, the latter being the hallmark of type 2 diabetes). In a more recent study, the same authors found that, among diabetic patients without overt CAD, those with impaired CFR had event rates comparable to those of patients with prior CAD, whereas those with preserved CFR had event rates comparable to those of non-diabetics. These findings highlight the role of CMD in these patients, although it should be noticed that coronary angiographic findings were unknown in most patients included in the latter study [79].

It is also possible that a lack of matching of the heterogeneous changes in perfusion and in metabolic requirements across the myocardial regions related to increased insulin levels might contribute to the abnormal CFR in diabetic patients. In one study, indeed, insulin administration caused a comparable heterogeneous rise in myocardial perfusion in both healthy subjects and in type 2 diabetic patients. The magnitude of changes, however, followed the heterogeneous metabolic requirements across myocardial regions in the control group, whereas such coordination was lacking in diabetic patients [80].

The possibility that CMD is not caused by the metabolic abnormalities of diabetes and glucose intolerance, but rather that systemic microangiopathy (including CMD) related to other causes can be responsible for insulin resistance and, eventually, diabetes is a fascinating, although speculative, hypothesis that should be considered. Baron et al., indeed, found, both in animal and human

studies that the effects of insulin on glucose uptake are partly dependent on blood flow [81]. Thus, impairment of organ perfusion due to microvascular dysfunction might reduce insulin and glucose availability to cells, thus leading to insulin resistance and impaired glucose uptake. This notion does not appear unlikely when considering that, despite very intensive research, there are still no satisfying cellular explanations for insulin resistance [82]. The causes of microvascular alterations remain to be clarified, although several conditions, frequently present in prediabetic and diabetic patients, including overweight and obesity [83, 84], other cardiovascular risk factors (e.g., hypertension, dyslipidemia) [85], hormonal alterations (as in the polycystic ovary syndrome) [86], and hypoxia (as in patients with obstructive sleep apnea) might variably be involved. Genetic factors [87] also have been suggested to contribute to the microvascular dysfunction, eventually causing insulin resistance.

In agreement with this hypothesis is the observation that anti-glycemic drugs may improve CMD by metabolic effects independent of hyperglycemia. Thus, in a study of 26 patients with familial combined hyperlipidemia without any evidence of diabetes, Naoumova et al. [88] found that treatment with the insulin sensitizer pioglitazone, added to conventional lipid-lowering therapy, improved adenosine hyperemic MBF and myocardial glucose utilization, as assessed by PET. As these patients did not have abnormalities in glucose metabolism, it might be speculated that the improvement of CMD was secondary to the favorable effects that the drug had on lipid levels and on other metabolic parameters [89].

4.1.5 Inflammation

Inflammation has emerged in the last decades as a relevant risk factor for atherosclerosis and its complications, including ACSs. Importantly, a role for inflammation has also been shown for CMD in several clinical conditions.

Support to the role of inflammation in causing CMD also comes from studies in patients affected by chronic inflammatory diseases. Thus, hyperemic response to adenosine at PET was found significantly lower in patients with systemic lupus erythematosus or rheumatoid arthritis with angiographically normal coronary arteries and no other cardiovascular risk factor, as compared to healthy controls (Fig. 4.6). Notably, in this study CFR was particularly impaired in patients who developed ischemic ECG changes during adenosine administration, and an inverse relation existed between CFR and disease duration as well as disease activity [90].

Increased levels of markers of inflammation, including CRP and interleukin-1 receptor antagonist, have also been reported in patients with MVA. Of note, a significant correlation of CRP levels with the frequency of angina attacks and with a reduced coronary microvascular dilator response to acetylcholine and to adenosine has been found in these patients [91–93].

Inflammation can act in multiple ways to impair coronary microvascular function. Relevant negative effects of inflammatory reactions have first of all been

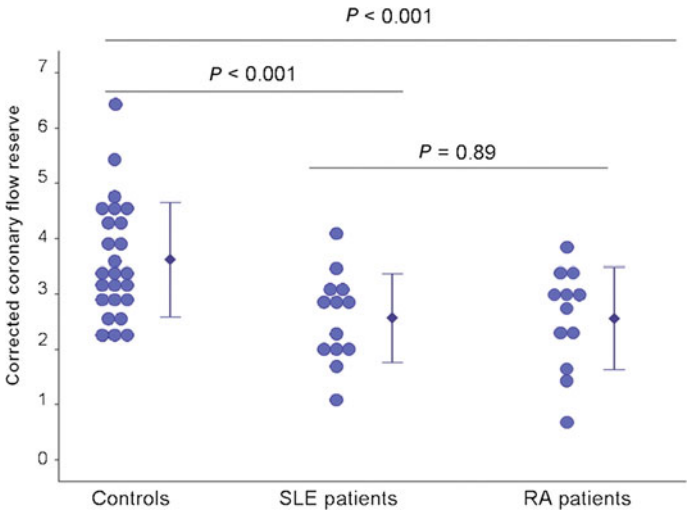

Fig. 4.6 CFR assessed by PET and adenosine in rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE) patients and in controls. Bars represent means ± standard deviations Adapted from Recio-Mayoral et al. [90]

described on endothelial cells, and therefore in endothelium-mediated coronary microvascular function. Inflammatory cytokines, including CRP, interleukin-6, tumor necrosis factor-alpha, have direct negative effects on endothelial cell function, but also indirect effects through increase of oxidative species, which results in inhibition of NO synthase and NO release, as also proved by the consistent impairment of flow-mediated dilatation found in peripheral arterial circulation [94].

However, as shown above, a large body of data indicates that inflammation may also significantly impair endothelium-independent vascular function, although the mechanisms behind this kind of effect remain to be elucidated.

Importantly, inflammatory reactions have been suggested to play a relevant role, in particular, in the CMD occurring in ischemia–reperfusion damage (see Chaps. 2 and 6). A large number of experimental studies have indeed proven that inflammatory cytokines increase in the ischemic area. The increase in TNF-alpha, in particular, up-regulates arginase and increases oxidative stress, thus reducing NO production and availability. Cytokines have also been shown to reduce EDHF, C-type natriuretic peptide, and H_2O_2. Furthermore, inflammatory cell infiltration is increased in the ischemic area following reperfusion, and the presence of ischemic tissue damage facilitates inflammatory cell activation, which contributes to increase vascular and myocardial injury. Increased microvascular permeability, leading to edema and cell infiltrates, further facilitates the final myocardial damage.

It should be underscored that most of the data concerning inflammatory-related coronary microvascular damage in ischemia–reperfusion have been obtained in

experimental studies, the applicability of which to man can be questionable due to differences between species, use of normal animals versus patients with multiple risk factors and co-morbidities, use of different drugs, and differences in time of ischemia and of reperfusion.

4.2 Primary Stable MVA

Primary stable MVA is defined as the occurrence of anginal attacks in relation to effort, in the absence of obstructive CAD, myocardial diseases, and any other significant cardiovascular disease. In these patients CMD is the cause of myocardial ischemia and chest pain. In a subset of cases, these patients also report episodes of chest pain not associated with physical activity.

In clinical practice, primary MVA should be suspected in patients with typical chest pain in whom stress testing is indicative of myocardial ischemia, but coronary angiography shows normal coronary arteries.

In this pure and largely investigated form, MVA includes only patients with angiographically normal or near normal (any detectable stenosis <20 %) epicardial coronary arteries, normal regional and global LV function and dimensions, and no evidence of any other significant cardiovascular or systemic disease [95]. Thus, it should be noted that these patients represent a well-selected subset of the wider heterogeneous population of patients who present with chest pain and normal or "near" normal coronary arteries at angiography. This wider population, indeed, can variably include patients with intermediate stenoses, significant arrhythmic or conduction disorders, LV dysfunction, severe LVH, as well as patients with other well-defined cardiac diseases, such as vasospastic angina or myocarditis (Fig. 4.7).

While CMD can certainly induce angina in various subsets of these patients, the clinical outcome is likely to be largely influenced by the coexistence of other relevant cardiac or systemic diseases, which probably accounts for the different rates of cardiovascular events observed in different studies including heterogeneous groups of patients characterized by the common phenotype of "angina and normal coronary arteries" [96, 97].

The discussion of this section is specifically focused on the well-characterized group of patients with primary MVA, as defined above.

4.2.1 Evidence of Myocardial Ischemia

The most common sign of myocardial ischemia in patients with MVA is the occurrence of transient ST-segment depression on the ECG during exercise stress (Fig. 4.8). ST-segment depression, however, can also be induced during pharmacological stress with adenosine, dipyridamole, or dobutamine, or can be documented during normal daily activities during Holter ECG monitoring. In about

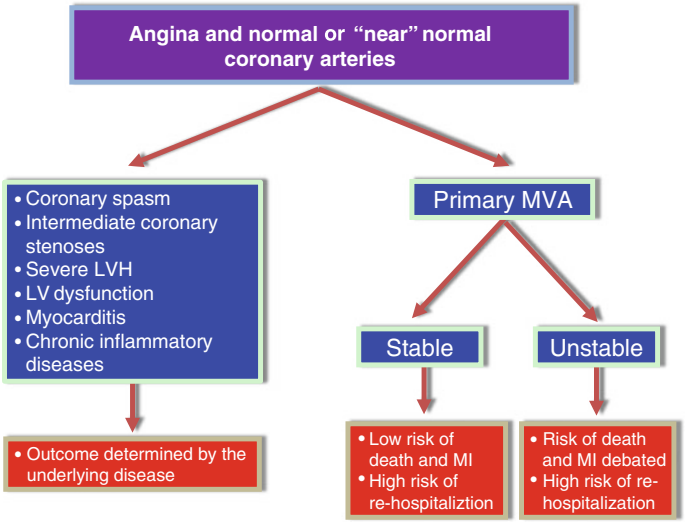

Fig. 4.7 Angina with normal or "near" normal coronary arteries represents a label which identifies a large and heterogeneous group of patients with different causes and mechanisms of angina. Microvascular angina is a well-characterized subset defined by the presence of angina associated with normal coronary arteries and evidence of spontaneous or stress-induced myocardial ischemia, in the absence of other causes of angina chest pain. MI = myocardial infarction

50–60 % of patients with MVA reversible defects during stress myocardial perfusion imaging (exercise or pharmacological) can be demonstrated (Fig. 4.8) [98, 99].

The ischemic nature of these signs has been questioned by some authors [100] due to the fact that more unequivocal markers of myocardial ischemia, such as lactate release in the coronary sinus during pacing stress or induction of reversible LV dysfunction during pharmacological stress tests, have often been undetectable in these patients.

Myocardial lactate production, however, has been found in a significant proportion of patients [101–114] (Table 4.2), although with a striking variability among the different studies, possibly reflecting different inclusion criteria.

Furthermore, oxygen desaturation [115] and pH reduction [116] in the coronary sinus during atrial pacing compatible with myocardial ischemia have been reported in 20–30 % of these patients. Similarly, metabolic changes of myocardial 31-phosphorus metabolism typical of ischemia, and similar to those found in a group of CAD patients, have also been shown in about 20 % of women with MVA using CMR spectroscopy during a mild stressor as handgrip [117]. Finally, Buffon et al. showed a high release of myocardial lipoperoxide products in the coronary sinus following atrial pacing, comparable to that found in a group of CAD patients following balloon occlusion of a coronary artery during PCIs (Fig. 4.9) [118]. Thus, on balance, a careful assessment of available data shows that metabolic

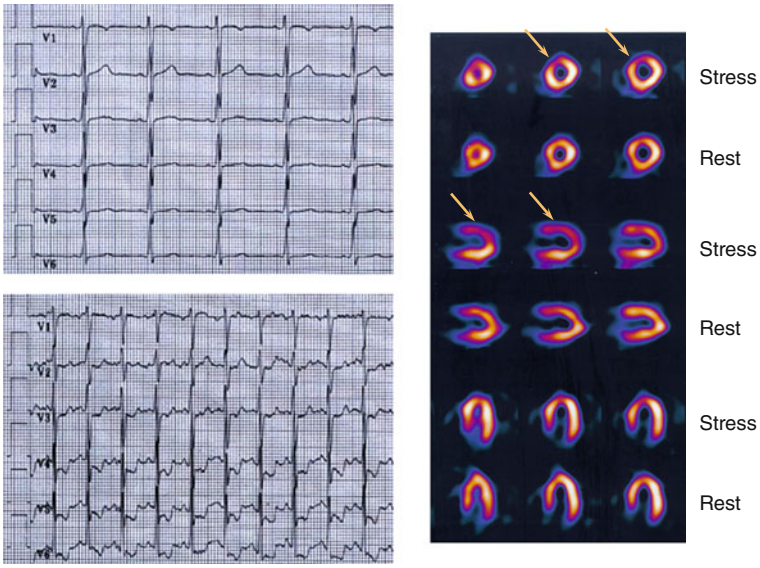

Fig. 4.8 ST-segment depression on the ECG and reversible perfusion defects on myocardial perfusion scintigraphy during exercise stress test in a patient with typical stable MVA (effort angina with normal coronary arteries). Adapted from Lanza et al. [95]

evidence of stress-induced myocardial ischemia can be documented in a proportion of these patients.

Development of LV dysfunction during echocardiographic stress tests, on the other hand, is unusual in patients with MVA [119–121], although it has been demonstrated in some cases [122–124].

Although LV contractile abnormalities and typical myocardial metabolic changes are believed more reliable than electrical changes and perfusion defects for the diagnosis of myocardial ischemia [125], it has been suggested that a plausible explanation for the lack of regional wall motion abnormalities can reside in the fact that CMD is patchily distributed across the myocardial wall [126]. Thus, contractile dysfunction in small myocardial regions characterized by the presence of CMD might be obscured by the normal, or even enhanced, myocardial contraction of interposed myocardial areas. The local release of significant amounts of metabolic vasodilators might limit the impairment of total flow and the degree of metabolic and mechanical 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 [126]. Similar considerations apply to ischemic metabolites: their stress-induced release from the small ischemic areas might indeed go undetected in the coronary sinus, as they are diluted by venous blood draining normal myocardial regions.

This is in sharp contrast with what happens in patients with CAD and flow-limiting stenosis, where stress testing induces ischemia in large LV areas supplied

Table 4.2 Results of studies which assessed myocardial lactate metabolism in patients with angina and normal coronary arteries (NCAs) or typical stable MVA

	Population	No. patients	Abnormal findings (%)	Stress test
Kemp et al. [103]	Angina, NCAs	100	20	Isoproterenol, atrial pacing
Bemiller et al. [105]	Angina, NCAs	14	71	Atrial pacing
Richardson et al. [106]	Angina, NCAs	7	100	Atrial pacing
Boudoulas et al. [108]	Angina, NCAs	29	31	Atrial pacing
Mammohansingh and Parker [107]	CSX	15	27	Atrial pacing
Jackson et al. [109]	Angina, NCAs	35	54	Atrial pacing
Opherk et al. [45, 132]	Angina, NCAs	8	100	Lactate production during atrial pacing
Cannon et al. [143]	Angina <50 % CAD	22	63	Atrial pacing and CPT
Greenberg et al. [110]	Angina, NCAs	27	37	Atrial pacing
Lagerqvist et al. [111]	Angina, NCAs	20	55	CPT, atrial pacing, dipyrdamole
Camici et al. [112]	CSX	12	0	Atrial pacing
Waldenström et al. [113]	Angina, NCAs	7	100	↑ lactate concentration in myocardial biopsy
Nagayama et al. [114]	MVA	7	100	Exercise stress test
Bøtker et al. [104]	CSX	18	0	Atrial pacing

by the obstructed vessel, making easier to detect lactate release and contraction abnormalities (Fig. 4.10) [95].

4.2.2 Evidence of CMD

The pathogenic mechanisms responsible for CMD in patients with stable MVA are likely multiple and heterogeneous, including a variable combination of structural and functional abnormalities which cause impaired microvascular dilatation and/or enhanced constriction. Characterization of CMD might theoretically be very

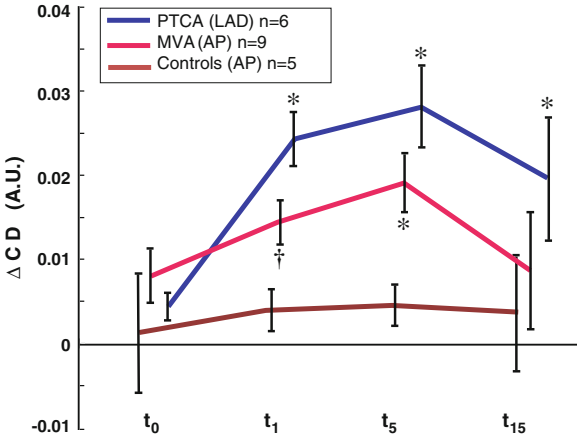

Fig. 4.9 Mean transcardiac arteriovenous conjugated dienes (ΔCDs) in patients with MVA and in controls at baseline (t_0) and 1 (t_1), 5 (t_5), and 15 min (t_{15}) after atrial pacing (AP) and in patients with CAD undergoing coronary angioplasty (PTCA). A consistent and similar increase in cardiac levels of CDs was observed at t_1, t_5, and t_{15} compared with t_0 in both patients with MVA and patients with CAD. No significant changes were detectable in controls. The pattern of cardiac production of CDs at t_1 and t_5 in patients with MVA was remarkably similar to that observed in patients undergoing a brief episode of myocardial ischemia during PCI (PTCA). $^*P < 0.01$ versus t_0; $^\dagger P < 0.05$ versus t_0. Adapted from Buffon et al. [118]

helpful for an appropriate clinical management of patients, but is difficult to obtain in individual patients, due to the requirement of multiple complex tests.

4.2.2.1 Structural Abnormalities

Although data have been discordant and the role of structural microvascular alterations in the pathogenesis of MVA remains to be elucidated, some studies have reported the presence of structural abnormalities, such as intimal thickening and SMC hypertrophy, in myocardial biopsies from MVA patients (Table 4.3) [48, 127–130]. Of note, some studies have suggested that capillary rarefaction might contribute to CMD in these patients [48, 131], but its precise role and its relation with the dysfunction of small coronary arteries need further investigation.

4.2.2.2 Alterations of Endothelium-Independent Vasodilatation

Opherk et al. [132], using the argon wash-out method, were the first to report a blunted increase of CBF following the intravenous administration of the endothelium-independent vasodilator dipyridamole in patients with MVA. The presence of a reduced CFR related to abnormalities of SMC relaxation of small coronary arteries was subsequently confirmed by several studies, using other methods (e.g., PET, intracoronary Doppler wire recording, contrast echocardiography, CMR, TTDE) and stimuli (e.g., adenosine, papaverine) [133–135]. Interestingly, in a recent study reversible myocardial perfusion defects were found at CMR during dobutamine stress test in 56 % of MVA patients [136]. Importantly,

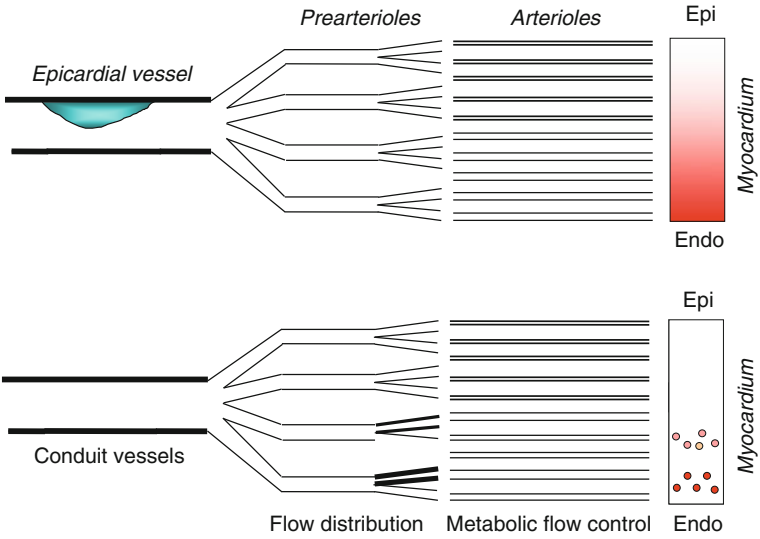

Fig. 4.10 Differences in myocardial ischemia caused by a coronary artery stenosis (*upper drawing*) or coronary microvascular abnormalities (*bottom drawing*). In case of an epicardial stenosis, ischemia involves the myocardial territory subtended by the stenotic vessel and is more severe in the subendocardium (*red* area resulting in impairment of regional contractile function). In case of microvascular dysfunction ischemia 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. Adapted from Lanza et al. [95]

the presence of dobutamine-related perfusion defects correlated with a lower CBF response to adenosine in the LAD coronary artery at TTDE (Fig. 4.11) [136]. In another study concordant results were observed in patients with MVA using contrast echocardiography and TTDE in showing reduced coronary microvascular dilatation in response to adenosine [137].

Of note, two PET studies have shown abnormally heterogeneous myocardial perfusion during dipyridamole administration in patients with MVA as compared to healthy controls, thus supporting the notion of a patchy distribution of CMD [138, 139]. This was also supported by a CMR study, in which CBF response to adenosine in subendocardial layers was not found to be diffuse, but rather limited to 47 % of the regions of interest in which the subendocardium was divided [135].

4.2.2.3 Alterations of Endothelium-Dependent Vasodilatation

An impairment of endothelium-dependent coronary microvascular dilatation has also been shown in several studies in patients with MVA.

Motz et al. [140] first reported a blunted increase of CBF in response to the intracoronary administration of acetylcholine in 14 out of 23 patients with the MVA. Of note, an impaired vasodilator response to the endothelium-independent stimulus dipyridamole was observed in the same study. Similar data were found by

Table 4.3 Main results of studies which assessed histological abnormalities on endomyocardial biopsy specimens in patients with angina and normal coronary arteries or typical MVA

	No. of patients	No. of patients with abnormal findings	Histologic abnormalities
Richardson et al. [106]	15	15	No relevant histological abnormalities
Opherk et al. [45, 132]	18	17	Normal small coronary artery vessels
			Alterations of myocardial mitochondria
Mosseri et al. [127]	6	6	Medial hyperplasia and hypertrophy
			Myointimal proliferation
			Endothelial degeneration
			Swollen capillaries
			Myocardial hypertrophy
			Lipofuscin deposition and patchy fibrosis
Schwartzkopff et al. [48]	14	n.a.	Medial arteriolar hypertrophy Periarteriolar fibrosis
Satake et al. [128]	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. [129]	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. [130]	13	13	Viral genomes in intramural vessels (9 patients) and in cardiomyocytes (8 patients)
			Cardiomyocyte hypertrophy and degeneration
			Interstitial fibrosis
			Focal lymphocytic myocarditis (3 patients).

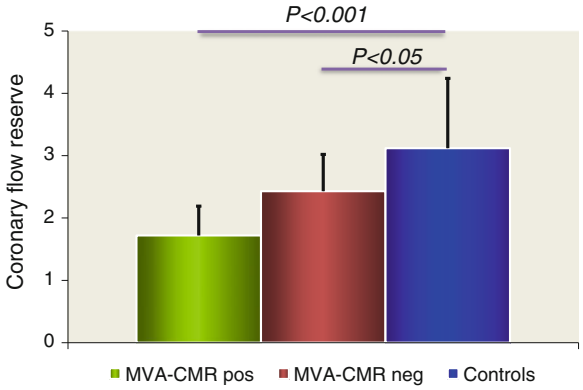

Fig. 4.11 Adenosine CFR, assessed by TTDE in the LAD coronary artery, in 18 patients with MVA and in 10 healthy controls. Patients were divided in two subgroups, based on the presence of reversible regional perfusion defects in the LAD territory at CMR during dobutamine stress test (group MVA/CMR pos, n = 10) or absence of perfusion defects at dobutamine CMR (group MVA/CMR neg, n = 8). CFR showed the lowest value in the MVA/CMR pos group; however, also the MVA/CMR neg group showed a lower CFR compared to controls. Adapted from Lanza et al. [136]

Chahuan et al. [133], who showed an impairment of CBF response to both acetylcholine and papaverine. Impaired acetylcholine-mediated coronary microvascular dilatation in MVA was subsequently confirmed in several other studies [141, 142].

A reduced increase, in CBF in response to CPT, has been reported in a few studies in MVA, using different methods (e.g., thermodilution [143], PET [134] and TTDE) to measure myocardial perfusion. In one of these studies, both the response to CPT and to adenosine as assessed by TTDE was impaired in about half of the patients with MVA while in some of the patients only one of the tests was abnormal [144]. Although in one study the normal response to a pure endothelium-dependent vasodilator substance as substance P has questioned the presence of alterations in endothelium-dependent coronary microvascular dilatation in MVA [145], the evidence that L-arginine (the substrate for NO synthesis) [146] and tetrahydrobiopterin (an NO synthase cofactor) [147] may normalize the dilator response to acetylcholine, suggests that a lower release of NO by endothelial cells is involved in the microvascular abnormalities in at least a subset of these patients.

The presence of alterations in endothelial function in MVA patients is also supported by the evidence of qualitative and quantitative abnormalities in endothelial progenitor cells shown in recent studies [148, 149].

4.2.2.4 Abnormalities in Vasoconstrictor Response

An enhanced response of small coronary arteries to vasoconstrictor stimuli has also been shown in patients with stable MVA. Intravenous ergonovine (0.15 mg) was found to blunt the increase in CBF and induce chest pain during atrial pacing

[143]. Moreover, a reduction of CBF at rest was reported during administration of low-dose acetylcholine [140], hyperventilation, mental stress, and esophageal stimulation [150, 151].

The involvement of vasoconstrictor mechanisms in MVA is also supported by the evidence of increased plasma levels of endothelin-1 [152]. Furthermore, systemic endothelin-1 levels were found to correlate with CFR [153]. Notably, one study demonstrated that in patients with MVA, endothelin-1 levels in the coronary sinus were higher than in aortic blood during atrial pacing, while they were similar in control subjects, suggesting that CMD might be caused, at least in some patients, by enhanced myocardial release of vasoconstrictor substances (Fig. 4.12) [154].

Finally, abnormalities in some cellular pathways potentially able to promote vasoconstriction, have been reported in some studies in patients with MVA, including increased activity of membrane Na^+-H^+ exchanger, which increases intracellular Ca^{2+} availability [155, 156], and increased activity of Rho-kinase, an intracellular enzyme which increases SMC sensitivity to calcium [157].

4.2.3 Causes of CMD

The causes responsible for CMD in stable MVA are heterogeneous. Traditional cardiovascular risk factors (e.g., hypertension, hypercholesterolemia, blood glucose disorders, and smoking) probably play a significant pathogenic role in some patients, due to their ability to impair endothelium-dependent and independent coronary microvascular dilatation, and to enhance coronary microvascular constriction [32, 79, 158, 159]. In fact, in several cases MVA may simply represent

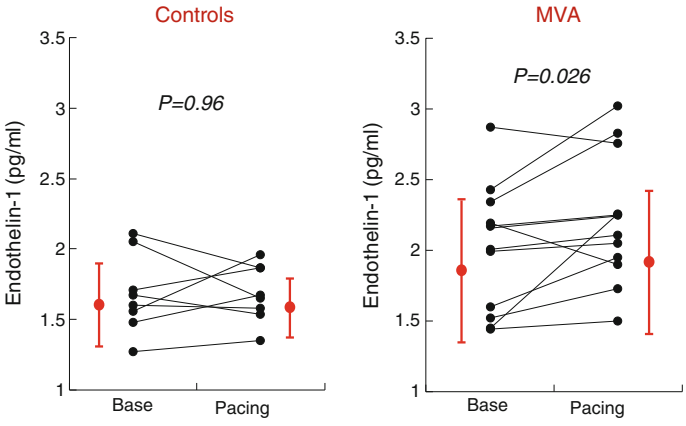

Fig. 4.12 Basal and post-atrial pacing levels of endothelin-1 in the coronary sinus in patients with MVA and in a control group of patients with paroxysmal supraventricular ventricular tachycardia. Adapted from Lanza et al. [154]

the symptomatic phase or phenotype of the well-documented CMD occurring in individuals with risk factors, as discussed above. Several other causes, however, have been proposed to be involved in the CMD of stable MVA.

Estrogen deficiency has been suggested to be a major pathogenic mechanism of stable MVA in female patients, based on the epidemiologic evidence that MVA is more prevalent among peri-menopausal women [160].

Several studies have highlighted the potential role of impaired insulin sensitivity and low-grade inflammation in the pathogenesis of MVA. A hyperinsulinemic response to glucose administration in MVA patients, compared to matched controls, has consistently been demonstrated, mainly using the euglycemic hyperinsulinemic clamp method [161], also suggesting a role for increased concentrations of insulin in CMD [162]. One study reported lower levels of insulin-like growth factor-1, which correlated with an enhanced insulinemic response to glucose administration, suggesting that they might mediate the negative effects of hyperinsulinemia on the microcirculation [163].

A role for inflammation is supported by the consistent detection of higher serum levels of CRP and other markers of inflammation in several studies on MVA [93]. CRP levels have also been shown to correlate with angina symptoms [91], as well as with impairment of endothelium-dependent and endothelium-independent coronary microvascular dilatation [134]. Of note, recent independent data, using TTDE and PET, respectively, showed that high levels of CRP were significant predictors of impaired CFR in MVA patients [144, 164].

Increased adrenergic activity is another pathogenetic mechanism that has been proposed in MVA; this is supported by the faster increase in heart rate during exercise and evidence of sympatho-vagal imbalance as assessed by heart rate variability analysis [165, 166]. Moreover, global and/or regional abnormal cardiac handling of meta-^{123}iodo-benzylguanidine, a norepinephrine analogue, have consistently been observed in patients with MVA, suggesting an impaired re-uptake of norepinephrine by nerve endings, with a likely increase in norepinephrine concentrations in the synaptic cleft [167]. Yet, one study failed to find a correlation between impaired cardiac meta-^{123}iodo-benzylguanidine uptake and coronary microvascular dilatation [168]; interestingly, in the latter study impaired uptake was the strongest predictor of symptomatic status [169].

4.2.4 Enhanced Pain Perception

Several studies have unequivocally shown that a subset of patients with MVA present an increased painful perception of usually innocuous cardiac stimuli, as intracardiac catheter manipulation, heart chamber electrical stimulation, or simple intracardiac saline or contrast medium injection [170–172]. This notion is also supported by the observation that patients with MVA are more susceptible to the algogenic effects of intravenous injection of adenosine, which is known to be the main mediator of ischemia-induced chest pain [173].

The causes and site of this neurophysiologic abnormality remain undefined. The severe abnormalities of efferent cardiac adrenergic fibers [167] suggest possible concomitant alterations of afferent cardiac nerve fibers, and a randomized sham-controlled crossover study showed that the enhanced pain perception can mainly involve the left ventricle [171], thus questioning whether the neural abnormality can be a consequence of microvascular ischemia [174].

Other findings, however, suggest that abnormalities in the central processing of peripheral stimuli may play a primary role at least in some patients [175, 176]. In one study, Rosen et al. [177], using PET, measured the changes in regional cerebral blood flow, as an index of neuronal activity during dobutamine stress test. In patients with MVA, but not in controls, dobutamine caused severe chest pain associated with increased activity in the right anterior insula/frontal operculum junction in the presence of ischemia-like ECG changes, but in the absence of LV dysfunction on echocardiography (Fig. 4.13).

Thus, the symptomatic status of patients with MVA patients appears to be significantly influenced by the variable combination of the severity of CMD and the intensity of pain perception, and might therefore range from severe recurrence of chest pain to totally silent CMD. The importance of these two components in determining angina severity is not limited to MVA. Indeed, patients with obstructive CAD present a similar large inter-individual as well as intra-individual variability in angina severity [178] and similar central abnormalities in pain perception [177].

4.2.5 Diagnosis

Although angina episodes caused by CMD are often indistinguishable from that caused by obstructive CAD, some clinical features of chest pain strongly suggest MVA. The latter is the likely diagnosis when chest pain persists for several minutes after interrupting efforts and/or shows poor or slow response to short-acting nitrates [95, 179].

While ST-segment changes at ECG and perfusion defects at radionuclide studies during exercise or pharmacological stress tests are usually poorly helpful for the differential diagnosis, the induction of typical angina and ECG changes, in the absence of LV wall motion abnormalities during echocardiographic stress is a strong clue to a microvascular origin of symptoms [119, 120, 180].

Another feature that helps in the differential diagnosis is the response of ECG exercise stress testing to sublingual nitrates [179]. Indeed, while the results of the test typically improve after sublingual nitrates in patients with CAD and stable angina, they remain unchanged or may even worsen in patients with MVA. The reasons for these detrimental effects of nitrates in MVA are still largely unknown, but a reduced coronary microvascular dilator response to nitrates seems to play a role [181].

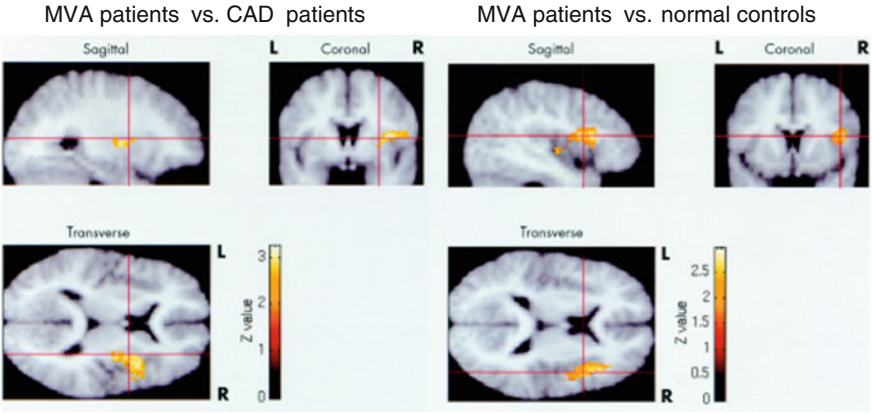

Fig. 4.13 Activation of the right anterior insula during dobutamine-induced chest pain. This feature distinguishes patients with MVA from patients with coronary artery disease *(on the left)* and from normal controls *(on the right)*. The images are obtained by projecting the results derived from the PET data onto a CMR template. The color coding shows the degree of statistical significance (Z score) and the physical extent of those volume elements (voxels) in which regional cerebral blood flow, measured with PET and $H_2^{15}O$, was significantly different between the patient groups for the comparison of high dose dobutamine versus rest. L, *left*; R, *right*. For the stereotactic coordinates, see original article (Adapted from Rosen et al. [177])

In patients with angina and normal coronary arteries epicardial coronary artery spasm should be excluded, in particular, if they present episodes of angina at rest. A provocative test of coronary artery spasm in these cases usually allows the correct diagnosis. Importantly, vasospastic angina and MVA may coexist in some patients, suggesting a diffuse dysfunction of the coronary circulation. This should be suspected when patients continue to suffer from typical effort angina despite full control of coronary spasm with vasodilator therapy.

Although the diagnosis of MVA is usually done in clinical practice after excluding structural and functional abnormalities of epicardial coronary arteries, the diagnosis is more convincing when objective evidence of CMD and, possibly, of myocardial ischemia can be obtained.

Tests to identify CMD should explore both vasodilator and vasoconstrictor activity of coronary microcirculation. In stable MVA patients vasodilator tests are of first-choice, but when they are normal or inconclusive the response to vasoconstrictor stimuli should be assessed.

Coronary microvascular function might be investigated invasively, during coronary angiography, using, for example, intracoronary Doppler recording. Complete evaluation, however, would be complex and time-consuming, and usually presents unjustified adjunctive risks.

Noninvasive tests, instead, are usually free of significant risks and can allow repeated assessment of coronary microvascular function under multiple stimuli.

The ideal noninvasive method should be easy to perform, reproducible, largely available and, possibly, not expensive.

TTDE recording of CBF velocity satisfies several of these criteria; thus, it might be used as a first routine test to identify CMD in patients with suspect MVA. CMD can be reliably diagnosed when CFR is <2.0, with borderline values being between >2.0 but <2.5. Mild CMD, however, might not be identified by this method. CMD can reliably be assessed, however, only in the myocardium subtended by the LAD artery, as other coronary arteries are less easily imaged.

More sophisticated methods for the assessment of myocardial perfusion (contrast echocardiography, CMR, PET) can be utilized in the presence of borderline results, whereas invasive methods appear justified only in the presence of suspected obstructive coronary atherosclerosis.

The objective documentation of myocardial ischemia in MVA patients can be obtained only using some sophisticated diagnostic methods, which, however, cannot be proposed for routine application at present. The demonstration of release of products of lipid peroxidation in the coronary sinus during atrial pacing is a sensitive method to detect myocardial ischemia in patients with MVA [118] although poorly applicable in clinical practice. CMR spectroscopy can detect ischemic abnormalities of phosphorus metabolism during stress [117]; however, this technique is expensive, scarcely available, and can only explore the anterior wall of the heart.

4.2.6 Prognosis

Longitudinal studies in well-characterized patients with typical primary stable MVA have consistently shown that prognosis is good (Table 4.4) [182–186].

In contrast, some studies have in fact suggested that patients with chest pain and normal or near normal coronary arteries with or without evidence of CMD (endothelium-dependent, endothelium-independent, or both) might have an increased risk of cardiovascular events, as compared with matched healthy individuals [96, 97, 187]. However, patients enrolled in these studies cannot be taken as representative of primary stable MVA. Indeed, these studies pooled together heterogeneous groups of patients characterized by the common clinical descriptor of “chest pain and normal coronary arteries,” including those with an acute, unstable clinical presentation [188], evidence of intermediate coronary stenoses, previous coronary interventions, significant LVH or impaired LV function. All these conditions may indeed negatively influence clinical outcome, while the prognostic contribution, in these patients’ subgroups, of the additional presence of chest pain probably related to CMD needs to be to be adequately clarified.

Of note, 20–30 % of patients with well-documented primary stable MVA have progressive worsening of symptoms, with angina becoming more frequent and prolonged over time leading to a poor quality of life. Worsening of symptoms

Table 4.4 Prognostic studies of stable MVA

	No. of patients	FU (years)	MACE
Chauhan et al. [192]	41	3	No
Romeo et al. [184]	30	5	No
Kaski et al. [183]	99	7	No
Radice et al. [185]	30	10.2	No
Bugiardini et al. [186]	42	10.3	1 death
Lamendola et al. [182]	154	11.4	2 CAD

FU follow-up; *MACE* major cardiac events; *CAD* development of obstructive CAD

suggests progression of CMD and/or worsening of enhanced pain perception [170, 189].

The reasons that risk factors cause only CMD and MVA in some patients, whereas in others induce obstructive atherosclerosis are still largely unknown. Recent data, however, suggest that patients with MVA might have some protective factors against the development of obstructive atherosclerosis [95]. For example, a lower platelet activation in response to both physical and mental stress tests has been found in MVA patients as compared to those with obstructive atherosclerosis [190].

4.3 Primary Acute MVA

4.3.1 Definition and Epidemiology

Five to ten percent of patients who present with acute chest pain typical enough to suggest a non-ST elevation acute coronary syndrome (NSTE-ACS) are found to have normal or near-normal coronary arteries at angiography [187]. Interestingly, this proportion can reach 30 % among women with typical NSTE-ACS [191]. In these patients chest pain most frequently occurs at rest, but pain may also be recurrent and precipitated by mild efforts.

The causes of angina in this setting are probably heterogeneous, but CMD might be the underlying pathophysiological mechanism in a sizeable proportion of patients.

The causes of NSTE-ACS with normal coronary arteries have not systematically been investigated; thus the exact role of CMD remains to be established [192–195]. CMD could reasonably be considered the cause for the syndrome when any other potential cause of angina has carefully been excluded and CMD is well documented.

4.3.2 Pathophysiology

Possible mechanisms of ACS with angiographically normal or near normal coronary arteries include CMD, transient thrombosis or embolism [196], spasm of epicardial coronary arteries and myocarditis [197] (Fig. 4.14).

The detection at angiography of slow coronary flow in some patients has been suggested to be a clue to CMD in this setting [194].

The prevalence of slow coronary flow in patients with NSTE-ACS and normal coronary arteries is unknown. Although it is not exclusively found in patients who show this clinical presentation, in one study slow coronary flow was reported in 35 % of patients with ACS without obstructive epicardial arteries [193]. Furthermore, among patients with a history of chest pain and evidence of normal coronary arteries and slow coronary flow at angiography, ACS was the admission diagnosis in 74 % of cases [195], suggesting that slow coronary flow can be a relatively frequent finding in NSTE-ACS patients with normal coronary arteries.

In these patients an increased coronary microvascular constriction in response to cold pressor and/or acetylcholine test has been documented [194, 195], while coronary microvascular dilator response to atrial pacing appeared to be normal, thus confirming that enhanced coronary microvascular constrictor is probably responsible for this clinical presentation of ACS.

Interestingly, the abnormality might persist for several months after the acute clinical syndrome, as shown in 12 patients with slow coronary flow, 10 of whom had undergone urgent admission for ACS, who underwent a follow-up angiography after a median of 10 months from admission.

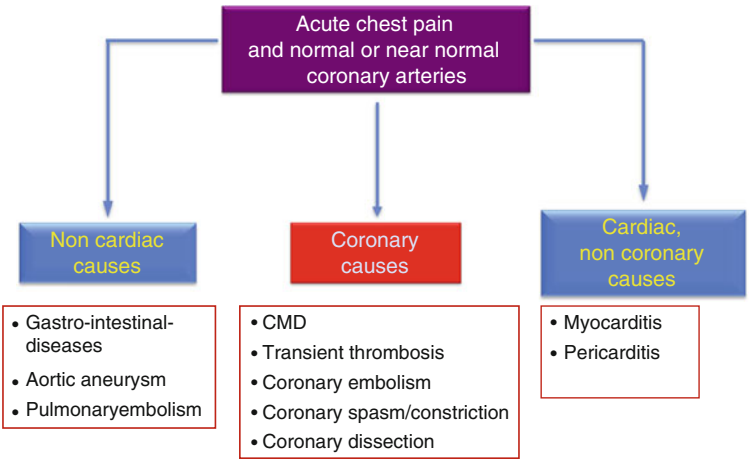

Fig. 4.14 Differential diagnosis of patients with ACS and normal or near normal coronary arteries. These patients constitute a heterogeneous group of patients. Accordingly, the outcome is influenced by the underlying mechanism of disease

The causes of coronary microvascular constriction in unstable MVA remain to be established and are probably multiple.

4.3.3 Diagnosis

In patients with acute chest pain and normal coronary arteries a myocardial ischemic origin of symptoms is suggested by the detection of ST-segment and/or T wave abnormalities on standard ECG and/or mild elevation of serum markers of myocardial damage (in particular troponins).

The diagnosis of acute primary MVA would require the evidence of CMD, together with the exclusion, with appropriate diagnostic work-up, of other possible causes of chest pain, mainly epicardial coronary constriction/spasm, transient coronary thrombosis, and myocarditis.

Enhanced coronary microvascular constriction in these patients can be assessed using vasoconstrictor stimuli (e.g., acetylcholine, ergonovine) during coronary angiography. The induction of typical angina and ST-segment/T wave changes, in the absence of epicardial coronary spasm would be highly suggestive of MVA.

4.3.4 Prognosis

Clinical outcome of patients with acute MVA remains poorly understood. Retrospective assessment of data from clinical trials have shown that in patients admitted for NSTE-ACS with normal or near normal coronary arteries, the rates of death/myocardial infarction and of readmission for NSTE-ACS at 1-year follow-up are 1.2 and 8.4 %, respectively (Fig. 4.15) [187]. However, it is not clear what was the proportion of these patients who actually had acute MVA; accordingly, prognosis of this condition remains to be ascertained [188].

Of note, in a study in which clinical outcome of 41 patients presenting with acute MVA was compared with that of 41 patients with typical stable MVA, no major cardiac events were observed in either group at a mean follow-up time of 36 months [192].

Discordant data have also been reported about symptom recurrence. Beltrame et al. showed that slow coronary flow patients (most with a history of ACS) had a higher rate of urgent readmission for chest pain, compared to those with normal coronary flow [193]. In contrast, Chauhan et al. [192] reported a higher rate of persistence of angina at follow-up in patients with stable MVA compared to those with acute MVA, with a similar proportion of re-hospitalization for chest pain.

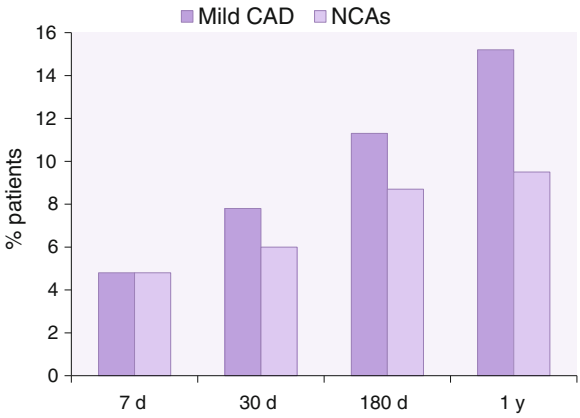

Fig. 4.15 One-year rate of the primary combined cardiovascular end-point (death, myocardial infarction, stroke, coronary revascularization, and re-hospitalization for unstable angina) in patients with normal or near normal coronary arteries enrolled in NSTE-ACS clinical trials. Adapted from Bugiardini et al. [187]

4.4 Microvascular "Variant Angina"

In some patients angina at rest has been found associated with ST-segment elevation, either during spontaneous or provoked episodes, in the absence of any structural or functional abnormality of epicardial coronary arteries, as demonstrated by intracoronary acetylcholine test. This condition seems therefore attributable to diffuse and intense coronary microvascular spasm [198]. The Rho-kinase inhibitor fasudil was found to prevent acetylcholine-induced microvascular spasm in this condition, suggesting that enhanced Rho-kinase activity, favoring hyperactivity of SMCs, might be involved as a pathogenetic mechanism [157].

Overall, this condition seems very rare, and, for this reason, poorly defined in its epidemiologic and clinical characteristics.

4.5 Takotsubo or Stress-Related Cardiomyopathy

Takotsubo cardiomyopathy (also called stress-related cardiomyopathy or apical ballooning syndrome) is usually triggered by an acute intense emotional or physical stress. A detailed discussion of stress-related cardiomyopathy can be found elsewhere [199]. Briefly, patients are usually postmenopausal women (>80–90 %) and usually present with symptoms and signs compatible with an ACS, including typical chest pain and ST-segment elevation or depression, T wave changes, and Q waves on the ECG. In some cases clinical presentation is dramatic, with acute heart failure or cardiogenic shock. Angiography shows normal coronary arteries, whereas left ventricular angiography shows depressed left ventricular function, usually with apical and midventricular akynesia and preserved contraction of basal segments (Fig. 4.16). Despite this severe clinical picture, only minor elevations of troponins and creatine kinase–MB are usually detectable, and clinical course is usually favorable, with symptoms improving in a few days and

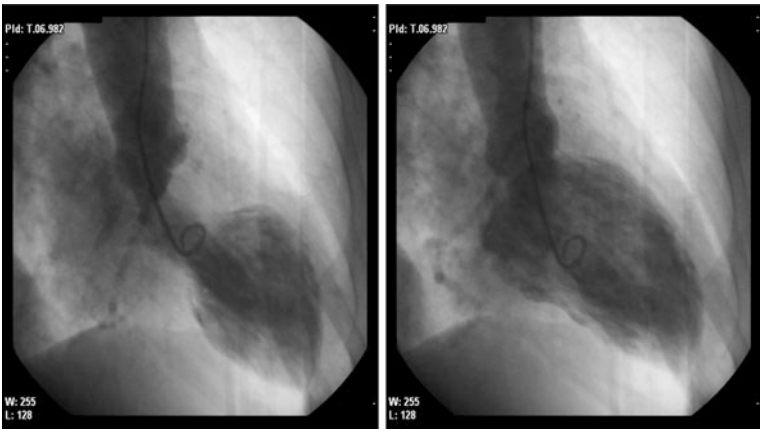

Fig. 4.16 Typical LV angiography in a patient with takotsubo cardiomyopathy. By comparing the end-systolic *(left)* and end-diastolic *(right)* frame, it can be observed a normal contraction of basal LV segments, whereas medial-distal myocardial regions show a severe impairment of contractility, which results in the characteristic aspect of the Japanese "takotsubo" vase

hemodynamic and ECG abnormalities recovering in 1–3 months. Some recent data, however, suggest that recurrence of takotsubo cardiomyopathy may occur in a sizeable proportion of patients at follow-up [200].

The pathogenetic mechanisms of stress-related cardiomyopathy are poorly known. Coronary thrombosis, multivessel epicardial spasm, and myocarditis have been suggested but seem unlikely in the majority of cases. Adrenergic mediated cardiomyopathy has also been suggested due to the usual stress-related onset of the disease. Accordingly, catecholamine levels have been found dramatically increased and endomyocardial biopsy has shown findings of catecholamine-mediated cardiotoxicity in some patients [201]. Of note, the unique distribution of cardiac wall motion abnormalities has been suggested to reflect the variable distribution of adrenergic innervation in the myocardium [201].

Excessive adrenergic activation, however, may not only cause myocardial cell damage, but also induce coronary vasoconstriction [202]. Thus, sustained intense coronary microvascular constriction or spasm, resulting in myocardial ischemia and stunning, might be responsible or contribute significantly to stress-related cardiomyopathy, in at least a subset of patients.

In line with this, one study showed that adenosine administration resulted in a transient improvement of myocardial perfusion associated with an improvement of regional wall motion abnormalities and LV ejection fraction (Fig. 4.17) [203]. Of note, in another study CMD was found to improve in the following few weeks, paralleling improvement of ejection fraction [204, 205]. Thus, although further studies are needed to clarify the exact role of CMD in stress-related cardiomyopathy, early data suggest that intense coronary microvascular constriction is the final common pathway leading to this clinical syndrome.

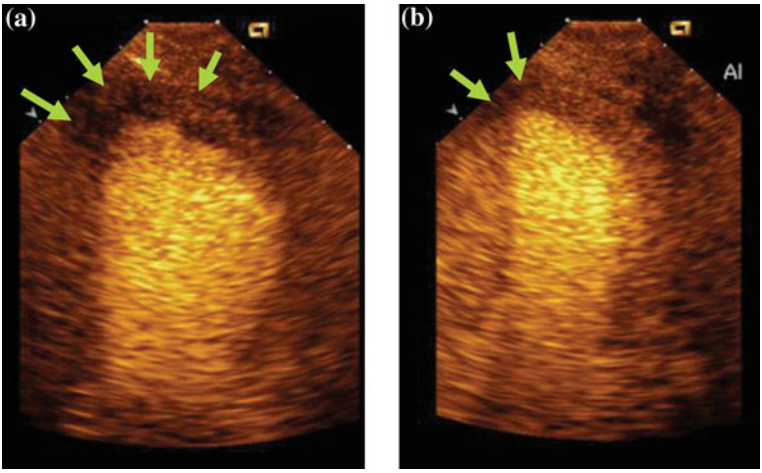

Fig. 4.17 Myocardial contrast echocardiography in a patient with takotsubo cardiomyopathy. **a** A clear perfusion defect is present at baseline within LV apical myocardium (*arrows*). **b** During administration of adenosine, a significant decrease in the extent of the perfusion defect is evident, suggesting severe basal arteriolar microvascular constriction. Adapted from Galiuto et al. [203]

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