Coronary Microvascular Dysfunction

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Foreword by E. Braunwald

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Foreword

Obstructive disease of the epicardial coronary arteries has been accepted as the cause of angina pectoris for more than two centuries, and sudden thrombotic occlusion of an epicardial coronary artery has been well established as the cause of acute myocardial infarction for more than one hundred years. Therefore, attention has focused on these vessels from both a diagnostic and therapeutic viewpoint. In 1958 Sones introduced coronary arteriography, which provided a "road map" of the epicardial coronary arterial tree. This was followed by the development, first of coronary artery bypass grafting by Favaoloro and Effler in 1970 and then of percutaneous coronary angioplasty by Gruntzig in 1977. These three procedures have been refined progressively over the years and have been successfully applied to tens, perhaps hundreds, of millions of patients worldwide. As a consequence, many lives have been extended and their quality improved.

However, the epicardial arteries, often referred to as the conductance vessels, are only one segment of the coronary circulation. These vessels give rise to the pre-arteriolar arteries and the latter divide into the arterioles which in turn feed the capillaries. The pre-arterioles and arterioles constitute the coronary arterial microcirculation. Most of the blood in the coronary arterial system resides in the microcirculation.

The cardiac pump is an aerobic organ which requires continuous perfusion with oxygenated blood to generate the ATP required for contraction. The importance of the coronary microcirculation in the maintenance of appropriate myocardial perfusion has been recognized by physiologists since the middle of the twentieth century. The mechanisms that control the lumina of the vessels in this circulation are complex; malfunction of this mechanism is often referred to as coronary microvascular dysfunction. Despite its obvious importance, this segment of the coronary arterial bed has not gained the attention that it deserves. The information in this field is scattered and there is no convenient reference source that encompasses both the mechanistic and clinical aspects. Therefore, this superb book by Professors Crea, Lanza and Camici is welcome and fills an important gap.

Coronary Microvascular Dysfunction begins with a clear presentation of the anatomy, biochemical and physiologic control of the coronary microcirculation. It presents current theories of the pathogenesis of microvascular dysfunction. Attention is directed to the risk factors for the development of this condition and,

interestingly, many are similar to the familiar risk factors for atherosclerosis of the epicardial arteries, such as hypercholesterolemia, diabetes, smoking and obesity. The authors then describe a variety of non-invasive techniques that have been developed to assess the microcirculation. Primary microvascular angina is an important but still somewhat mysterious illness which is characterized by myocardial ischemia in the absence of epicardial disease. The diagnosis and prognosis of this circulatory disturbance is presented in some detail. Acute microvascular angina represents a challenge to clinicians and includes microvascular variant angina, as well as tako-tsubo (stress-related) cardiomyopathy.

Coronary microvascular dysfunction occurs in many myocardial diseases, including hypertrophic as well as dilated cardiomyopathy, myocarditis and cardiac amyloidosis. When this dysfunction is severe, it aggravates the prognosis of the underlying disease. It has long been puzzling why angina and other evidence of demand-induced ischemia sometimes persist after what is considered to be anatomically successful percutaneous coronary intervention or bypass grafting in patients with epicardial disease. These patients often have associated microvascular dysfunction. Elucidation of its prevention and management require additional investigation.

Coronary Microvascular Dysfunction is a remarkable book which is written entirely by the three authors. This avoids the duplication and sometimes the inconsistencies observed in multi-authored texts. Crea, Lanza and Camici are experienced investigators and clinicians and their complementary abilities shine through. Their book is eminently readable, and guides the reader through the complexities of this field. It will be appreciated by investigators as well as clinical cardiologists. It will stimulate basic research on microvascular dysfunction and will enhance the diagnosis as well as the clinical care of patients with this important condition.

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Contents

Abbreviations

ACS	Acute coronary syndrome
ADMA	Asymmetric dimethylarginine
ADP	Adenosine diphosphate
ATP	Adenosine triphosphate
BMS	Bare metal stent
CABG	Coronary artery by-pass grafting
CAD	Coronary artery disease
CBF	Coronary blood flow
cAMP	Cyclic adenosine monophosphate
CFR	Coronary flow reserve
cGMP	Cyclic guanosine monophosphate
CK-MB	Creatine kinase MB
CMR	Cardiovascular magnetic resonance
CMD	Coronary microvascular dysfunction
CPT	Cold pressor test
CRP	C-reactive protein
CVR	Coronary vascular resistance
DES	Drug eluting stent
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
EDHF	Endothelium derived hyperpolarizing factor
FFR	Fractional flow reserve
GP IIb/IIIa	Glycoprotein IIb/IIIa
GTP	Guanosine triphosphate
HCM	Hypertrophic cardiomyopathy
HDL	High density lipoprotein
LAD	Left anterior descending (artery)
LDL	Low density lipoprotein
LV	Left ventricular
LVH	Left ventricular hypertrophy
MBF	Myocardial blood flow
MBG	Myocardial blush grade
MVO	Microvascular obstruction
NADPH	Nicotinamide adenine dinucleotide phosphate

NOS	Nitric oxide synthase
NSTE-ACS	Non ST elevation ACS
PCI	Percutaneous coronary intervention
PET	Positron emission tomography
STEMI	ST elevation acute myocardial infarction
TIMI	Thrombolysis in myocardial infarction
TnI, TnT	Troponin I/T
TNF	Tumor necrosis factor
TTDE	Transthoracic Doppler echocardiography

Part I
Physiology, Pathophysiology and Assessment of Coronary Microcirculation

Physiology of Coronary Microcirculation

1

1.1 Functional Anatomy of the Coronary Circulation

Understanding the anatomy and physiology of the coronary circulation is the prerequisite for understanding the mechanisms that lead to its derangement. The coronary arterial system is composed of three compartments with different functions, although their precise borders cannot be clearly defined anatomically or histologically (Fig. 1.1).

The proximal compartment is represented by the large epicardial coronary arteries which have a capacitance function and offer little resistance to CBF. During systole, epicardial coronary arteries accumulate elastic energy as they increase their blood content up to about 25 %. This elastic energy is transformed into blood kinetic energy at the beginning of diastole and contributes to the prompt reopening of intramyocardial vessels that are squeezed and closed by systole.

The intermediate compartment is represented by prearterioles. They are characterized by a measurable pressure drop along their length. They are not under direct vasomotor control by diffusible myocardial metabolites because of their extramyocardial position or arterial wall thickness. Proximal prearterioles are more responsive to changes in flow, while distal prearterioles are more responsive to changes in pressure. Their specific function is to maintain pressure at the origin of the arterioles within a narrow range when coronary perfusion pressure and/or flow change.

The distal compartment is represented by arterioles. They are characterized by a considerable pressure drop along their path and represent the site of the metabolic regulation of MBF, as their tone is influenced by substances produced during myocardial metabolism. Their specific function is the matching of myocardial blood supply and myocardial oxygen demand.

Large epicardial arteries have a diameter ranging from a few millimetres to $\sim$500 μm and are visible at coronary angiography. Prearterioles (diameter from $\sim$500 to $\sim$100 μm) and arterioles (diameter <100 μm), that together form the

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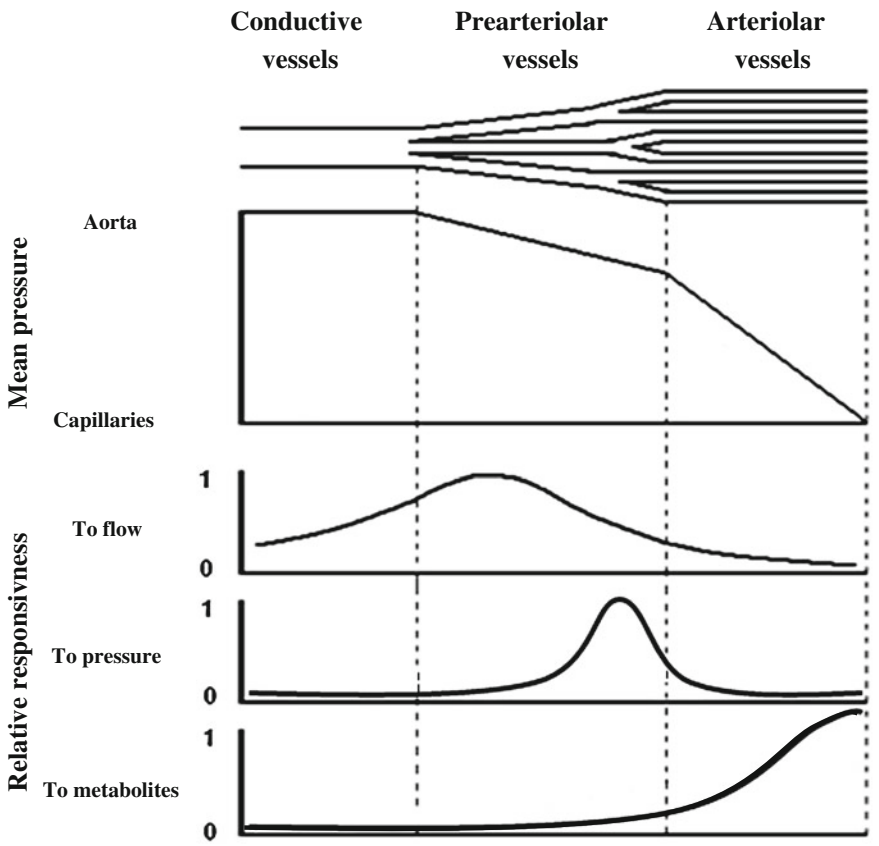

Fig. 1.1 *Top panel.* Schematic representation of the functional subdivision of the coronary arterial system in conductive vessels, prearterioles, and arterioles. The pressure drop along conductive vessels is negligible, that through prearterioles is appreciable and that through the arterioles is the largest one. Prearterioles, by definition, are not exposed to dilator substances derived from myocardial metabolism because of their extramyocardial position and the thickness of their wall. *Bottom panel*. Conductive vessels and, even more, proximal prearterioles are more responsive to flow-dependent dilatation. Distal prearterioles are more responsive to changes in intravascular pressure and are mainly responsible for autoregulation of CBF. Arterioles are more responsive to changes in the intramyocardial concentration of metabolites and are mainly responsible for the metabolic regulation of CBF

microcirculation, are below the resolution of current angiographic systems and hence are not visible at angiography. Notably, each compartment is governed by distinct regulatory mechanisms.

1.1.1 Distribution of Coronary Vascular Resistance in Series

The vascular resistance is distributed in series along the coronary vascular bed, but it also varies in parallel vascular segments in different layers of the ventricular wall. The individual contribution of successive coronary vascular segments to total resistance can be inferred from the progressive drop in mean pressure from the aorta to the coronary sinus. About 10 % of the pressure drop occurs in epicardial coronary arteries, 30 % in prearterioles, 40 % in arterioles, and 20 % from capillaries to large veins (Fig. 1.2) [1, 2]. Notably, vascular resistance and MBF vary considerably during the cardiac cycle. Indeed, because the LV wall compresses intramyocardial vessels during systole, most of the blood flow to the left ventricle occurs during diastole. Thus, the contracting heart obstructs its own blood supply. At peak systole there is even backflow in the coronary arteries, particularly in the intramural and small epicardial vessels. During diastole, the driving pressure is the pressure gradient between the coronary arteries and either the right atrium or the left ventricle (for veins that drain directly into the ventricle). If perfusion pressure is progressively lowered, diastolic blood flow ceases when the coronary driving pressure reaches 40–50 mmHg, the so-called *pressure at zero flow*, which is largely determined by diastolic compressive forces.

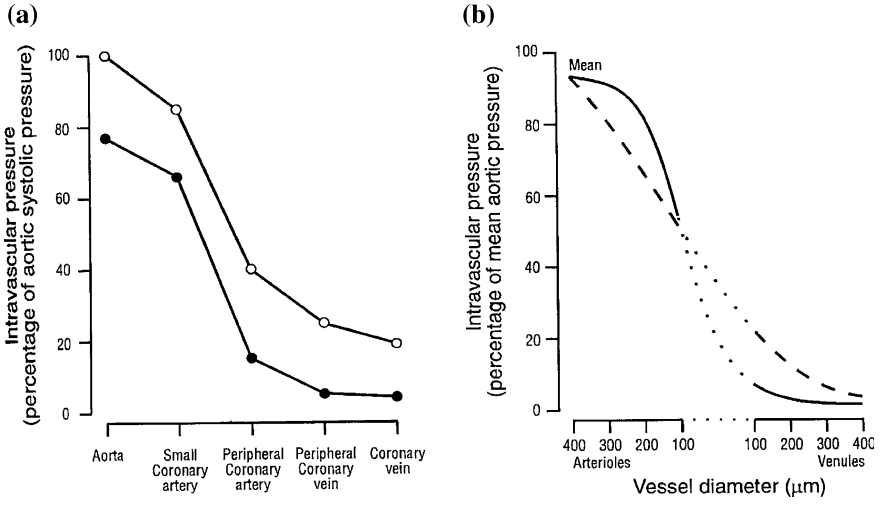

Fig. 1.2 *Panel A.* Systolic (*open dots*) and diastolic (*closed dots*) pressures (expressed as percentages of systolic aortic pressure) in a distal epicardial coronary artery, in a coronary arteriole, in a small coronary vein, and in a large coronary vein of anesthetized dogs. The greatest pressure drop occurs at the level of small coronary arteries. *Panel B.* Mean coronary pressure drop from the aorta to small coronary arteries and veins in a rabbit heart, measured on the surface of the epicardium (continuous line). The greatest pressure drop occurs at the level of arterioles less than 100 μm in diameter. During intravenous dipyridamole infusion (*dashed line*) the pressure drop across prearteriolar vessels increases, indicating insufficient flow-mediated dilatation. Adapted from Klassen et al. [1] and Chillian et al. [2]

1.1.2 Transmural Distribution of Coronary Vascular Resistance

The distribution of coronary resistance in parallel vascular segments in different layers of the ventricular wall can be studied by pressure/flow curves which provide information on the differences in vascular resistance between subendocardial and subepicardial layers of the left ventricle. In nonbeating hearts, maximal conductance is higher in the subendocardial than in the subepicardial layers. Conversely, in beating hearts, maximal conductance is lower in the subendocardial layers because of greater extravascular compressive forces during both systole and diastole. The extravascular systolic compressive forces have two components. The first is intracavitary LV pressure, which is directly transmitted to the subendocardium, but falls off to almost zero at the epicardial surface. The second is vascular narrowing caused by compression and bending of vessels coursing through the ventricular wall from subepicardium to subendocardium (intramyocardial pressure). Hence, during ventricular contraction, subendocardial arterioles become more narrowed, or even occluded, in comparison to those in the subepicardium and, at the onset of diastole, they present a higher resistance to flow, needing a longer time to resume their full diastolic caliber.

Nevertheless, in conscious dogs, under normal resting conditions, the subendocardial flow is higher than the subepicardial flow (with a ratio of about 1.25:1), because of a greater conductance in the subendocardial arterioles. The latter finding is consistent with the higher subendocardial oxygen demand, which is secondary to the greater wall stress in the subendocardial, compared to the subepicardial layers [2]. Under physiologic conditions the sufficiently high perfusion pressure, the sufficiently long diastole, and the adequate systolic expansion of conductive arteries contribute to maintain the subendocardium adequately perfused. However, when perfusion pressure at the origin of arteriolar vessels is reduced compared to that of the aorta (e.g., due to epicardial coronary stenosis or aortic stenosis) perfusion becomes jeopardized earlier in the inner compared to the outer layers of the left ventricle. The inner layers then become even more susceptible to underperfusion if diastolic time is short and in the presence of myocardial hypertrophy (e.g., in patients with aortic stenosis). Of note, selective constriction of subepicardial vessels can influence perfusion pressure in subendocardial vessels and hence subendocardial flow. Accordingly, some vasoconstrictors, such as endothelin and α-adrenergic agonists, or adenosine antagonists, such as theophylline [3], can cause selective subepicardial constriction while improving subendocardial perfusion.

1.1.3 Mechanisms Regulating Myocardial Blood Flow

The term MBF is currently used to indicate myocardial perfusion, i.e., the volume of blood per unit of time per unit of mass of cardiac tissue (e.g., ml of blood per minute per gram of tissue) [4]. The term MBF should be kept distinct from CBF,

which is generally used to indicate the volume of blood that flows along a vascular section over a time unit (ml/min).

Several methods can be used to measure CBF, based, for instance, on the use of thermodilution [5] and Doppler catheters [6, 7], while measurement of MBF can be obtained by measuring the amount of a substrate (e.g., oxygen) supplied to myocardial tissue per unit of time. The latter can be calculated as $C_a \times$ CBF, where C_a is the arterial blood concentration. PET is currently the most accurate and reproducible noninvasive technique for measuring both global and regional MBF [8] (Chap. 3).

The measurement of MBF has been achieved in animal experiments in the past 40 years mainly by measuring the distribution of microspheres under the basic principle that their deposition is proportional to the flow per unit mass of tissue at capillary level. Radionuclide imaging techniques have enabled the assessment of nutritive tissue perfusion in man as opposed to the measurement of epicardial coronary flow by either a thermodilution or a Doppler catheter. Before the advent of PET imaging technology, directional changes in regional MBF could only be assessed by the use of either planar gamma scintigraphy or single-photon emission computed tomography. Quantification of MBF with these techniques was rendered impossible by the physical limitations of the imaging systems and the available tracers. The use of PET overcame the physical limitations of previously available imaging systems by providing the means for accurate attenuation and scatter correction, thus limiting the inaccuracies in the measurement of the concentration of radiolabeled tracers in the organ of interest. As PET technology has advanced and rapid dynamic imaging has become possible, quantification of MBF has been achieved following the development of suitable tracer kinetic models.

1.1.3.1 Response to Changes in Flow

The shear stress, the tractive force that acts on the vascular wall, is proportional to blood shear rate or velocity and to viscosity.[1]

Arteries exhibit an intrinsic tendency to maintain a constant shear stress, despite changes in blood flow velocity and viscosity. Indeed, very high or very low shear stress may jeopardize the interaction between blood elements and the endothelium. In the absence of changes in perfusion pressure, variations of flow in epicardial coronary arteries can be achieved by intracoronary injection of arteriolar vasodilators such as adenosine. Angiographic studies in man have shown that epicardial coronary arteries dilate in response to an increase in blood flow and that the increase in coronary diameter is proportional to the increase in flow, thus maintaining shear stress constant [9].

Flow-mediated dilatation occurs also in proximal prearterioles during the dilatation of distal prearterioles occurring in response to a reduction in perfusion pressure and during arteriolar dilatation in response to increased myocardial

[1] Shear stress of blood flow (τ) is calculated as: $\tau = \mu(\theta u/\theta y)$, where μ is blood viscosity, u blood flow velocity and y the distance from the vessel wall, with $\theta u/\theta y$ representing the local shear velocity.

oxygen consumption or following myocardial ischemia. In this setting, flow-mediated dilatation serves mainly to minimize any fall in pressure along the course of proximal prearterioles during dilatation of more distal vessels [10].

1.1.3.2 Mechanisms of Flow-Mediated Dilatation

Flow-mediated dilatation is determined by vasodilators released by endothelial cells in response to an increase in shear stress, in particular NO, EDHF, and prostacyclin. EDHF causes hyperpolarization and relaxation of smooth muscle cells by opening K^+ channels, whereas prostacyclin causes relaxation by activating adenylate cyclase, which leads to the formation of cyclic adenosine monophosphate (Fig. 1.3).

NO is synthesized from the amino acid, L-arginine, by NOS. The NOS endothelial isoform (eNOS, or NOS III), is constitutive and is predominantly, although not exclusively, found in endothelial cells. eNOS is a highly regulated protein at both transcriptional and functional levels. Full function of the enzyme is dependent on its existence as a dimer, disassociation from the membrane protein caveolin, activation through calcium–calmodulin, and sufficient supply of substrate (L-arginine) and co-factors, most notably tetrahydrobiopterin. The normal coronary endothelium causes vasodilatation as eNOS produces NO, which induces relaxation of vascular smooth muscle via an increase in cGMP and consequent opening of calcium-activated potassium channels, possibly ATP-dependent K-channels. Endothelial production of NO can be triggered by specific receptors (e.g., muscarinic, bradykinin, and histamine receptors) or by mechanical deformation resulting from shear forces or pulsatile strain caused by blood flow.

The contribution of NO to maintenance of CBF has been studied by administering analogs of L-arginine that act as competitive inhibitors for NO synthesis. NO appears to play a key role in flow-mediated relaxation of the large epicardial vessels, as the latter is prevented by N^g-monomethyl-L-arginine, a specific inhibitor of NO synthesis [11].

The contribution of EDHF to endothelium-dependent relaxation varies as a function of the size of the artery; indeed, it is more pronounced in resistance vessels and might play an important role in prearteriolar flow-mediated dilatation [12]. In contrast, the contribution of prostacyclin to flow-mediated relaxation appears to be modest. Yet, prostacyclin-mediated relaxation might be important in the presence of endothelial dysfunction with reduced bioavailability of NO, when it may provide a useful compensatory mechanism [13].

1.1.3.3 Response to Changes in Perfusion Pressure: Autoregulation

When metabolic requirements do not vary, the coronary circulation exhibits an intrinsic tendency to maintain blood flow at a constant rate despite changes in perfusion pressure, a mechanism known as autoregulation.

Variations of coronary perfusion pressure in the beating heart, in the presence of unaltered myocardial metabolic requirements, can be achieved by perfusing the coronary circulation independently from the aorta, so that aortic pressure

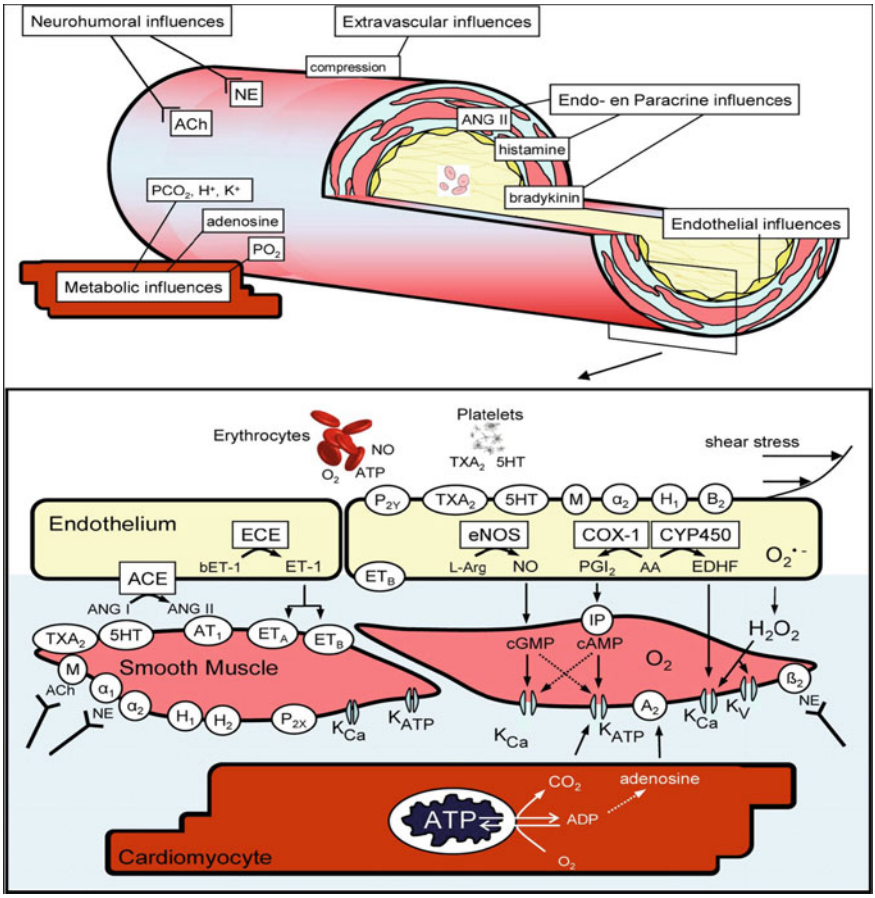

Fig. 1.3 Schematic drawing of a coronary arteriole and the various factors that influence coronary vasomotor tone and diameter. PO_2, oxygen tension; TxA_2, thromboxane A_2 (receptor); 5HT, 5-hydroxytryptamine receptor; P_{2X} and P_{2Y}, purinergic receptor subtypes 2X and 2Y that mediate ATP-induced vasoconstriction and vasodilatation, respectively; ACh, acetylcholine; M, muscarinic receptor; H_1 and H_2, histamine receptors type 1 and 2; B_2, bradykinin receptor subtype 2; ANG I and ANG II, angiotensin I and II; AT_1, angiotensin II receptor subtype 1; ET, endothelin; ET_A and ET_B, endothelin receptor subtypes A and B; A_2, adenosine receptor subtype 2; $ß_2$, $ß_2$-adrenergic receptor; β_1 and α_2, α-adrenergic receptors; NO, nitric oxide; eNOS, endothelial NO synthase; PGI_2, prostacyclin; IP, prostacyclin receptor; COX-1, cyclooxygenase-1; EDHF, endothelium derived hyperpolarizing factor; CYP_{450}, cytochrome P_{450} 2C9; K_{Ca}, calcium-sensitive K channel; K_{ATP}, ATP-sensitive K channel; K_V, voltage-sensitive K channel; AA, arachidonic acid; L-Arg, L-arginine; O_2^-, superoxide. Receptors, enzymes, and channels are indicated by an oval or rectangle, respectively. Adapted from Jones et al. [10]

(a determinant of myocardial oxygen consumption) remains constant when coronary artery pressure is varied. In this setting, pressure/flow curves show that when perfusion pressure is varied, flow remains almost constant over a wide range of pressures, i.e., from 60 to 120 mmHg (Fig. 1.4). The level at which flow remains

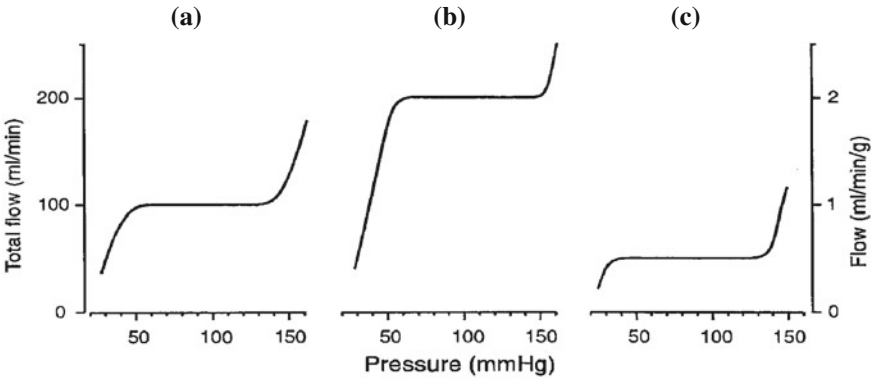

Fig. 1.4 Autoregulation of CBF (total flow) under normal (**a**), high (**b**) or low (**c**) oxygen consumption. In the presence of autoregulation, coronary flow is determined by the level of myocardial oxygen consumption, by the oxygen saturation of arterial blood and by neurohumoral modulation of coronary vasomotor tone. Autoregulation fails when perfusion pressure either decreases or increases beyond the range of pressures within which autoregulation acts

constant is determined by the level of myocardial oxygen consumption; when this is low the plateau of flow is low, when oxygen consumption is high the plateau is high. Notably, for decreasing perfusion pressures, autoregulation is better maintained in the subepicardium than in the subendocardium, which, therefore, is more susceptible to the detrimental effects of very low perfusion pressures.

The mechanism responsible for autoregulation is probably a myogenic response of distal prearteriolar vessels: they dilate in response to a reduction of perfusion pressure and constrict in response to an increase of perfusion pressure (Fig. 1.5) [14]. Myogenic responsiveness in the coronary microcirculation, independent of the endothelium, has been directly demonstrated in vivo in vessels that contribute to coronary microvascular resistance, and is more pronounced in subepicardial than in subendocardial prearterioles. The mechanisms of the myogenic constriction in response to an increase in distending pressure are not well understood. They probably involve activation of a nonselective cation channel and subsequent influx of Na^+, K^+, and Ca^{2+} ions. The consequent membrane depolarization enables the recruitment of voltage-dependent calcium channels, which contribute to the increased calcium inflow. Furthermore, stretch initiates hydrolysis of membrane phospholipids, a process which contributes to increased intracellular calcium release. Myogenic contraction is ultimately caused by activation of myosin light chain kinase [15].

1.1.3.4 Response to Changes in Myocardial Oxygen Consumption: Metabolic Regulation

Energy production in the normally functioning heart is primarily dependent on oxidative phosphorylation. Because of this dependence on oxidative energy production, increases of cardiac activity require almost instantaneous parallel

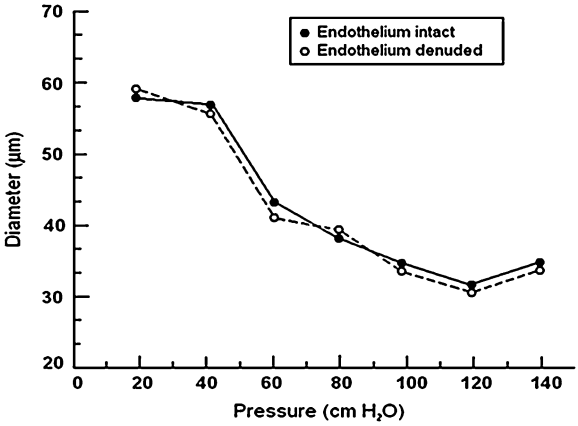

Fig. 1.5 Effects of increasing perfusion pressure in a canine coronary prearteriole. Progressive prearteriolar constriction was observed at increasing pressures. After mechanical denudation of the endothelium, spontaneous tone and myogenic responses were preserved. Thus, endothelium-independent, pressure-induced myogenic constriction is the main determinant of coronary autoregulation in arterioles. Adapted from Kuo et al. [14]

increases of oxygen availability. In contrast to skeletal muscle, which is quiescent with very low metabolic requirements during resting conditions, the heart has high oxygen consumption already at rest (20-fold higher than that of skeletal muscle). As an adaptation to the high oxygen demands, the heart maintains a very high level of oxygen extraction already under resting conditions, so that 70–80 % of the arterially delivered oxygen is extracted, compared with only 30–40 % in skeletal muscle. Therefore, any further increase in oxygen demand can only be met by augmenting myocardial perfusion. The coronary circulation is able to supply the myocardium with blood for its widely and rapidly changing needs. It can supply oxygen in amounts up to five times the baseline consumption, and carries substrates and removes metabolic waste products, all to ensure optimal working conditions for myocardial cells. This demanding function takes place in an organ that generates its own perfusion pressure.

Under basal resting conditions, the tone of coronary resistive vessels is high and CBF is at its lowest level. This intrinsically high resting tone provides the coronary circulation with the ability to increase flow by reducing vasomotor tone when myocardial oxygen consumption increases, a mechanism known as functional hyperemia. This metabolic control of CBF is very precise and is fundamental for adequate myocardial oxygen supply.

For any level of myocardial oxygen consumption, average CVR, and hence flow, can be modulated by a wide variety of neurotransmitters, by autacoids produced by the vessel wall, by blood-borne substances, and by drugs acting on different segments of resistive vessels. Neurotransmitters are released at nerve endings. Autacoids are generated locally by endothelial cells (NO, prostaglandins, EDHF, and endothelin) or by adventitial cells (histamine, kinins, and

leukotrienes), while others are released by circulating platelets (thromboxane A_2, serotonin) or carried in the bloodstream (adrenaline). Notably, when myocardial oxygen consumption remains constant, any change in flow caused by neurohumoral modulation is mirrored by a change in oxygen extraction, so that vasodilatation or constriction are associated, respectively, with a proportional increase or decrease in coronary sinus PO_2 and oxygen saturation [16].

1.1.3.5 Determinants of Myocardial Oxygen Consumption

The most important determinant of oxygen consumption is cardiac work, as in the nonbeating heart oxygen consumption is only 15–20 % of that under normal resting conditions. Oxygen consumption, as in other tissues, is also influenced by the type of substrate used; indeed, it is higher when using fatty acids (which have a respiratory quotient of 0.7) than when using carbohydrates (which have a respiratory quotient of 1.0). Furthermore, myocardial oxygen consumption varies among myocardial layers being about 15–20 % higher in the subendocardium than the subepicardium.

The determinants of cardiac work, and therefore of myocardial oxygen consumption, include heart rate, aortic pressure, myocardial inotropism, and cardiac preload. In most cases, these factors vary concurrently in influencing myocardial metabolic activity. However, when they are artificially separated under experimental conditions in a canine model, they rank in the following order [17].

- *Heart rate*. Myocardial oxygen consumption approximately doubles during atrial pacing when heart rate is doubled. However, this is probably an overestimation, as during pacing (but not during exercise) the stroke volume decreases, also causing a decrease in ventricular volume and wall tension.
- *Aortic pressure*. Myocardial oxygen uptake approximately doubles as mean aortic pressure is increased from 75 to 175 mmHg at constant heart rate and stroke volume.
- *Myocardial inotropic state*. Myocardial oxygen consumption increases by about 30 % when d*P*/dt (the first derivative of systolic LV pressure over time) is doubled by extrasystolic potentiation or by noradrenaline administration at constant heart rate, aortic pressure, and cardiac output.
- *Preload*. Myocardial oxygen consumption increases for any increase in preload, which is proportional to LV diastolic tension (pressure and volume).

An accurate measurement of myocardial oxygen consumption requires the determination of CBF and of arterial-venous difference in blood oxygen content (which is generally achieved by sampling blood simultaneously from the aorta and the coronary sinus). As coronary sinus sampling is required, and as the measurement of coronary flow presents considerable methodological problems, a number of indirect indices have been proposed. Of these, the rate-pressure product (i.e. the product of systolic pressure times heart rate) is the simplest and yet it correlates closely in a wide range of values with measured changes in myocardial oxygen consumption [18].

1.1.3.6 Mechanisms of Metabolic Regulation of Coronary Blood Flow

Flow control under physiological conditions

A typical feature of blood flow adaptation to exercise is an only small or even absent change of coronary venous pO_2. Such a feature may be explained by feed-forward control of CBF. Metabolites that control blood flow in a feed-forward manner must be produced at a rate in proportion to oxidative metabolism. Examples for such metabolites are carbon dioxide, which is generated in decarboxylation reactions of the citric acid cycle, and reactive oxygen species, which are formed in the respiratory chain in proportion to oxygen consumption [19].

Carbon dioxide is produced in proportion to oxygen consumption and results from the pyruvate dehydrogenase reaction (pyruvate → acetyl coenzyme A) and further decarboxylation reactions in the citric acid cycle (tricarboxylic acid cycle). Despite changing substrate preference (fatty acids, lactate, and glucose), the respiratory exchange ratio is typically maintained between 0.8 and 0.9 in the heart [20, 21]. Increased concentrations of carbon dioxide result in an increase of proton concentration, which likely constitutes the direct stimulus for coronary vasodilatation [22]. Increases in coronary arterial pCO_2 result in arteriolar vasodilatation, while decreases in coronary arterial pCO_2 result in arteriolar vasoconstriction [23]. However, the role that increased carbon dioxide production plays in connecting myocardial oxygen consumption to CBF is not entirely clear. Several studies have addressed the potential involvement of adenosine in the flow response toward increased arterial pCO_2. Hypercapnia with arterial pH-values of 7.1 to 6.8 enhanced coronary flow and adenosine release in rabbit heart, whereas inosine and hypoxanthine release remained unchanged [24].

Similar to the production of CO_2, the production of H_2O_2 is a feed-forward response in that the production of this reactive oxygen species is directly linked to myocardial oxygen consumption [25].

H_2O_2 is generated by two-electron reduction of oxygen. This can occur in one enzymatic step, or more typically it involves generation of the intermediate reactive oxygen species, superoxide. Multiple cellular sources are capable of generating superoxide, including NADPH oxidase (NADPH oxidase 1 and 4 in the endothelium), xanthine oxidase, cyclooxygenase, uncoupled eNOS, mitochondria, lipoxygenases, and some CYP450 enzymes. Cellular free radical generation can stimulate other intracellular signaling pathways, making it difficult to determine which free radical source is responsible for superoxide increase [26]. With regard to the origin of H_2O_2 associated with metabolic vasodilatation, there is evidence supporting its endothelial mitochondrial generation. Indeed, superoxide is rapidly converted to H_2O_2 by the action of superoxide dismutase, and the mitochondria possess high activities of both cytosolic superoxide dismutase 1 between the inner and outer membranes, and mitochondrial superoxide dismutase 2 in the matrix; thus any superoxide that is generated will leave the mitochondria as H_2O_2 (Fig. 1.6) [27]. The vasodilator properties of H_2O_2 have been well appreciated for a number of years. Although whether the vasodilator effects of H_2O_2 are endothelium-dependent or endothelium-independent is controversial, there is no

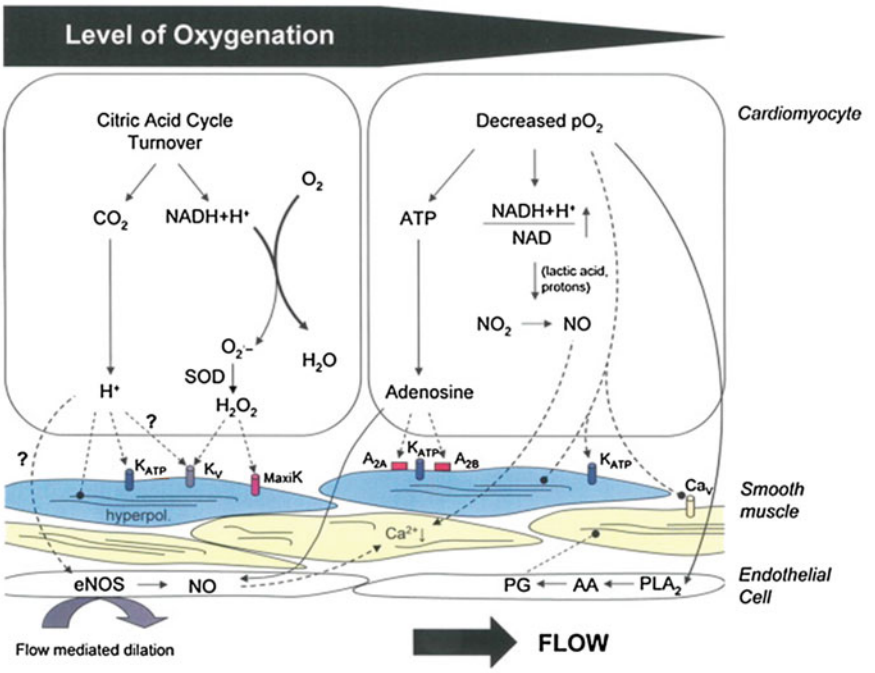

Fig. 1.6 Current concepts of metabolic CBF regulation. The regulation of CBF during physiological conditions is shown on the *left* (normal myocardial oxygenation), whereas the regulation of CBF during pathological conditions is shown on the *right* (decreased myocardial oxygenation). Biochemical reactions and metabolic interaction are indicated by solid *arrows*, links to effectors are indicated by broken *arrows*. *Blue* and *yellow* colors indicate the primary response at the level of smooth muscle cells, membrane hyperpolarization, and decreased cytosolic calcium concentration, respectively. Arrows indicate activation, closed pointed ends indicate inhibition. PLA_2: phospholipase A_2, AA: arachidonic acid, PG: prostaglandins. Adapted from Deussen et al. [19]

question that H_2O_2 produces robust dilatation of coronary resistance vessels. H_2O_2-induced dilatation is principally mediated by 4-aminopyridine sensitive ion channels, presumably Kv channels, although 4-aminopyridine blocks channels other than Kv. The coronary dilator effect of H_2O_2 might also be mediated by the large conductance Maxi-K channel or by prostanoids. As H_2O_2 is a reactive oxygen species, it is likely that its vasoactivity is due to its actions as an oxidant, presumably on thiol groups, which are sensitive to the actions of oxidants. This view was supported by the observation that H_2O_2-induced dilatation is reversed by thiol reducing compounds, such as dithiothreitol [19].

Flow control during tissue hypoxia

A decrease of arterial pO_2 is probably the most powerful stimulus for coronary vasodilatation [23]. Cardiac hypoxia occurs under a variety of pathological conditions. Brief periods of hypoxia may be related to reversible ischemia

(e.g., transient flow impairment or exercise related angina). Chronic cardiac hypoxia may be related, for example, to anemia, or high altitude exposure. For methodological reasons, it is difficult to establish whether the resulting decrease of CVR is mediated by the fall in oxygen pressure per se or by a consecutive change in the availability of vasoactive metabolites. It should be stressed again, that a critical fall of myocardial oxygenation does not usually occur under physiological conditions, even during conditions of strenuous exercise [28].

In 1963, Berne [29] and Gerlach et al. [30]. independently proposed that adenosine may be an important regulator of CBF in response to hypoxia. Adenosine is formed by degradation of adenine nucleotides under conditions in which ATP utilization exceeds the capacity of myocardial cells to resynthesize high energy compounds (a process dependent on oxidative phosphorylation in mitochondria). This results in the production of adenosine monophosphate, which is converted to adenosine by the enzyme 5′-nucleotidase. Adenosine then diffuses from the myocytes into the interstitial fluid, where it exerts powerful arteriolar dilator effects through the stimulation of A_2 adenosine receptors on smooth muscle cells. Several findings support the critical role of adenosine in the metabolic regulation of blood flow. Indeed, its production increases in cases of imbalance in the supply/demand ratio of myocardial oxygen, with the rise in interstitial concentration of adenosine paralleling the increase in CBF. Inhibition of adenosine, however, does not reduce the magnitude of functional hyperemia entirely, thus suggesting that other substances can play a critical role [31].

Several studies have shown an increase of prostaglandin release from isolated vessel preparations in response to a decrease of pO_2 [32–34]. Under hypoxic conditions, endothelial phospholipase A_2 may respond to an increase of cytosolic calcium enhancing the production of the prostaglandin precursor arachidonic acid [35]. While evidence supports a role of prostaglandins in the regulation of epicardial coronary vessel diameter, there is controversy about whether prostaglandins significantly contribute to the control of CBF (which is largely controlled via resistance vessels). In pig, inhibition of cyclooxygenase results in a fall of CBF under baseline physiological conditions [25]. However, the increase in CBF during exercise was unaffected. Similarly, in dog CBF adaptation during treadmill exercise was unchanged in the presence of cyclooxygenase blockade [36]. Hypoxic coronary vasodilatation in isolated perfused guinea pig heart was proposed to be mediated in part by NO [37]. Under physiological in vivo conditions, the application of a NOS inhibitor reduced baseline coronary venous pO_2, but did not affect flow adaptation during exercise [25]. Aside from production via eNOS, cardiac NO production may result from nitrite reduction (enzymatically or non-enzymatically) under conditions of a low pH or during severely anaerobic conditions. Such conditions occur only during severe ischemia and thus the related mechanisms of NO production are likely not relevant for instantaneous metabolic CBF regulation under physiological conditions, when coronary pO_2-values are maintained.

It is worth emphasizing that the response of the coronary circulation to changes in myocardial oxygen consumption triggers a complex and integrated

microvascular response. The arterioles dilate in response to the release of myocardial metabolites and this dilatation decreases both resistance in the overall network and pressure in distal prearterioles, which in turn induces myogenically sensitive vessels to dilate. Furthermore, dilatation of distal prearterioles and arterioles results in an increase in shear stress and triggers flow-dependent dilatation in larger prearterioles and in conductance arteries.

Thus, as proposed by Chilian [38], the coronary circulation matches blood flow with oxygen requirements by coordinating the resistances within different microvascular domains, each governed by distinct regulatory mechanisms. Such integration appears advantageous, because the system does not rely on a single mechanism of control. Accordingly, if a pathological process renders a mechanism dysfunctional, other mechanisms, at least to some extent, can compensate for it, although the price to pay is a reduction of regulatory mechanism reserve.

1.1.4 Neural and Bio-Humoral Regulation of the Microcirculation

Cardiac myocytes and the coronary circulation are innervated by both sympathetic and parasympathetic fibers which constitute the autonomic nervous system [39, 40]. The autonomic outflow is controlled by regulatory centers in the midbrain, hypothalamus, pons, and medulla which integrate inputs from other brain areas as well as afferent stimuli from the periphery. The efferent signals follow descending pathways in the lateral funiculus of the spinal cord that terminate on cell bodies in the intermediolateral and intermediomedial columns. Sympathetic fibers leave the spinal cord at T1-L2/L3. These myelinated preganglionic fibers synapse in the paravertebral ganglia while small unmyelinated postganglionic fibers connect with body organs [41]. Both sympathetic and parasympathetic innervations play an outstanding role in the regulation of CBF. Small coronary arteries and arterioles, that are the principal determinants of CVR [42], receive abundant autonomic innervation [43].

1.1.4.1 Sympathetic Control

Sympathetic innervation to the heart is provided by fibers originating from the superior, middle and inferior (stellate) cervical ganglia and the first 5 thoracic ganglia of the sympathetic nerve chain. These fibers branch and terminate as sympathetic nerve endings in atrial and ventricular, as well as vascular, tissues. The main neurotransmitter of the sympathetic system is noradrenaline that, after its release by sympathetic nerve terminals, can bind to a series of different postsynaptic receptors (α and β) whose activation determines the stimulatory and inhibitory effects of the system.

Under normal circumstances, sympathetic activation results in an increased heart rate (chronotropic effect), a more forceful contraction (inotropic effect) and enhanced atrioventricular conduction (dromotropic effect).

Direct sympathetic vasodilatation of the coronary vessels is an attractive hypothesis for matching coronary flow and oxygen consumption during exercise, because in this case the same stimulus responsible for increasing oxygen consumption will simultaneously increase oxygen delivery. Thus β-adrenoceptor (β_2 subtype) vasodilatation is a "feedforward" mechanism that does not require an error signal such as decreased cellular oxygen tension [44, 45]. The dominant site for β-vasodilatation is in small arterioles. The potential for coronary β-adrenoceptor vasodilatation can be seen most clearly in isolated blood vessels. Small coronary vessels dilate in response to epinephrine and norepinephrine, even without prior α-adrenoceptor blockade [46–48]. Thus, the net effect of sympathetic stimulation on coronary resistance vessels appears to be vasodilatation. However, demonstration of β-adrenoceptor coronary vasodilatation during exercise is difficult because of the simultaneous presence of a large metabolic vasodilatation. The key to separating these effects is to produce metabolic vasodilatation free from direct vascular catecholamine effects. In conscious animals this has been achieved by exercise during simultaneous α- and β-adrenoceptor blockade [49, 50]. These responses are then compared with exercise during α-adrenoceptor blockade, a situation that includes both metabolic vasodilatation and β-adrenoceptor vasodilatation. Thus, the difference between these two conditions will reflect the influence of β-adrenoceptor vasodilatation. When coronary venous oxygen tension is plotted versus myocardial oxygen consumption in these experiments, it can be seen that venous oxygen tension is considerably lower at any given myocardial oxygen consumption when both α-and β-adrenoceptors are blocked. The conclusion is that coronary arteriolar β-receptors contribute substantially to exercise vasodilatation.

Sympathetic α-adrenoceptor-mediated coronary vasoconstriction has been repeatedly demonstrated whenever there is adrenergic activation of the heart, as during exercise or a carotid sinus baroreceptor reflex in dogs or during a cold pressor reflex in humans. Experimental evidence indicates that there is a beneficial effect of this paradoxical vasoconstrictor influence in that it helps preserve flow to the vulnerable inner layer of the left ventricle, but only when both heart rate and coronary flow are high. The dominant site for α-adrenoceptor-mediated coronary vasoconstriction is in microvessels larger than approximately 100 μm diameter. Both α_1- and α_2-adrenoceptors mediate coronary vasoconstriction, but there is a gradient of their distribution, with α_1-adrenoceptors being more predominant in larger vessels and α_2-adrenoceptors being more predominant in the microcirculation. As proposed by Feigl [51], α-mediated coronary vasoconstriction seems to play an important role in preventing overperfusion of the subepicardial layers. This is particularly relevant during exercise, when subendocardial perfusion is hampered by the shortening of diastolic time, and overperfusion of the subepicardial layers is prevented by selective α-mediated coronary vasoconstriction of the subepicardial vessels.

In the past, the study of α-adrenergic coronary vasoconstriction in man has been limited by lack of adequate techniques to quantify CBF and myocardial perfusion. More recently, quantitative coronary angiography has allowed quantification of the

diameter of coronary arteries down to approximately 0.5 mm. Study of the human coronary microcirculation is indirect [52] and relies on parameters such as coronary flow velocity, measured invasively with Doppler flow probes, or MBF, quantified noninvasively with PET [53]. Recently, these techniques have become more widely available and directed toward the study of α-adrenergic coronary vasoconstriction in man. These studies in humans have confirmed prior animal experiments, showing that there is no evidence for α-adrenergic coronary constrictor tone at rest. Again confirming prior experiments, responses to α-adrenoceptor activation are augmented in the presence of coronary endothelial dysfunction and atherosclerosis, involving both α_1- and α_2-adrenoceptors in epicardial conduit arteries and in microcirculation. Such augmented α-adrenergic coronary constriction is observed during exercise and coronary interventions, and it is powerful enough to induce myocardial ischemia and limit myocardial function.

1.1.4.2 Parasympathetic Control

Parasympathetic control of CBF has been extensively studied in dogs, and a clear vasodilator effect not dependent on changes in myocardial metabolism was observed. Parasympathetic vasodilatation is mediated via NO and is activated during carotid baroreceptor and chemoreceptor reflexes [54]. The action of NO in parasympathetic coronary vasodilatation has been tested using a specific inhibitor of NO synthesis, nitro-L-arginine methyl ester (L-NAME). Experiments were conducted on closed-chest, alpha-chloralose-anesthetized dogs with the heart paced at a constant rate. Phentolamine and propranolol were administered to block alpha- and beta-adrenergic receptors, and ibuprofen was given to inhibit prostaglandin synthesis. Intracoronary infusion of L-NAME decreased the coronary vasodilatation in response to intracoronary acetylcholine or vagal stimulation. The coronary response to the endothelium-independent vasodilator nitroglycerin was unaffected by L-NAME. These data demonstrate that L-NAME specifically inhibits coronary vasodilatation caused by acetylcholine and vagal stimulation, indicating that parasympathetic coronary vasodilatation is dependent on NO [55]. Intracoronary infusion of acetylcholine in humans results in increased CBF and epicardial coronary artery dilatation except in atherosclerotic epicardial coronary vessels, which show a paradoxical vasoconstriction.

1.1.5 Reactive Hyperaemia and Coronary Flow Reserve

1.1.5.1 Response to a Brief Coronary Occlusion

When a major epicardial coronary artery is occluded for a short period of time, occlusion release is followed by a significant increase in CBF, a phenomenon known as reactive hyperemia. The maximum increase in blood flow occurs within a few seconds after the release of the occlusion and the peak flow, which has been shown to reach four or five times the value of preischemic flow, is dependent on

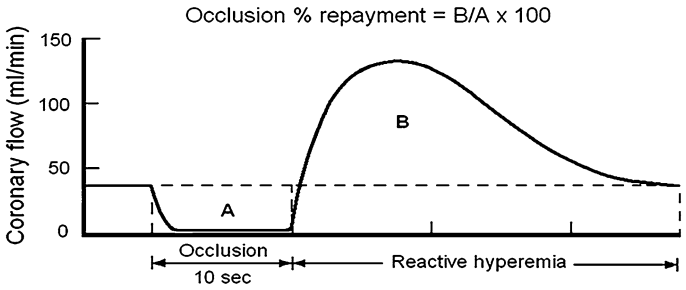

Fig. 1.7 Reactive hyperemia. Mean CBF before, during and after a brief coronary occlusion. Area A is the flow debt acquired during occlusion, whereas area B its repayment following restoration of blood flow. Maximum flow following release of the occlusion is known as reactive hyperemic flow and is generally considered the expression of maximal coronary vasodilatation. Typically, the repayment is larger than the flow debt incurred during the ischemic period. Adapted from Berne et al. [29]

the duration of the ischemic period for occlusion times up to 15–20 s. Although occlusions of longer duration do not modify further the peak of the hyperemic response, they do affect the duration of the entire hyperemic process, which increases with the length of the occlusion [56]. Generally, the excess flow that follows the occlusion, known as flow repayment, is larger than the flow debt incurred during the ischemic period (Fig. 1.7) [57]. From the previous observations, it is generally accepted that myocardial ischemia, even of brief duration, is the most effective stimulus for vasodilatation of coronary resistive vessels and that, under normal circumstances, reactive hyperemic peak flow represents the maximum flow available at a given coronary perfusion pressure. Values of CBF comparable to the peak flow of reactive hyperemia can be achieved using coronary vasodilators such as adenosine or dipyridamole, which induce a 'near maximal' vasodilatation of the coronary microcirculation. This concept, however, has been challenged by studies in experimental animals, as well as in human subjects, that have demonstrated that reactive hyperemic peak flow may not represent the true ceiling of blood flow achievable at a given perfusion pressure [58, 59]. Reactive hyperemia occurs also in denervated isolated hearts, thus suggesting that flow-mediated, myogenic, and metabolic mechanisms (see above) are its main determinants [60].

1.1.5.2 Coronary Flow Reserve

The concept of CFR was first introduced by Gould et al. in 1974 [61] as an indirect parameter to evaluate the global function of the coronary circulation. CFR is the ratio of CBF or MBF during near maximal coronary vasodilatation to resting flow and is an integrated measure of flow through both the large epicardial coronary arteries and the microcirculation (Fig. 1.8) [62].

CFR is a relative, rather than absolute, value that depends on four main variables:

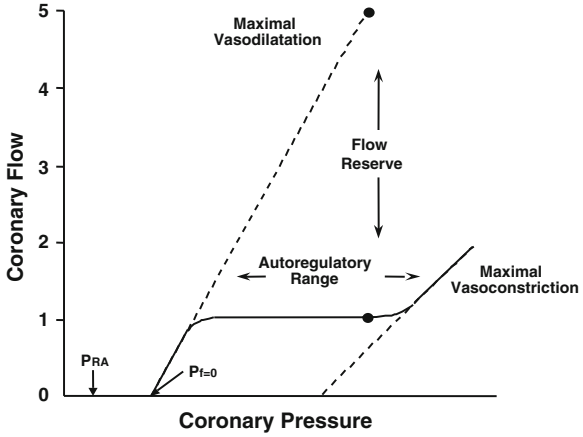

Fig. 1.8 Relationship between CBF and coronary perfusion pressure in the LV. At a constant level of myocardial oxygen consumption, CBF is maintained constant over a wide range of coronary perfusion pressures (*solid line*), included within the boundaries of maximal resistive coronary vessel dilatation or constriction (*dashed lines*). In the presence of maximal resistive vessels dilatation, CBF and coronary perfusion pressure are linearly related (*dashed line* on the *left*). The black circles represent the basal state and the maximal CBF under normal conditions, resulting in a CFR of 5.0. P_{RA} = right atrial pressure, $P_f = 0$ = pressure at zero flow. Adapted from Klassen et al. [1]

- resting blood flow
- cross-sectional area of resistance vessels per unit volume of myocardium
- extravascular coronary compression
- arteriolar perfusion pressure.

Since resting blood flow is the denominator in the formula used to compute CFR, any increase in resting blood flow (e.g., the increase in resting perfusion seen in patients with arterial hypertension) will lead to a net decrease in the available CFR.

The total cross-sectional area of resistive vessels per unit volume of myocardium influences coronary flow conductance and hence the slope of the pressure/flow curve in inner and outer layers of the ventricular wall. The greater the vascular cross-sectional area, the steeper the slope of the pressure/flow curve (the greater the increase in flow per unit increase in pressure). In the presence of maximal vasodilatation, the vascular conductance per unit volume of myocardium can be reduced, because the total number of resistive vessels per unit volume is decreased or because the lumen of individual vessels is reduced.

Extravascular compressive forces reduce CFR mainly in the subendocardial layers of the left ventricle, in particular during tachycardia and in the presence of elevated diastolic intracavity pressures (Fig. 1.9) [63, 64] (see below).

The perfusion pressure that determines flow for any given level of vascular resistance is the pressure at the origin of arteriolar vessels. During maximal

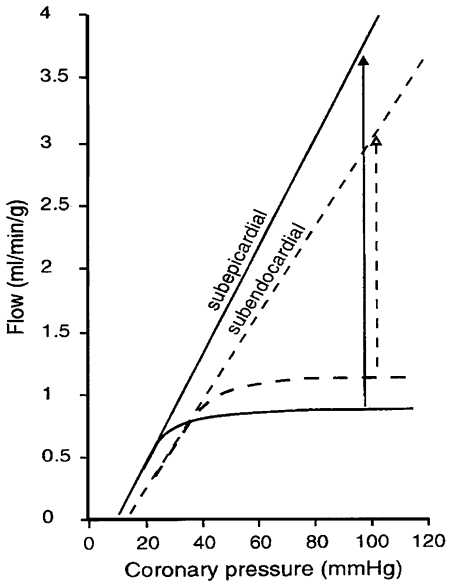

Fig. 1.9 CFR in subendocardial and subepicardial layers of the *left ventricle*. Under physiologic conditions CFR is lower in subendocardial myocardium, where resting blood flow is a higher due to a higher oxygen consumption and a lower pressure/flow *curve* related to the presence of higher extravascular compressive forces. This difference between subepicardial and subendocardial layers increases progressively with tachycardia and with elevation of diastolic pressure. Adapted from Canty [63]

coronary dilatation, the slope of the pressure/flow curve is very steep; thus, the increase of CBF/MBF with increasing pressure is substantial. Under physiological conditions, the coronary perfusion pressure that determines CBF/MBF corresponds closely to aortic pressure.

Resting and hyperemic MBF are heterogeneous both between and within individuals and exhibit a similar degree of spatial heterogeneity, which appears to be temporally stable [65]. Since resting coronary/myocardial blood flow parallels myocardial oxygen consumption, care must be taken to normalize CFR measurements obtained on different occasions by using a "corrected" resting flow. This is generally obtained by correcting resting flow for the relative rate-pressure product. Furthermore, several factors may influence resting CBF/MBF, including gender (women tend to have higher resting CBF/MBF) and drugs, which, therefore, must also be taken into account. Of note, the value of hyperemic CBF/MBF can be influenced by a number of factors, which may "artificially" limit the maximum flow response (Table 1.1). These include submaximal coronary vasodilatation caused by the assumption of substances, such as caffeine, that antagonize the effect of some vasodilator drugs (adenosine and dipyridamole). Of note, there is a direct linear relation between age and resting MBF, partly related to changes in external cardiac workload with age, whereas hyperemic MBF declines in people over 65 years of age [66]. The type of the vasodilator stimulus also can influence the assessment of CFR. Indeed, hyperemic MBF was found to reach higher values in subjects in whom the standard dose of i.v. adenosine (140 μg/kg/min) was used as compared to those in whom dipyridamole (0.56 mg/kg infused over 4 min) was

Table 1.1 Factors affecting coronary flow reserve

Factors that affect resting coronary/myocardial blood flow
• Age
• Gender
• Oxygen consumption (heart rate and blood pressure)
• Drugs
• Endothelial dysfunction
• Presence of scar/fibrosis
Factors that affect hyperemic coronary/myocardial blood flow
• Age
• Submaximal coronary vasodilatation
• Perfusion pressure
• Caffeine and caffeine derivatives[a]
• Anatomical remodeling of the microcirculation
• Increased microvascular tone
• Increased extravascular resistance
• Endothelial dysfunction
• Presence of scar/fibrosis
• Cardiac denervation

[a] When adenosine or dipyridamole are used to assess coronary flow reserve

used [62]. On the whole, the inter-individual variability of hyperemic MBF is greater than that observed for resting MBF.

1.1.5.3 Coronary Flow Reserve Versus Maximum Blood Flow

There is growing evidence showing that maximal MBF (i.e., the blood flow measured during near maximal vasodilatation with adenosine, dipyridamole, or papaverine) is superior not only to the semiquantitative measurement of myocardial tracer retention, but also to CFR in the assessment of coronary microvascular function.

Hajjiri et al. [67], in agreement with previous reports, recently showed that the degree of impairment of maximum MBF bears important prognostic information. In fact, it has been shown that in both hypertrophic [68] and dilated [69] cardiomyopathies, the severity of MBF impairment measured during dipyridamole stress test is predictive of major adverse cardiac events at follow-up.

The reason why maximal MBF may provide prognostic information superior to CFR resides in the fact that CFR is a ratio, and therefore both the numerator or the

denominator may affect its calculation. Accordingly, a low CFR does not necessarily reflect a reduction of maximum flow, but it can be caused by an abnormally elevated resting flow in face of a normal hyperemic flow. This problem can be overcome, at least in part, by normalizing resting flow for the external cardiac workload, which is generally obtained using the rate-pressure product [70].

1.1.6 Collateral Circulation

Collaterals develop from preexisting anastomotic channels (thin-walled structures ranging in diameter from 20 to 200 μm), as a result of both the release of chemical mediators during tissue hypoxia and of the establishment of a pressure gradient between their origin and termination, with increase in shear stress, a process known as arteriogenesis.

In experimental models, collateral growth in the heart is promoted by ischemia even in the absence of pressure gradients across collateral vessels (i.e., eliminating the effects of shear stress) [71]. These observations, however, do not dismiss the potential importance of shear stress, because it is clear that as collateral vessels outwardly remodel, they carry more oxygenated blood to the ischemic zone, which progressively ameliorates ischemia; yet growth continues also after the ischemic signal wanes. This may be the transition point where shear stress becomes important in the remodeling process, i.e., after the process has been initiated.

It is also worth mentioning that growth inhibitors play an important role in collateral development. Indeed, the levels of angiostatin, probably the most important growth inhibitor of collateral circulation development, were found to be higher in pericardial fluid obtained from patients with angiographically poor collaterals compared to those with well-developed collaterals [72]. Accordingly, the production of endostatin by the myocardium was found to be increased in patients with poor collaterals compared to those with well-developed coronary collaterals [73]. Although the potential complicating effects of growth inhibitors on collateral growth has not systematically been pursued, it is likely that this negative influence could be one of the contributing reasons to the failed "therapeutic angiogenesis" trials in patients with severe CAD [74]. Finally, disturbed signaling, ranging from that inducing expression of growth factors, signaling of the growth factors, signaling and actions of mechanic transduction, likely contribute to poor collateral growth. For example, reactive oxygen species make important contributions to collateral growth in the activation of specific redox sensitive mitogen-activated protein kinases. Yet, excessive production of superoxide or inhibition of superoxide production, resulting in oxidative or reductive stress, respectively, inhibit collateral growth along with inactivation of mitogen-activated protein kinases [75].

Another issue regarding growth inhibition pertains to regression of the coronary collateral circulation. This phenomenon has been related to the time it takes for collaterals to open (for example, in response to repetitive coronary occlusions)

after the stimulus inducing collateral growth is removed after full development of the collateral circulation [76, 77]. If the stimulus is applied soon after the end of the protocol, the increase in collateral flow occurs within seconds; however when the stimulus is applied a week after the end of the procedure, the increase in flow takes several minutes. The basis for this "regression" is unknown. Moreover, it is not known whether the regression is first functional, perhaps related to constriction or spasm, and then anatomical, with a rarefaction of coronary collateral vessels.

Thus, the adaptive response of collateral growth in the heart is a coordinated event that most likely has different stimuli during different stages of growth. There are probably specific times during which stem cell recruitment also plays a role. More research is mandated, however, to better understand the mechanisms by which stem cells confer their favorable effects, e.g., paracrine mechanisms or engraftment, so that these mechanisms can be amplified to better exploit the effect of cell therapy.

From a temporal standpoint, arteriogenesis occurs in three stages: the first stage (first 24 h) is characterized by passive widening of preexisting channels and endothelial activation, followed by secretion of proteolytic enzymes which dissolve extracellular matrix. The second stage (from 1 day to approximately 3 weeks) is characterized by migration of monocytes into the vascular wall, followed by secretion of cytokines and growth factors, which trigger proliferation of endothelial and smooth muscle cells and of fibroblasts. The third stage (3 weeks to ~3 months) is characterized by thickening of the vascular wall as a result of deposition of extracellular matrix.

Inter-coronary arterial anastomoses are present in variable numbers in different species. They are indeed so numerous in guinea pigs that they can prevent infarction following sudden coronary occlusion, whereas, at the other extreme, they are virtually absent in rabbits. In dogs, the density of anastomotic channels can deliver 5–10 % of preocclusion resting flow. Humans have a slightly worse collateral circulation than dogs, but with a marked inter-individual variability.

Fulton [78] was the first to demonstrate, by post-mortem angiography, that the human heart contains a collateral network already before the onset of obstructive atherosclerotic disease (Fig. 1.10). In his studies he observed a remarkable variety in number and diameter of collateral vessels and already suspected a genetically determined variation. More recently, these angiographic data were confirmed by intracoronary measurements of collateral flow. Intracoronary measurements of collateral flow in patients without stenotic lesions have been performed to investigate whether preexisting collaterals generate detectable collateral flow in individuals with angiographically normal coronary arteries [79]. Results showed that one-fifth of individuals exhibited immediately recruitable collateral flow, sufficient to prevent myocardial ischemia in case of brief coronary occlusions. Thus, also using intracoronary measurements of collateral flow, a preexisting collateral circulation can be detected. These data demonstrate that not only the post-mortem appearance, but also the function of this preexisting network varies largely in humans. In addition, Tomai et al. found that the correlation between stenosis severity and collateral development was rather weak, documenting large

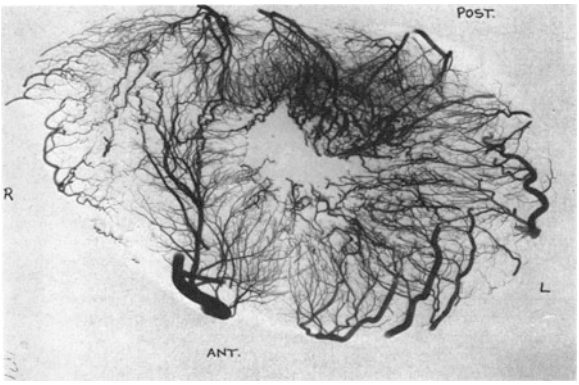

Fig. 1.10 Post-mortem angiography showing enlargement of deep anastomoses and increased vascular density in the posterior quadrant of a LV cross-section subtended by a severely stenotic coronary artery branch. This historical image showed for the first time in man that collateral circulation develops from preexistent collateral network already before the onset of obstructive atherosclerotic disease. Adapted from Fulton et al. [78]

inter-individual differences in the arteriogenic response for stenoses of comparable severity [80]. Accordingly, in another study in a large population of unselected patients with CAD, the extent of the collateral circulation followed a Gaussian-like distribution [81]. Only in patients with chronic total occlusion of a coronary artery a strong shift to the right was observed (Fig. 1.11) [82], but again with large inter-individual differences. Of note, patients with underdeveloped collateral circulation were found to exhibit a higher cardiovascular mortality at 10-year follow-up compared with patients with well-developed collateral circulation [81].

This large variability of the preformed collateral network in human coronary circulation has also been observed in the cerebral and peripheral circulation [83–85].

This extreme variability is probably related to environmental as well as genetic factors. However, experimental and clinical findings on the influence of risk factors such as dyslipedemia [86, 87], smoking [88], diabetes [89, 90] and obesity

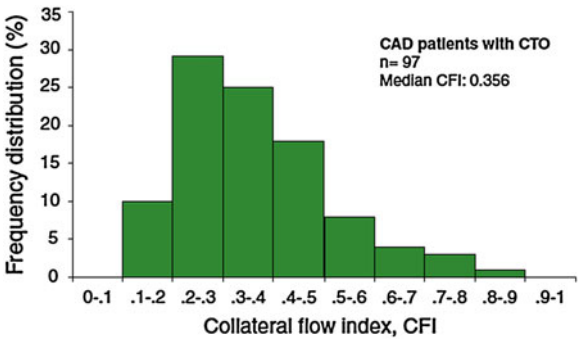

Fig. 1.11 Distribution of collateral flow index in CAD patients with total coronary occlusion (CTO). See text for details. Adapted from Teunissen et al. [82]

are remarkably conflicting, while ageing has consistently been found to be associated to a reduction in the extent of the collateral circulation.

Several of the observations on genetic determinants of collateral artery growth are derived from experimental models of hind-limb ischemia. In one study [91], ribonucleic acid was extracted from adductor muscle in mice and array expression profiling was used to determine the time course of differential expression of 12,000 genes after ligation of the femoral artery. Between the femoral artery ligation group and the sham group, 783 genes showed a differential expression where 518 were induced and 265 were repressed. Interestingly, a number of angiogenesis-related genes such as MCP-1, placental growth factor, and cysteine-rich protein-61, were differentially up-regulated in the femoral artery ligation group as compared to the sham group. Also, a significant up-regulation was found in genes thought to exert angiostatic activities, including interferon gamma, inducible protein-10, and matrix metalloproteinase-12 in the ligated group. Of the different gene clusters, the inflammatory response-related genes cluster was the largest that was up-regulated. Gene expression analysis has been carried out also in peripheral blood monocytes of a large population of patients with CAD and with poorly or well-grown collaterals. The authors found differential expression of 203 genes, which were involved in integrin, platelet-derived growth factor, and transforming growth factor beta-signaling [92]. Another factor that was recently distilled from patient data and experimentally validated is galectin-2. This factor is overexpressed in patients with poor collateral arteries and exogenous application of this factor leads to a strong reduction in the arteriogenic response in the murine hind-limb model [93].

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Mechanisms of Coronary Microvascular Dysfunction

2

CMD can be sustained by several pathogenetic mechanisms, as summarized in Table 2.1. The importance of these mechanisms appears to vary in different clinical settings, but several of them may coexist in the same condition [1].

2.1 Structural Alterations

Structural abnormalities responsible for CMD have, in particular, been consistently documented in patients with HCM and in those with arterial hypertension. In both these conditions morphologic changes are characterized by an adverse remodeling of intramural coronary arterioles consisting in vessel wall thickening, mainly due to hypertrophy of smooth muscle cells and increased collagen deposition in the tunica media, with variable degrees of intimal thickening (Fig. 2.1) [1]. The remodeled hypertrophied vascular wall leads to an increase in medial wall area, with a relative reduction of the lumen that correlates with the increase of minimal coronary resistance and the reduction of CFR. Although qualitatively similar in the two conditions, these anatomical changes are usually quantitatively more severe in patients with HCM.

An important feature common to patients with arterial hypertension and to those with HCM is the diffuse nature of the microvascular remodeling, which is extended to the entire LV independently of the distribution of ventricular hypertrophy (i.e., symmetric vs. asymmetric), and may also involve portions of the right ventricle (Fig. 2.2) [2]. The functional counterpart of this phenomenon is the demonstration that, in most of these patients, maximum MBF and CFR are blunted in the whole left ventricle [3].

Interestingly, similar changes have been described in the spontaneously hypertensive rat, which is therefore a good model of coronary microvascular remodeling associated with hypertension (Fig. 2.3) [4].

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Table 2.1 Pathogenetic mechanisms of CMD

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

Adapted from Camici and Crea [1]

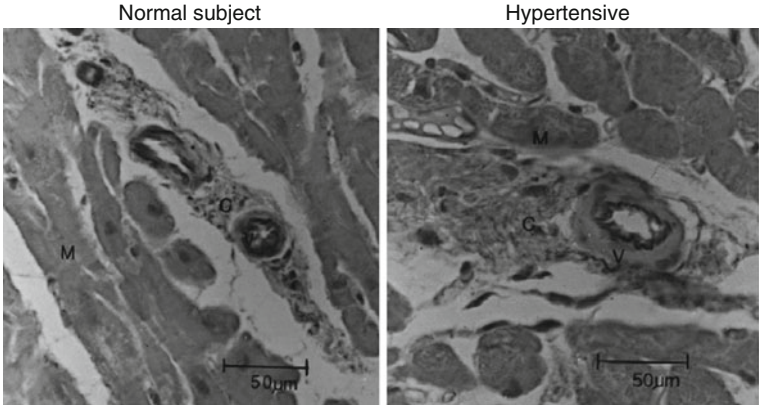

Fig. 2.1 *Left* coronary arteriole from a healthy subject. *Right* coronary arteriole from a patient with arterial hypertension with typical medial hypertrophy, increased wall/lumen ratio and perimyocytic and perivascular fibrosis. Adapted from Camici et al. [1]

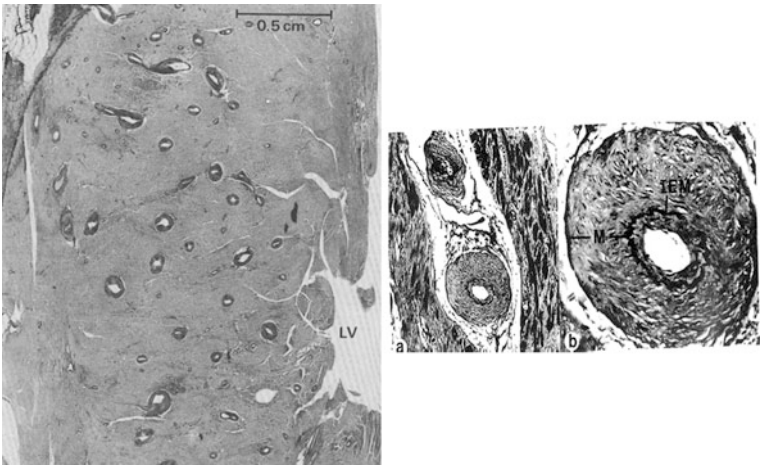

Fig. 2.2 *Left* section (at low magnification) of the left ventricle at the level of the interventricular septum from a patient with HCM. Intramural arterioles are mainly characterized by marked wall thickening. *Right* Details of the same section at higher magnification reveal marked medial hypertrophy, together with increased wall/lumen ratio and peri-vascular fibrosis. Adapted from Maron et al. [2]

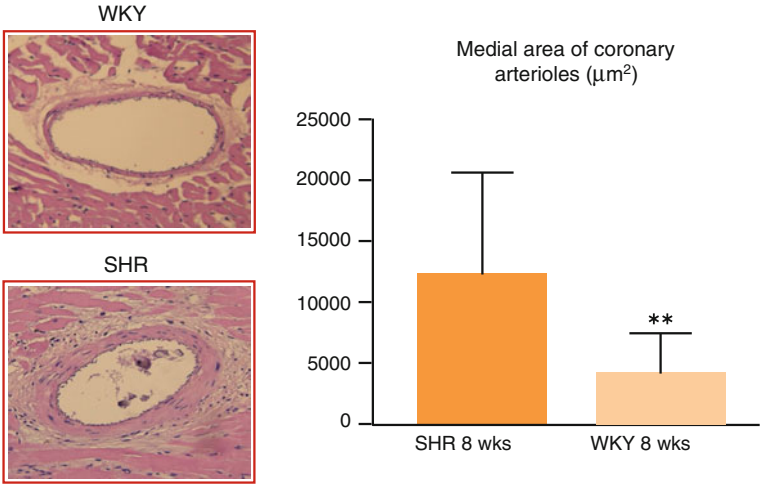

Fig. 2.3 *Top left* coronary arteriole from a normotensive Wistar Kyoto rat (WKY). *Bottom left* coronary arteriole from a spontaneously hypertensive rat (SHR) showing vascular remodeling with medial hypertrophy similar to that seen in hypertensive patients. Coronary arteriolar remodeling in the SHR is already evident at 8 weeks of age, before the development of arterial hypertension. *Right panel* graph showing the values of arteriolar medial area (the surface comprised between the vessel's adventitia and endothelium) demonstrating that medial area in the SHR is three times that in the WKY. Adapted from Mancini et al. [4]

Tanaka et al. [5] reported that the percent lumen area of intramural arterioles with a diameter <60 μm was significantly smaller in hypertensive patients as compared with normotensive controls. In this study, similar alterations were found both in the left and the right portions of the interventricular septum. Schwartzkopff et al. [6] demonstrated that pre-capillary arterioles (external diameter <20 μm) also had thickened walls so that remodeling of the arterial network down to its smallest branches is to be assumed. Van Hoeven and Factor [7] reported qualitatively markedly thickened walls, mainly due to medial hypertrophy, and reduced lumen of intramyocardial arterioles with an external diameter of 50–200 μm in patients with arterial hypertension and chest pain. As noted by Schwartzkopff et al. [6], it is of interest that wall thickening of intramyocardial coronary arterioles is also found in the right septal subendocardium, which is not directly exposed to pressure overload. This may suggest that remodeling of small coronary arteries is related to some pathogenetic factors involved in the development of hypertension, rather than being merely secondary to vascular overload or cardiomyocyte hypertrophy.

In line with this observation, recently Mancini et al. [4] have provided evidence that structural remodeling of intramural coronary arterioles in the spontaneously hypertensive rat is already present at 4 weeks of age, when arterial blood pressure is still within normal limits. This is in line with previous reports describing similar findings in brain, kidneys, and mesenteric arterioles of young spontaneously hypertensive rats [8–11] and suggests a genetic control behind medial structural and functional remodeling, independent of the environment. Intriguingly, Mancini et al. found that coronary arterioles, at 4 weeks of age, mainly presented an outward remodeling, together with a less evident inward remodeling, with medial hypertrophy and a greater lumen diameter compared to normotensive rats, suggesting that this early microvascular phenotype can be related to the underlying genetic background and is subsequently modified by the onset of hypertension-related medial changes [11, 12]. In fact, the hypertensive phenotype in the spontaneously hypertensive rat model, which is already well established at 8 weeks of age, is characterized by a further increase in medial thickness and narrowing of the lumen. The development of outward remodeling seen in older animals could be interpreted as an adaptive change of the arterioles [11, 13] in an attempt to restore the blunted coronary flow. However, as the data of Mancini et al. [4] show, this is ineffective due to the contemporary increase in medial thickness.

In their classic study published in 1986, Maron et al. [2] determined the prevalence and extent of abnormal intramural coronary arteries in patients with HCM. They carried out a histologic analysis of LV myocardium obtained at necropsy in 48 patients with HCM (but without atherosclerosis of the extramural coronary arteries) and in 68 control patients with either a normal heart or acquired heart disease. In HCM, abnormal intramural coronary arteries were characterized by thickening of the vessel wall and a decrease in luminal size. The wall thickening was due to proliferation of medial or intimal components, or both, particularly smooth muscle cells and collagen. Of the 48 patients with HCM, 40 (83 %) had abnormalities of intramural coronary arteries located in the ventricular septum

(33 patients), anterior LV free wall (20 patients) or posterior free wall (9 patients); an average of 3.0 ± 0.7 abnormal arterioles were identified per tissue section. Altered intramural coronary arteries were also significantly more common in tissue sections having considerable myocardial fibrosis [31 (74 %) of 42] than in those with no or mild fibrosis [31 (30 %) of 102; $p < 0.001$]. Abnormal intramural coronary arteries were also identified in 3 of 8 infants who died of HCM before 1 year of age. In contrast, only rare altered intramural coronary arteries were identified in 6 (9 %) of the 68 control patients (0.1 ± 0.05 abnormal arteries per section; $p < 0.001$) and those arteries showed only mild thickening of the wall and minimal luminal narrowing. Moreover, among subjects with abnormal intramural coronary arteries, such vessels were about 20 times more frequent in patients with HCM (0.9 ± 0.2/cm^2 myocardium) than in control patients (0.04 ± 0.02/cm^2 myocardium). Hence, abnormal intramural coronary arteries with markedly thickened walls and narrowed lumens are present in increased numbers in most patients with HCM studied at necropsy, and may represent a congenital component of the underlying cardiomyopathic process. In a subsequent study, Schwartzkopff et al. [14] investigated the architecture of subendocardial arterioles in 13 patients with HCM and angina pectoris and in 5 normotensive controls, by means of stereologic morphometry of transvenous biopsy samples. In this study, limited to the analysis of very small subendocardial arterioles, the authors did not find a statistically significant thickening of this preterminal arteriolar wall in HCM as compared to controls, yet percent lumen was significantly reduced, indicating eutrophic vascular remodeling. Furthermore, arteriolar density in the subendocardium was found to be reduced in patients, correlating inversely with coronary resistance and concordantly with CFR assessed with pharmacologic vasodilatation. This finding gives further evidence of a reduced total cross-sectional arteriolar lumen area that is probably an important factor for the reported clinical and metabolic signs of myocardial ischemia, especially in the subendocardium. Furthermore, the authors argued that the observed increased content of collagen in the subendocardium could be a consequence of myocardial ischemia.

Structural abnormalities of coronary microcirculation have also been described in other clinical conditions characterized by CMD, including primary MVA. Analysis of endomyocardial bioptic samples obtained from these patients, however, have given discordant results, showing no alterations in some and heterogeneous findings in others [15–19], including medial hyperplasia and hypertrophy, myointimal proliferation and degeneration and proliferation of endothelial cells, and capillary vessels rarefaction.

2.2 Functional Alterations

Functional CMD may be caused by a variable combination of mechanisms leading to impaired coronary microvascular dilatation and mechanisms resulting in increased coronary microvascular constriction (Fig. 2.4).

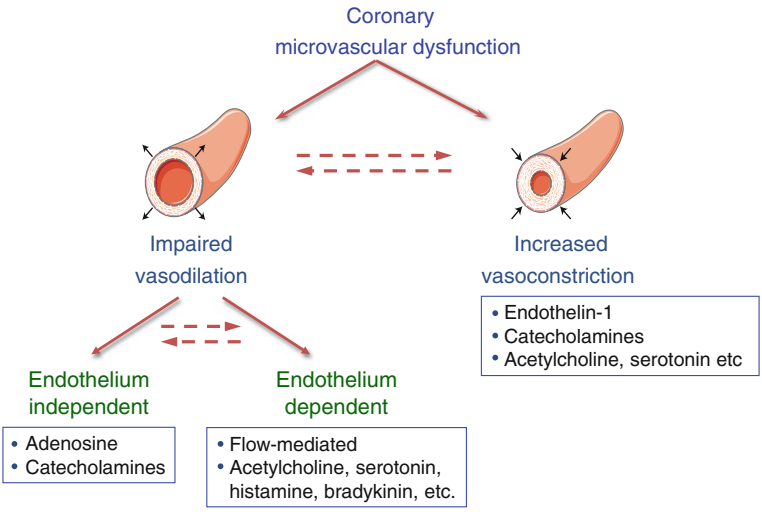

Fig. 2.4 Functional CMD may result from a variable combination of impaired coronary microvascular dilatation, which can variably involve endothelium-dependent and endothelium-independent mechanisms, and increased microvascular constriction in response to various stimuli

2.2.1 Alterations of Endothelium-Dependent Vasodilatation

As previously discussed, endothelial cells play a major role in the regulation of blood flow in the coronary microcirculation, in particular at the level of pre-arteriolar vessels, both in resting conditions and during increased myocardial oxygen consumption. Accordingly, alterations in endothelial function may impair CBF both at rest and in the case of increased myocardial work, as it typically occurs during exercise [20].

NO production and release are the most important mechanisms of endothelium-mediated vasodilatation, and also the first to be lost in case of endothelial dysfunction. Unfortunately, NO is a volatile molecule, with a very short half-life (5–6 s only); thus its direct measurement in vivo is difficult.

The identification of abnormalities in endothelium-dependent coronary microvascular dilatation in the clinical setting is mainly based on the reduced increase of CBF and/or decrease of CVR in response to stimuli known to exert their vasodilator effect by inducing release of NO from endothelial cells. Intracoronary acetylcholine, in association with intracoronary Doppler flow recording, has been the most frequent stimulus used to this scope in clinical research. This method, however, can only be applied during invasive procedures. A valid alternative to assess endothelium-dependent CMD is represented by CPT, which can be applied non invasively in association with imaging techniques (e.g., PET) to measure MBF (see Chap. 3). In presence of endothelial dysfunction the vasodilator response to these stimuli is blunted, and can even turn into vasoconstriction in case of severe impairment of endothelial function, due to the direct vasoconstrictor effects of

acetylcholine and the indirect, sympathetic-mediated vasoconstrictor effect of CPT, respectively [21–24].

Impaired NO generation as a cause of endothelial dysfunction has been shown in several experimental studies. The most usual cause is reduced activity of NO synthase, the enzyme that catalyzes NO synthesis from the amino-acid L-arginine, which can be caused by a number of noxious stimuli. In some cases, the administration of the NO synthase co-factor tetrahydrobiopterin can improve and even normalize endothelial dysfunction [25–27], thus suggesting that a reduction of this co-factor can be involved in the impairment of endothelium-mediated dilatation, at least in some cases.

The addition of L-arginine, the substrate for NO generation, has also been reported to improve endothelial CMD in some studies [28, 29]. However, a low availability of L-arginine seems unlikely to be a major cause for impaired NO generation, as its endothelial concentrations can hardly achieve such low levels to significantly compromise NO synthesis.

An increase of ADMA serum levels seems to be a further possible mechanism of reduced NO generation. ADMA is a major endogenous inhibitor of NO synthesis, acting by competing with L-arginine as a substrate for NO synthase. Increased intracellular ADMA levels, therefore, antagonize NO generation from L-arginine [30]. Increased ADMA concentrations may depend on enhanced synthesis or reduced degradation, the latter being usually due to a decreased activity of dimethylarginine dimethylaminohydrolase II, which regulates ADMA concentrations in endothelial cells by splitting it into citrulline and methylamines. Increased ADMA levels have been reported in several clinical conditions characterized by impaired endothelium-dependent coronary microvascular dilatation [31–34].

Of note, impairment of endothelium-dependent vasodilatation can be caused not only by reduced NO generation, but also by increased degradation. NO can indeed be inactivated by several factors, a major role being played by superoxide anion.

Excess generation of reactive oxygen species, eventually leading to increased superoxide anion production at tissue/microcirculatory level, frequently occurs in several conditions that have been associated with impaired endothelium-dependent coronary microvascular dilatation, including diabetes, obesity, smoking, and other cardiovascular risk factors [35, 36]. Accordingly, administration of antioxidant substances, which prevent superoxide anion formation, including glutathione and antioxidant vitamins, improves or normalizes endothelium-dependent coronary microvascular dilatation both in experimental and in clinical conditions [37–40].

NO exerts its vasodilator effects by diffusing into smooth muscle cells cytoplasm where it activates the intracellular guanilate cyclase pathway by binding the heme groups of the enzyme. Accordingly, in some conditions, impaired NO-dependent vasodilatation might be related to an alteration of smooth muscle cell response to normal levels of NO, including oxidation of the heme groups of guanilate cyclase [41].

Endothelial dysfunction is also likely to reduce the activity of two other major vasodilator substances released by endothelial cells, i.e., EDHF and *prostacycline* [42–44]. How much and in which cases perturbation of these factors significantly contribute to CMD in the clinical setting remains substantially unknown, largely due to the lack of specific tests to assess these pathways in clinical practice.

2.2.2 Alterations of Endothelium-Independent Vasodilatation

An impaired endothelium-independent dilatation as a cause of CMD has been demonstrated in several experimental and clinical conditions, in which CBF increase and/or CVR decrease in response to direct arteriolar/pre-arteriolar vasodilators (e.g., adenosine, dipyridamole, papaverine) were significantly reduced.

Despite the large amount of data documenting the role of endothelium-independent dilatation in CMD, the cellular mechanisms involved remain incompletely understood.

There are two main known intracellular pathways leading to smooth muscle cell relaxation. One pathway is based on the activation of the enzyme adenilatocyclase, which results in the production of cAMP, which acts by inhibiting calcium influx into smooth muscle cells. This pathway is mainly activated by stimulation of adenosine A_2 receptors and of adrenergic beta-2 receptors [45, 46]. The second intracellular pathway, as discussed above, relies on the activation of guanosine triphosphate cyclase, which results in the production of cGMP. The latter pathway is mainly activated by NO released by the endothelium [47].

Thus, an impaired smooth muscle cell response to vasodilator stimuli is likely to be different in different clinical settings, as it might be related to abnormalities in specific receptors or in one or both the main intracellular signaling pathways regulating smooth muscle cell relaxation. A reduced response to the vasodilator effect of prolonged nitrate administration (nitrate resistance), for instance, has been shown to occur because of a reduced production of cGMP, which might also be involved in a reduced response to NO (see above) [48, 49].

Notably, abnormalities in endothelium-independent coronary microvascular dilatation might also involve impaired opening of ATP-dependent K^+ channels [50, 51]; indeed, activation of intracellular cAMP and cGMP results in the opening of these channels eventually resulting in cell hyperpolarization and closure of voltage-dependent calcium channels. Finally, alterations in other K^+ channels, such as K^+Ca^{++} and K^+v channels might also be involved in the impairment of endothelium-independent coronary microvascular dilatation in some conditions [52, 53].

In conclusion, alterations in endothelium-independent smooth muscle cell relaxation in coronary microcirculation may result in impaired vasodilator response to substances that mediate metabolic regulation of CBF, autoregulation and reactive hyperemia, as well as flow-mediated dilatation, including adenosine, H^+, CO_2, H_2O_2, $beta_2$-agonists, prostacyclin and NO [54]. Their exact contribution

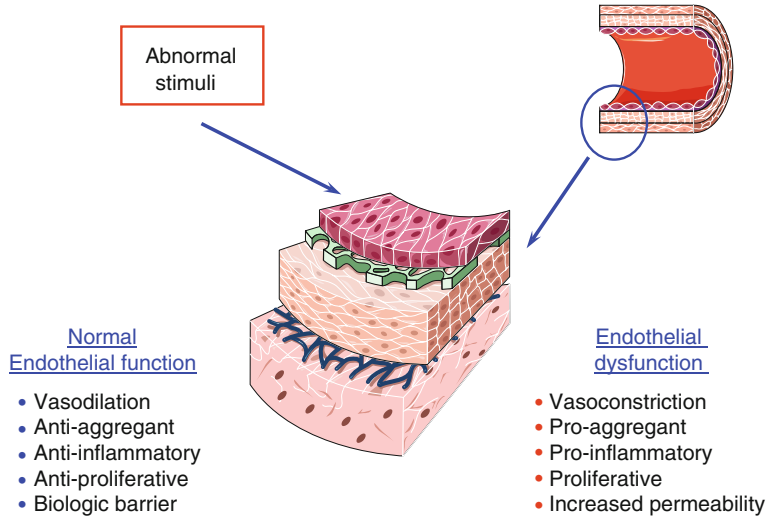

Fig. 2.5 Principal properties of the normal endothelium and modifications induced by abnormal stimuli, such as cardiovascular risk factors, causing endothelial dysfunction

to CMD in the clinical setting, however, remains to be defined due to the lack of specific tests.

Finally, it should be noted that abnormal stimuli, like cardiovascular risk factors, which cause endothelial dysfunction and activation transform the endothelium from a vasodilator to a vasoconstrictor organ, leading to an increased production and release of endothelin-1, which is the most powerful vasoconstrictor substance produced in the body [55, 56]. Moreover, dysfunctional endothelium can be also loose its anti-aggregant, anti-inflammatory and anti-proliferative effects and assume detrimental pro-aggregant, pro-inflammatory and proliferative properties [55] (Fig. 2.5).

2.2.3 Vasoconstriction

The notion that coronary microvascular constriction may cause myocardial ischemia has been demonstrated both in experimental models and in man. Some vasoconstrictor substances, indeed, cause selective intense microvascular constriction with minimal effects on epicardial coronary arteries.

In one study in dogs, the injection of endothelin-1 in the LAD coronary artery caused a dose-dependent reduction of CBF leading to myocardial ischemia in the absence of any significant effect on epicardial arteries [57]. Similar effects were also observed in dogs with intracoronary injection of angiotensin II or phenylephrine [58] and, in rabbits, with the intracoronary injection of the tripeptide *N*-formyl-L-methionin-L-leucil-L-phenylamine, which acts through release of

leucotriens from activated neutrophils [59]. Of note, the constrictor effects of these substances involve in a similar way subendocardial and subepicardial small coronary arteries, thus resulting in diffuse and relatively homogeneous myocardial ischemia.

In man, evidence of myocardial ischemia related to coronary microvascular constriction comes from a few studies showing that the intracoronary injection of neuropeptide Y [60] or high doses of acetylcholine [61, 62] in patients with normal coronary arteries causes chest pain and objective evidence of myocardial ischemia, in the absence of significant changes in epicardial coronary arteries. Furthermore, in patients with obstructive coronary stenoses, the intracoronary infusion of serotonin caused myocardial ischemia associated with small changes in stenosis severity, but with diffuse intense constriction of distal branches and reduced filling of collateral vessels [63].

In the clinical setting enhanced vasoconstriction of coronary microcirculation can be related to either an increased release of vasoconstrictor agonists (either systemically or locally) or to an increased susceptibility of smooth muscle cells to vasoconstrictor stimuli. The latter may involve one or more surface receptors or intracellular pathways leading to vascular smooth muscle cell contraction.

Abnormal microvascular constriction has been shown in patients with MVA [21, 64] and in those with stable angina [65]. The occurrence of intense microvascular constriction at rest, has been reported in patients with unstable angina [66, 67], with myocarditis [68] or with tako-tsubo disease [69]. Finally, intense coronary microvascular constriction is an important pathogenetic component of MVO observed in about one-third of patients after primary PCI [70, 71]. MVO obstruction can be occasionally and unpredictably observed during PCI in stable patients.

2.2.4 Intravascular Plugging

Intravascular plugging of coronary microcirculation can be caused by atherosclerotic debris, microemboli and neutrophil-platelet aggregates.

Intravascular plugging caused by atherosclerotic debris and thrombus material, typically occurs during PCI and is related to intracoronary manipulation of friable plaques, in particular in degenerated saphenous vein grafts [72]. In these cases, microvascular plugging often causes “infarctlets”, as indicated by a modest raise of markers of myocardial necrosis, and is associated with a worse prognosis as compared to PCIs that are not followed by any raise in markers of necrosis [73] (see Chap. 7).

Intravascular plugging caused by microemboli and leukocyte-platelet aggregates is an important component of MVO occurring in the setting of STEMI in spite of successful recanalization obtained through fibrinolysis or, most typically, primary PCI [74]. MVO results from a complex interplay of ischemia–reperfusion

related events, including endothelial dysfunction, inflammatory reaction, platelet activation and vasoconstriction [75] (see Chap. 6).

2.3 Extravascular Mechanisms

2.3.1 Extramural Compression

During the cardiac cycle the pulsatile pattern of CBF follows typical physiologic variations, which are influenced by the variations in intramyocardial and intraventricular pressures occurring during systole and diastole (Fig. 2.6) [20]. CBF mainly occurs in diastole, and therefore diastolic abnormalities more importantly affect myocardial perfusion. Nevertheless, an increase in systolic intramyocardial and ventricular pressures, as it typically occurs in primary and secondary LVH, may negatively impact on myocardial perfusion [76, 77]. Indeed, an increased microvascular compression generated during contraction makes subendocardial

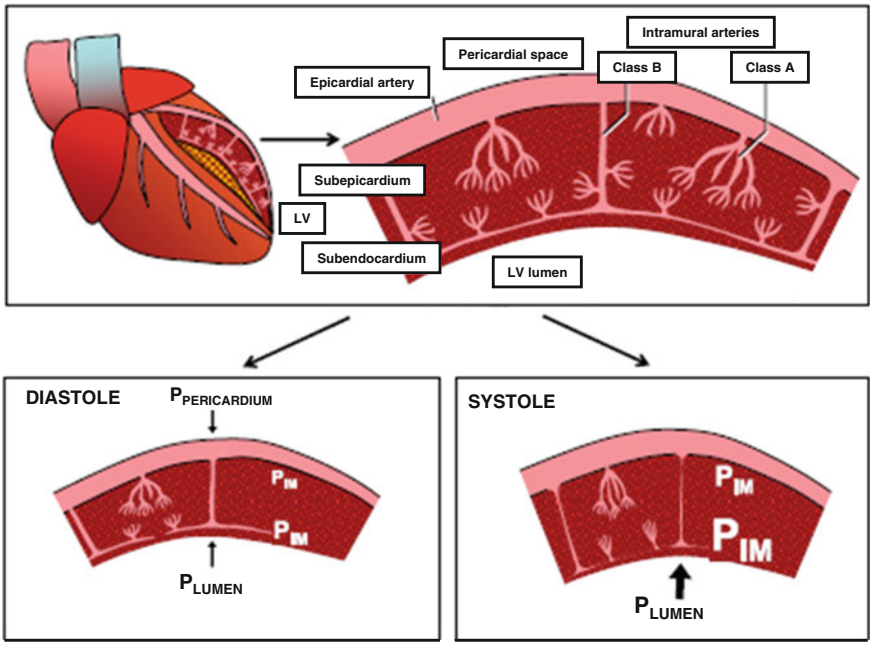

Fig. 2.6 Graph showing a schematic drawing of the intramyocardial microvasculature (*top panel*) and the extravascular forces acting on the coronary microvasculature during diastole (*bottom, left panel*) and systole (*bottom, right panel*). The relative magnitude of extravascular intramyocardial forces acting during the two phases of the cardiac cycle are proportional to the size of *letters* and *arrows*. Class A and class B refer to intramural arteries with non transmural or transmural course. P_{IM} intramyocardial pressure, P_{LUMEN} pressure in LV lumen, P_{PERI} pressure in the pericardial space. Adapted from Duncker [20]

vessels less ready to resume their tone in diastole, mainly impairing diastolic microvascular CBF in subendocardial layers [78].

Diastolic CBF is impaired by all conditions that increase intraventricular diastolic pressure. This is the case in the presence of LVH and also in the presence of diastolic dysfunction related to an increased collagen content within the myocardial tissue. Of note, conditions which make arteriolar driving pressure during diastole significantly lower than intraventricular pressure, as the presence of aortic stenosis, critical coronary stenoses, prearteriolar constriction or merely hypotension, may facilitate diastolic impairment of CBF in this setting.

The detrimental effects of increased systolic intramyocardial pressure and of diastolic intraventricular pressure on CBF are more pronounced in subendocardial than in subepicardial layers because of the lower CFR in the latter, as discussed in Chap. 1.

2.3.2 Tissue Edema

Myocardial edema is another extravascular cause of CMD. It is typically the consequence of abnormalities in capillary permeability, which favor migration of intravascular fluid into the interstitium. Experimental studies suggest that edema per se does not reduce CFR [79]. Nevertheless, edema can contribute to the impairment of CBF in the setting of MVO occurring after successful primary PCI [80, 81] (see Chap. 6). Edema results from a combination of several mechanisms [79], including (1) increased osmolality, caused by ischemic myocardial catabolites diffusing to the interstitial space, during the ischemic phase, which recall fluid from the intravascular compartment during reperfusion; (2) increased vascular permeability to water and protein, as well as abnormal ionic transport, consequent to endothelial damage occurring during ischemia/reperfusion; (3) inflammation associated with reperfusion (Fig. 2.7). Besides impairing substance exchange between blood and myocardial cells, edema can also increase interstitial pressure, thus increasing CVR. Moreover, edema can cause coronary microvascular compression, thus favoring intravascular cell plugging by neutrophil-platelet aggregates. Myocardial edema is also observed in both viral and auto-immune myocarditis, but it is unlikely that it causes CMD in this setting.

Finally, myocardial edema can occur during open heart surgery [82], as a result of several combined mechanisms, including exposure to ischemia and reperfusion, use of hypo-oncotic cardioplegic solutions, reduced lymphatic drainage following cardiac arrest and inflammatory response to extracorporeal circulation. Increased venous pressure, mainly in the right chambers, may contribute to interstitial edema due to increase in hydrostatic capillary pressure. The clinical relevance of edema-related CMD in these conditions is still limited.

Importantly, the detection of myocardial edema in patients is now possible by cardiac magnetic resonance [83, 84]. This will allow to better establish the role of edema in causing CMD in different clinical settings.

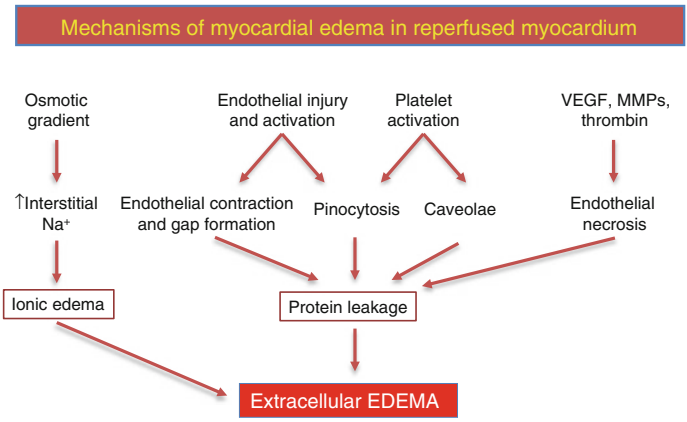

Fig. 2.7 Mechanisms of interstitial myocardial edema during post-ischemic myocardial reperfusion. *MMP* matrix metalloproteinasis, *VEGF* vascular endothelial growth factor. Adapted from Garcia-Dorado et al. [79]

2.3.3 Reduction of Diastolic Time

As CBF mainly occurs during diastole, the duration of diastolic time plays an important role in preserving myocardial perfusion. In the normal heart both subendocardial and subepicadial perfusion is preserved even in the presence of the shortest physiological diastolic time durations, as it is the case during intense physical exercise. In contrast, a reduction of diastolic time can contribute to determine a critical reduction of myocardial perfusion when coronary driving pressure during diastole is significantly lower than intraventricular pressure, as it is the case in the presence of aortic stenosis, critical coronary stenoses, prearteriolar constriction or hypotension. Again, the detrimental effects of a reduction of the diastolic time on myocardial perfusion are more pronounced in subendocardial than in subepicardial layers because of the lower CFR in the latter, as discussed in Chap. 1. A number of studies suggest that a reduction of diastolic time plays an important role, in particular, in determining myocardial underperfusion in patients with severe aortic stenosis (see Chap. 5).

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Methods to Assess Coronary Microvascular Function

3

Several methods are now available to investigate coronary microcirculation. These methods, with their *pros* and *cons*, will be briefly discussed in this chapter. Some general considerations about their application in the clinical arena, however, need to be highlighted [1].

3.1 Issues Related to Assessment of CMD

In contrast with epicardial coronary arteries, the coronary microcirculation cannot be directly imaged in vivo with coronary angiography nor by intracoronary imaging techniques. Indeed, small coronary arteries are below the spatial resolution of coronary angiography (about 0.5 mm) and cannot be reached by catheters utilized for intravascular imaging.

Visual assessment of small coronary arteries might be possible by endomyocardial biopsy, which are usually obtained from the right side of the interventricular septum [2, 3], but this invasive approach is not justified in the majority patients with coronary microvascular dysfunction (CMD) and does not allow assessment of functional alterations. Furthermore, tissue specimens obtained with this procedure are minute and limited to the inner surface of the ventricular cavity; as a result, only arterioles with diameters of approximately 20 μm or less can be examined, whereas the regulation of MBF in the microcirculation requires the integrated response of arterioles ranging from <30–150 μm, and all these vessels might also be involved in processes of pathologic microvascular remodeling [4].

Although several methods have been proposed to investigate the functional state of coronary microcirculation [5], their application in the clinical setting presents several general and specific issues and limitations. First, CMD can only be assessed indirectly through measurements of CBF and/or CVR in response to appropriate vasoactive stimuli. Second, CMD can be difficult to demonstrate when it is confined to small myocardial regions. Third, as different mechanisms can be responsible for CMD, it can be difficult to identify the specific mechanism of CMD

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in individual patients. Fourth, the functional state of coronary microcirculation is influenced by a large number of factors (e.g., heart rate, blood pressure, inotropic state of the myocardium, ventricular mass, etc.), which can hardly be taken all into account. Finally, although there is clear-cut evidence that CMD plays an important role also in patients with obstructive CAD [6], the discrimination between the effects of macrovascular and microvascular coronary abnormalities on myocardial perfusion is difficult; thus, at present, the assessment of CMD in clinical practice is mainly confined to patients in whom coronary angiography shows normal or near-normal epicardial coronary arteries.

In spite of these complexities several noninvasive and invasive methods have been developed to assess CMD in patients [1, 7].

3.2 Vasoactive Stimuli for Assessment of CMD

Coronary microvascular function is usually assessed by measurement of coronary microvascular response to vasodilator stimuli. The stimulus should be administered at doses likely to achieve near-maximal microvascular dilatation, and therefore maximal reduction of coronary resistances. The vasodilator capacity is usually measured as the ratio of CBF during maximal vasodilatation over basal CBF.

Vasodilator stimuli can interrogate smooth muscle cells (SMCs) (endothelium-independent vasodilatation) or endothelial cells (endothelium-dependent vasodilatation), although the responses cannot be considered as "pure".

A complete assessment of coronary microvascular function would also include, at least in some patients, the assessment of coronary microvascular response to constrictor stimuli. These tests, however, need to be carried out during invasive investigation, as a significant constriction of epicardial vessels during the test can only be excluded by coronary angiography. The main vasodilator and vasoconstrictor stimuli that are utilized in clinical practice are summarized in Table 3.1.

The most widely used substance to assess coronary microvascular dilator function is *adenosine*. The latter is administered at the intravenous dose of 140 μg/Kg/min for 1.5–6 min, as this dose has been found to achieve maximal microvascular dilatation [8]. Possible side effects include bradycardia, due to atrioventricular or sino-atrial node blockade, and bronchoconstriction, both mediated by purinergic A_1 receptor stimulation. A relevant advantage of adenosine is its very short half life (10 s), that allows rapid regression of side effects and repetition of the test during the same session.

Another frequently used substance to assess endothelium-independent coronary microvascular dilatation is *dipyridamole*, which has similar effects to adenosine; in fact, it acts by inhibiting adenosine degradation by adenosine deaminase [9]. A CFR < 2.5 by either adenosine or dipyridamole is usually considered diagnostic for CMD, independently of the technique used to assess basal and hyperaemic CBF. However, in view of the significant variability of CFR, as well as of resting

Table 3.1 Pharmacological agents used to assess coronary microvascular function

	Dose	Action	Half life	Side effects
EI vasodilators				
Adenosine	140 mg/Kg/min, EV 2–16 μg/Kg/min, IC	Activation of SMC A2 receptors	10 s	Bradycardia Bronchoconstriction
Dipyridamole	0.56–0.84 mg/Kg, EV	Phosphodiesterase inhibition (inhibits adenosine degradation)	$\alpha = 3.4$ min $\beta = 40$ min $\gamma = 15$ h	Bradycardia Bronchoconstriction Headache Flushing Hypotension
Papaverine	10–12 mg, EV 10–20 mg, IC	Phosphodiesterase inhibition (inhibits adenosine degradation)	1.5–2 h	Ventricular arrhythmias Hepatic toxicity Somnolence-Vertigo
Sodium nitroprusside	0.3–0.9 μg/Kg, IC 0.5–2 μg/Kg/min EV	Release of NO	2 min	Headache Hypotension Methemoglobinemia Cyanide toxicity
ED vasodilators				
Acetylcholine	10–50 μg/min, IC	Ach-muscarinic receptor activation and release of NO	2 min	Bradycardia Hypotension Bronchoconstriction
Substance P	20–90 μg/min, IC	NK1 receptor activation and release of NO	1.5 min	Bronchoconstriction Hypotension
Bradykinin	0.2–2 μg/min, IC	B1 and B2 receptor activation and NO release	1–2 min	Hypotension Angioedema, cough
Vasoconstrictors				
Ergonovine maleate	10–50 μg, EV 40–64 μg, IC	α-Adrenergic and serotonin receptor agonists	30 min	Diffuse vasospasm
Methylergometrine	1–3 μg/Kg/min EV 0.4 mg EV 8,16,32 μg, IC			

EI endothelium independent, *ED* Endothelium-dependent, *EV* endovenous, *IC* intracoronary, *NO* nitric oxide, *SMC* smooth muscle cells

and hyperaemic MBF in healthy subjects [10], a cut-off <2.0 might be more clinically appropriate.

Papaverine is another potent coronary microvascular dilator that can be used to assess endothelium-independent coronary microvascular dilatation. However, its use is limited by the need of intracoronary administration and the potential risk of serious arrhythmias.

Acetylcholine is the most widely used substance to assess endothelium-dependent coronary microvascular dilatation [11, 12]. This substance can only be used during invasive procedures, as it requires intracoronary infusion, usually three bolus injections of 2, 20, and 50 μg at intervals of 2 min. Nevertheless, acetylcholine is not the ideal drug to assess endothelium-mediated vasodilatation because it also acts directly on smooth muscle cells, inducing vasoconstriction.

Alternative substances used (although more rarely) to assess endothelium-dependent coronary microvascular dilatation are serotonin and bradykinin, but they are affected by limitations similar to acetylcholine. Substance P would be the ideal substance to assess endothelium-dependent vasodilator function as it does not seem to have any direct effect on smooth muscle cells, but it is not easily available for clinical use.

CPT has widely been used to assess endothelium-dependent coronary vasodilator function [13]. CPT is a simple test, that can be applied noninvasively. The test consists in the immersion of one hand of the patient in ice water for 90–120 s. Cold and peripheral pain induce sympathetic stimulation increasing heart rate and blood pressure; the consequent enhancement of myocardial oxygen demand increases CBF associated with flow-mediated dilatation of prearteriolar vessels. Stimulation of endothelial α-adrenergic receptors also leads to the release of NO, contributing to dilatation of resistance arteries. Also in this case, however, a direct vasodilator effect through stimulation of smooth muscle cell $ß_2$-receptors or an increased response of α-adrenergic-mediated constriction of SMCs might complicate the interpretation of the response to CPT. The test is generally safe and well tolerated; rare side effects include the induction of vasovagal reflexes (with orthostatic syndrome and/or bradycardia). The normal increase of CBF in response to CPT has not clearly been defined, and significantly variable results have been reported in different studies, although the variability seems to be lower than that seen with other stimuli [13].

3.3 Noninvasive Methods for the Assessment of CBF and MBF

3.3.1 Transthoracic Doppler Echocardiography

TTDE allows the measurement of CBF velocity which is taken as an indirect measure of CBF (Fig. 3.1). Coronary microvascular function is usually assessed in the LAD artery, which is easier to visualize using this technique compared to other coronary artery branches; in several patients, however, the test can also be

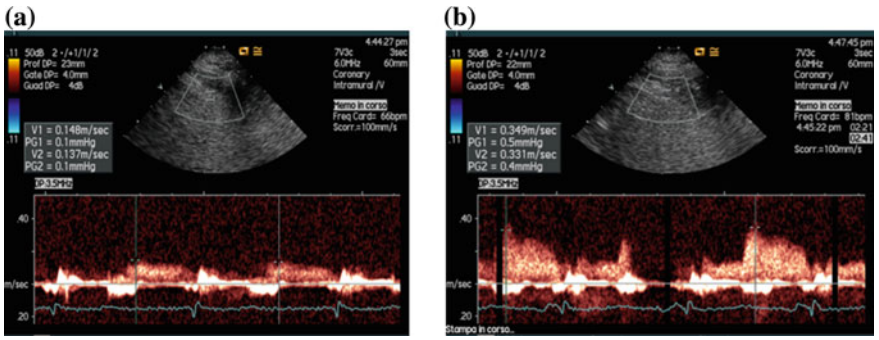

Fig. 3.1 CBF recording at baseline (**a**) and at peak adenosine (140 μg/Kg/min for 90 s; **b**) in the LAD coronary artery by TTDE. A clear increase of CBF velocity is seen during the pharmacologic stimulus

performed in the left circumflex coronary artery and in the posterior descending coronary artery [14, 15].

The arteries are visualized using color-Doppler flow mapping guidance, with a velocity range of 12–16 cm/s. A high-frequency transducer (5–7 MHz) is used to visualize the mid-distal LAD which is close to the chest. For the posterior descending coronary artery and the circumflex arteries, which are deeper, a low-frequency transducer (3.5 MHz) is instead used.

CBF in the mid-distal part of the LAD is identified in a parasternal view, with the patient in the left lateral decubitus. CBF in the posterior descending coronary artery can be visualized from a modified apical two-chamber view, whereas CBF in the distal part of the left circumflex coronary artery (or in its marginal branches) can be searched on the basal and mid-portion of the left ventricular lateral wall in the apical four-chamber view [14, 15].

CBF velocity is measured by pulsed wave Doppler echocardiography, using a sample volume of 3–4 mm placed on the color signal in the artery, with the incident angle kept as small as possible (below 40°). Diastolic CBF velocity measurements are performed offline by contouring the spectral Doppler signals, using the integrated software package of the ultrasound system. CBF velocity is measured at baseline and during vasodilator stimuli, and is usually determined as an average of three consecutive cardiac cycles (Fig. 3.1). CFR is measured as the ratio of hyperaemic diastolic peak flow velocity during maximal vasodilator stimulation over basal flow velocity. Notably, during the administration of the vasodilator stimulus, the probe must be kept in the same position as at baseline, and machine settings, including size of sample volume and velocity scale, maintained constant.

Reproducibility studies have shown that both intraobserver and interobserver variability of TTDE-CFR assessed by skilled operators does not exceed 5 %. Interestingly, the few studies that assessed intraindividual variability of TTDE

results have shown high reproducibility of measures, with a coefficient of variation not exceeding 6 % [16, 17].

Several studies have investigated the reliability of TTDE in assessing coronary microvascular dilator function by comparing the results with those obtained with the gold standard method of intracoronary Doppler flow wire recording [18–23]. These validation studies, usually performed in patients undergoing coronary angiography for suspected CAD, have shown that TTDE is feasible in the majority of patients, and show a high agreement with CFR obtained with intracoronary Doppler recording, with correlation coefficients ranging from 85 to 97 %, and consistent concordance by Bland-Altman analysis [18–20].

In most validation studies CFR was assessed in the LAD coronary artery, in which TTDE allows valuable measurements of CBF velocity in 78–91 % of patients [18–20]. The fewer studies performed in other arteries have shown that a reliable test could be obtained in 70–81 % and in 43–72 % in the posterior descending and in the left circumflex coronary arteries, respectively [21–23].

In a small study on 10 healthy volunteers, CFR assessed by TTDE was compared with that obtained by PET, showing again a high agreement with the reference method [24].

Accordingly, validation studies have shown good reliability in identifying patients with reduced CFR. This is usually identified by values lower than 2.0, which are unlikely to be detectable in apparently healthy subjects (Fig. 3.2) [25]. In these studies average CFR values in response to adenosine ranged from 2.92 to 4.5 [25–31] (Table 3.2), likely in relation to some differences among studies in age, gender, and/or presence of cardiovascular risk factors.

TTDE has been used to assess coronary microvascular dilatation in several clinical conditions known to be characterized by CMD, showing results comparable to those found in the same groups of patients with other, more standardized methods. Although studies directly validating TTDE in these clinical conditions

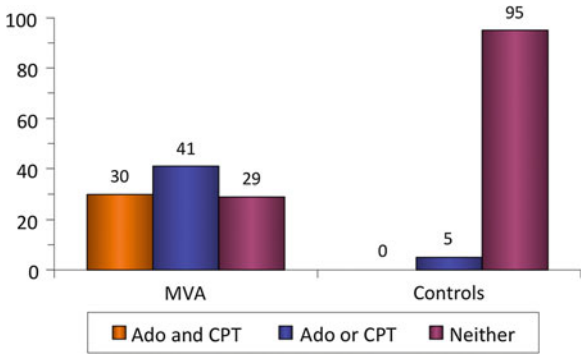

Fig. 3.2 Abnormal CBF response to adenosine (Ado; CFR < 2.0) and/or to CPT (CFR < 1.56) in 72 patients with MVA and in 20 healthy subjects controls. Impaired vasodilation in response to at least one of the two stimuli (according to the cut-off levels indicated) was present in 5 % only of controls compared to 71 % of patients. Data from Lanza et al. [1]

Table 3.2 Coronary flow reserve assessed by transthoracic Doppler echocardiography in healthy subjects

Study	No. pts (M/F)	Age	Vasodilator stimulus	CFR value
Otsuka [26]	15 (15/0)	27	Adenosine	4.4 ± 0.91
Hozumi [27]	15 (15/0)	29 ± 4	Adenosine	4.02
Kiviniemi [28]	41 (41/0)	24 ± 2.3	Adenosine CPT	3.88 ± 1.0 1.31 ± 0.34
Oe [29]	28 (28/0)	65	Adenosine	3.85 ± 1.04
Khan [30]	27 (17/10)	26 ± 10	Adenosine	3.73 ± 0.72
Shiina [31]	39 (39/0)	29 ± 4	Adenosine	3.38 ± 0.49
Sestito [25]	20 (9/11)	52 ± 7	Adenosine CPT	2.92 ± 0.9 2.42 ± 0.7

CFR coronary flow reserve, *CPT* cold pressor test

are lacking, the concordant results with studies using other methods further support the reliability of this simple noninvasive tool.

TTDE has been used to assess the presence of CMD in several groups of individuals, including those with cardiovascular risk factors only [32, 33], as well as in patients with idiopathic dilated cardiomyopathy [34], HCM [35], MVA [25, 36], and takotsubo syndrome [37].

TTDE has also been used to assess the effects of antihypertensive treatment [32], and a relation between reduced CFR assessed by TTDE and clinical outcome has been observed in early studies in patients with dilated cardiomyopathy or HCM [34, 35].

TTDE presents several advantages compared to other methods used for assessment of coronary microvascular function and CFR. It is totally noninvasive, easily available at bedside, not time-consuming, cheap and suitable for serial measurements to follow coronary microvascular function over time or check the effects of therapeutic interventions.

However, some important limitations of the method should be acknowledged. First, at present there is sufficient evidence of its reliability only when coronary microvascular function is assessed in the LAD artery. Second, a valuable echographic window cannot be obtained in all patients. Third, the test requires appropriate experience by the operator.

3.3.2 Myocardial Contrast Echocardiography

Myocardial contrast echocardiography is a noninvasive imaging technique which exploits properties of intravenously administered microbubbles, which act as a contrast agent, to assess MBF. On standard echocardiography, indeed, blood flow

cannot usually be detected because red blood cells are very poor backscatters due to their small dimensions and to mild differences only in acoustic impedance as compared to plasma. Visualization of microbubbles can instead occur due to the peculiar ultrasound-bubble interaction. Due to their dimension smaller than the wavelength used in diagnostic echocardiography, microbubbles, such as red blood cells, would be unable to reflect transmitted ultrasound beam. However, they scatter ultrasound waves, producing a signal reliably detected by appropriate echocardiographic probes [38].

Microbubbles are constituted of high molecular weight gases (nitrogen or fluorocarbon gas) encapsulated in a shell of phospholipids or albumin, and act as intravascular agents, as they do not cross the endothelial layer [38]. When injected in a peripheral vein, microbubbles mix with blood and reach the right cardiac chambers. Then, due to their small sizes (1.1–8 μm), they freely pass throughout pulmonary capillaries and reach the left ventricular cavity and the coronary circulation, thus depicting the distribution of MBF.

When ultrasound energy, expressed as a mechanical index, is kept low within the diagnostic range, the scatter signal of microbubbles enhances detection of blood flow within the left ventricular cavity, but it is still too weak to be differentiated from that generated by the myocardial walls. By increasing the mechanical index, however, microbubbles initiate to resonate producing cycles of compression and rarefaction; this results in signals of low amplitude at a frequency (second harmonics) two times higher than the fundamental one, which can be detected by the probe and can therefore be processed to enable visualization of myocardial blood pool.

Similarly to microspheres in the experimental setting, the signal derived from microbubbles is proportional to their concentration in the blood compartment. During continuous intravenous infusion, the signal is related to myocardial blood volume and MBF. Accordingly, myocardial regions supplied by dysfunctional or damaged microcirculation appear as completely or partially not opacified (i.e., display perfusion defects) (Fig. 3.3).

Myocardial perfusion by contrast echocardiography can be assessed by a semiquantitative method based on a scoring system, which grades each of 16 or 17 segments of the left ventricle as 1, 2, or 3 when normal, reduced/delayed, or absent opacification is seen, respectively. Furthermore, perfusion defects can be quantitated by measuring their endocardial length or transmural area and expressing them as percentage of total endocardial border length or total myocardial wall area, respectively.

By plotting the curve of microbubble intensity over time, a quantitative measure of MBF can also be calculated as follows: $y(t) = A\ (1 - e^{-\beta t})$, where y is the signal intensity, A is the plateau intensity, β reflects the rate of rise of intensity from microbubbles (hence, blood velocity) and t represents the pulsing interval. A reliable measure of MBF is provided by $A \times \beta$ (44). Measures of MBF by this method were found to be comparable to those obtained by PET [39]. Of note, some software automatically encodes different grades of myocardial perfusion into various colors, thus providing a map of LV perfusion.

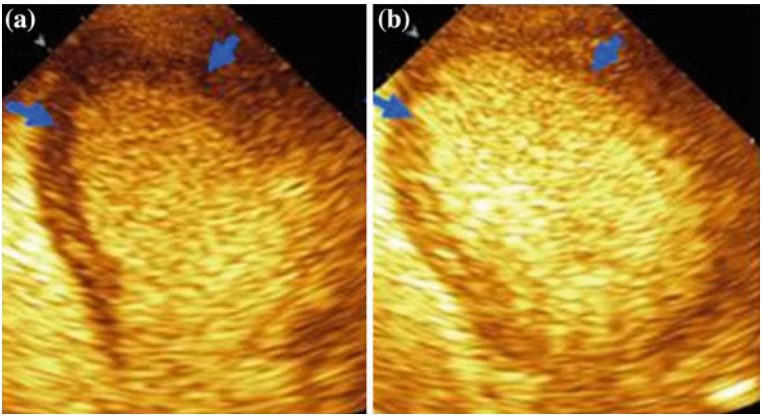

Fig. 3.3 Myocardial contrast echocardiography performed at rest (**a**) and at the peak of adenosine administration (**b**) in a patient with a tako-tsubo syndrome. Both panels show an apical 4-chamber view; the wide perfusion defect, clearly visible in dysfunctional segments (between *arrows*) in **a** improves significantly during adenosine infusion (**b**). Data from Lanza et al. [1]

To evaluate myocardial perfusion by contrast echocardiography, the contrast agent is given intravenously through an antecubital vein access, by continuous slow infusion (at the rate of 0.8–1 mL/min, depending on the concentration necessary to achieve the best compromise between clear visualization and avoidance of attenuation artifacts), which allows a better assessment of myocardial perfusion compared to bolus administration; the latter is instead usually sufficient for intracardiac shunt detection and intracavitary endocardial border delineation.

In the clinical setting myocardial contrast echocardiography has often been used to assess the state of coronary microcirculation in patients with acute myocardial infarction undergoing successful recanalization of the infarct-related artery [38, 40–56] (Table 3.3).

Importantly, a high agreement has been shown between contrast echocardiography and CMR, or single photon emission computed tomography [57], in detecting and quantifying the extent of regional myocardial underperfusion. Interestingly, quantitative measures of MVO by contrast echocardiography appeared the most reliable predictors of postischemic left ventricular remodeling in one study in patients treated by primary PCI [51].

Similar to TTDE, myocardial contrast echocardiography is an easy to perform method, friendly usable by the operators, with a favorable cost-effectiveness ratio. However, its wide application in clinical practice has been limited by safety issues following the report of some major adverse events occurring in a few critically ill patients after contrast administration, which urged Food and Drug Administration and European Medicines Agency (EMEA) to forbid use of microbubbles in the cardiovascular arena [58]. This black box warning was removed in April 2008,

Table 3.3 Myocardial contrast echocardiography applications in different clinical settings

	Subjects (n)	Clinical setting	Object of evaluation	Reference imaging technique
Senior [38]	52	CAD	Stress perfusion defect	Coronary angiography
Ito [40]	39	MI	No-reflow	Standard echo
Ito [41]	21	MI	Risk area	Standard echo
Kamp [42]	59	MI	Perfusion defect	Standard echo
Ballcells [43]	30	MI	Risk area/no-reflow	Dobutamine stress echo
Galiuto [44]	24	MI	No-reflow	Standard echo
Bolognese [45]	124	MI	No-reflow	Standard echo
Agati [46]	12	MI	No-reflow	SPECT
Janardhanan [47]	42	MI	No-reflow	CMR
Moir [48]	90	CAD	Stress perfusion defect	Coronary angiography
Galiuto [49]	50	MI	No-reflow	Standard echo
Trindade [50]	20	MI	No-reflow	CMR
Galiuto [51]	110	MI	No-reflow	Coronary angiography
Abdelmoneim [52]	2	HM	Vascularity	Standard echo
Hayat [53]	83	CAD	Stress perfusion defect	SPECT
Senior [54]	662	CAD	Stress perfusion defect	SPECT
Mansencal [55]	31	HM	Vascularity	Histopathology
Galiuto [56]	20	Tako-tsubo	Perfusion defects	Standard echo

A myocardial blood volume, *CAD* stable coronary artery disease, *CMR* cardiac magnetic resonance, *HM* heart masses, *MI* myocardial infarction, *PCI* percutaneous coronary intervention, *SPECT* single photon emission tomography

after excluding a strict cause-effect relation between microbubble injection and adverse clinical events. Nevertheless, EMEA has left a warning on the use of microbubbles in the acute phase of coronary syndromes, which still limits clinical application of myocardial contrast echocardiography.

3.3.3 Positron Emission Tomography

PET is a radionuclide technique that allows, using specific tracers, acquisition of images that reflect specific functional aspects of a specific tissue.

Imaging with PET offers unrivaled sensitivity and specificity for the noninvasive study of coronary microcirculation in man. Cardiac research with PET has flourished over the past 20 years, but it is only more recently that cardiology has fully exploited the potential advantages offered by this exciting technology. Scanning of the heart is more challenging than that of other organs mainly because of artifacts generated by cardiac and respiratory motion.

Positron emitters do not exist in nature and they must be produced artificially by means of a particle accelerator (generally a cyclotron). Positron emitters with very short half-lives have to be produced in the vicinity of the scanner and necessitate the installation of cyclotron and radiochemistry facilities. Positron emitters with long half life can be delivered from a relatively remote site of production.

Positrons are emitted with a continuous range of energies up to a maximum, which is characteristic of each particular isotope. Positron energy is reduced by Coulomb interaction with atomic electrons and *annihilates* with an electron when its energy has been reduced to close to zero resulting in a pair of photons flying off in opposite directions with energy of 511 keV. Positrons emitted from a tracer injected into the body are not measured directly, but indirectly from the photons emitted when the positron annihilates with an electron. Detectors placed on both sides of the active volume are connected in a so-called coincidence circuit so that if both detectors record an event within a very short interval (about 10^{-8} s), it is assumed that a positron annihilation has taken place [59].

PET has been shown to be a reliable tool to quantify MBF (Fig. 3.4) [60, 61]. The two tracers most widely used to measure MBF by PET are oxygen-15 labeled water ($H_2^{15}O$) [62–64], and nitrogen-13 labeled ammonia ($^{13}NH_3$) [65–68] (Fig. 3.5). $^{13}NH_3$ is administered intravenously as a bolus, whereas $H_2^{15}O$ can be given either intravenously, as a bolus injection or as a slow infusion, or by inhalation of oxygen-15 labeled carbon dioxide ($C^{15}O_2$), which is converted to $H_2^{15}O$ by carbonic anhydrase in the lungs.

Rubidium-82 (^{82}Rb) [69, 70], was initially used for quantification of MBF. PET studies with ^{82}Rb, however, are limited by the significant dependence of its myocardial extraction on flow rate and on myocardial metabolic state, which can make quantification of regional MBF less accurate, particularly during hyperemia and in metabolically impaired myocardium. In addition, the high positron energy of this radionuclide results in relatively poor image quality and in a reduced spatial resolution.

While PET cameras measuring MBF usually work in 2-dimensional mode, it has now become available a new generation of PET systems that works in 3-dimensional mode, with potential benefits, in particular, in efficiency [71].

The most important advantage of PET in assessing coronary microvascular function is a reliable noninvasive quantitative measure of MBF, both at rest and

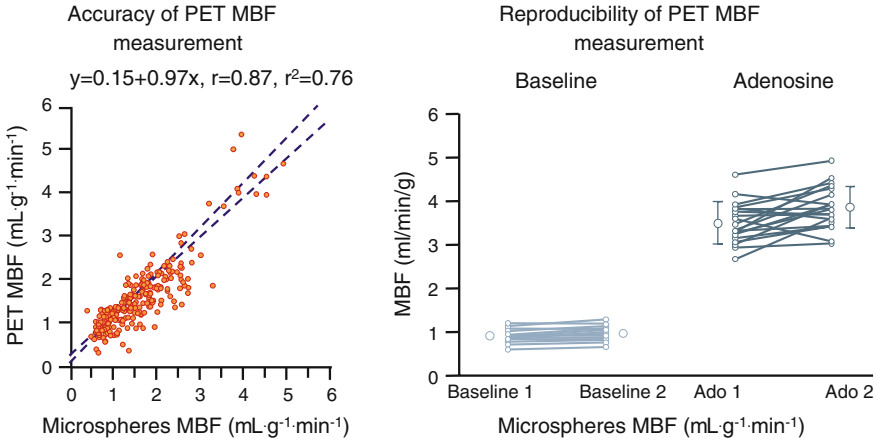

Fig. 3.4 Accuracy (*left*) and reproducibility (*right*) of absolute MBF (mL/min/g) measured with PET. *Left panel* comparison between MBF measured with radioactive microspheres (x axis) and PET with $H_2^{15}O$ (y axis) in anesthetized pigs. There is a good agreement between the two measurements over a wide range of flows. *Right panel* short term reproducibility of baseline and hyperemic (adenosine) MBF measured with PET and $H_2^{15}O$, in a group of healthy human volunteers. Adapted from Camici et al. [61]

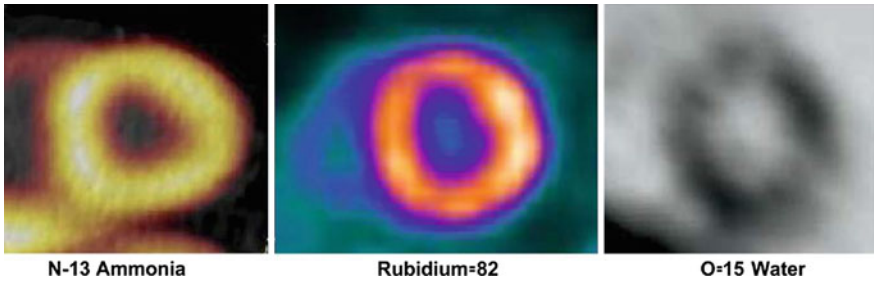

Fig. 3.5 Short axis PET images of MBF obtained with different flow tracers. Adapted from Schindler et al. [68]

during vasoactive stimuli, thus allowing to establish whether a reduction of CRF is related to a reduction of maximal MBF or rather than to an increase of MBF, as can be seen in hyper-adrenergic states. A further merit of PET is the possibility to assess both global and regional coronary microvascular function.

Some limitations, however, need to be highlighted. First, the technique is expensive, time-consuming, and can only be performed in highly specialized centers. Accordingly, the technique is poorly available and poorly suitable for serial assessment of coronary microvascular function. Its resolution is less than optimal (about 5 mm), making it difficult to detect small areas of MBF abnormalities. Finally, the potential risk of radiation exposure should be considered,

although the dose of radiation to which patients are exposed during MBF assessment with PET can be considered negligible [60].

3.3.4 Cardiac Magnetic Resonance

Magnetic resonance imaging uses the property of resonance of nuclei of atoms exposed to a magnetic field to reconstruct images of the body. The application of powerful magnetic and radio-frequency fields induces the nuclei to produce a rotating magnetic field which is detected by a scanner and used to reconstruct images of the scanned section. Magnetic fields of different nuclei rotate at different speeds, thus allowing accurate discrimination of different structures. Administration of paramagnetic contrast agents may improve discrimination of body tissues and organs.

The assessment of myocardial perfusion by CMR is based on the changes in myocardial signal intensity of gadolinium, an extracellular contrast agent [72, 73] (Fig. 3.6). After intravenous gadolinium injection, an ECG-gated acquisition of first-pass CMR images is obtained for the next 30–60 s, with the patient holding breathing to avoid interference motion with CMR image acquisition. Quantitative measurements of MBF (in units of mL/min/g of tissue) at rest and during hyperemia can be determined based on intensity curves of regions of interest [72].

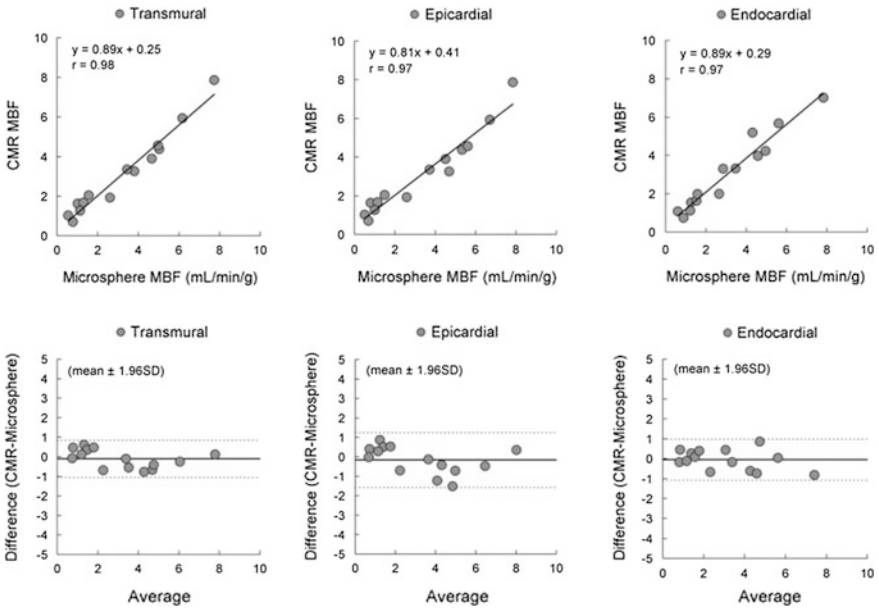

Fig. 3.6 A fully quantitative pixel-wise measurement of MBF using contrast-enhanced first-pass CMR perfusion imaging: microsphere validation in dogs and feasibility study in humans. Adapted from Hsu et al. [73]

CMR has been used to assess CMD in several clinical settings, including asymptomatic individuals with cardiovascular risk factors [74], revascularized patients with CAD [75], patients with tako-tsubo disease [76], and patients with HCM [77] or dilated cardiomyopathy [78]. Significant coronary microvascular abnormalities have also been documented by CMR in patients with MVA [79, 80]. Finally, CMR has become the method of choice to identify and characterize areas of MVO in patients with acute myocardial infarction undergoing successful primary PCI. These areas can indeed be identified as hypo-enhanced zones, suggesting coronary MVO, in the context of the infarcted regions [81], and correlated with a worse clinical outcome [82] (Fig. 3.7).

CMR perfusion imaging is characterized by high spatial resolution, lack of risk related to ionizing radiations, and lack of attenuation-related problems (e.g., for breast shadow). Furthermore, in the same examination it allows assessment not only of perfusion but also of global and regional myocardial contractility as well as tissue morphology [83, 84]. Moreover, CMR allows an accurate evaluation of subendocardial and subepicardial perfusion, as well as of regional coronary resistance, in combination with the estimated diastolic perfusion time [84–86]. Finally, by means of specific acquisition protocols it is possible to visualize areas of postischemic edema of the left ventricle [84].

Some important limitations, however, need to be acknowledged. To achieve an adequate signal-to-noise ratio of myocardial tissue enhancement, relatively large doses of gadolinium are needed. This affects the signal processing for MBF quantification, an issue that has only partially been resolved by using methods for nonlinear myocardial signal intensity correction [87]. Concerns about toxicity of

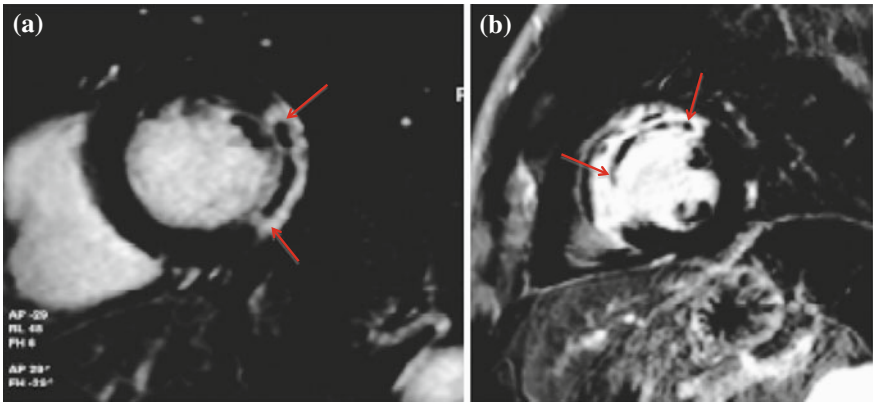

Fig. 3.7 Short axis images of the left ventricle obtained with CMR after injection of gadolinium (late enhancement), demonstrating MVO in a patient with posterolateral myocardial infarction from occlusion of the left circumflex artery (**a**), and in a patient with anteroseptal infarction (**b**). Note the area of hypoenhancement encompassed within the core of hyperenhanced infarcted myocardium (**a**), and the hypoenhanced area of MVO extending from the subendocardium (**b**). Adapted from Hombach et al. [82]

gadolinium-based contrast agents have also recently been highlighted, particularly in patients with chronic renal failure, in whom their use is associated with nephrogenic systemic fibrosis [88]. Accordingly, gadolinium should not be used in patients with a glomerular filtration rate $\leq$30 mL/min.

Postprocessing requires manual definition of myocardial regions of interest as well as of subendocardial and subepicardial areas, which can be time consuming and introduce some bias. Furthermore, during first pass, a fraction of gadolinium may diffuse into the interstitium; accordingly, myocardial signal intensity may depend not only on coronary perfusion, but also on tissue blood volume, size of the extravascular compartment and degree of capillary permeability, which can complicate quantitative assessment of MBF [89, 90]; to overcome these issues, however, specific models of signal analysis have been proposed and validated [91, 92].

Finally, some general conditions may preclude assessment of myocardial perfusion by CMR, including claustrophobia, arrhythmias, and implanted devices.

3.4 Invasive Methods

Several invasive techniques have been proposed for the assessment of coronary microvascular function, although this is now predominantly assessed by intracoronary recording of CBF by Doppler and pressure wires.

3.4.1 Thermodiluition

This method is based on the indicator-dilution (Fick's) principle [93]. Briefly, cold saline is infused at a known temperature and rate into the coronary sinus and blood temperature is measured downstream. The dilution of the tracer is indicated by the reduction of blood temperature, which is proportional to CBF, and can therefore be calculated. This method allows measurement of the whole CBF. However, if the procedure is performed in the great cardiac vein, CBF in the anterior ventricular wall (almost exclusively perfused by the LAD coronary artery) can be measured [93].

Importantly, intracoronary thermodilution can now be performed using intracoronary wires that incorporate thermal sensors. In this case, a 3 mL bolus of room-temperature saline is injected in a coronary artery; the entry of saline is registered by a shaft thermistor over the wire, while a distal sensor captures the resulting temperature shift. The mean transit time of the indicator is then calculated, which is inversely proportional to CBF. CFR in this case is calculated as the ratio between resting and hyperemic mean transit time [94, 95].

Thermodilution methods present some drawbacks. Stable positioning of the catheter, especially in the coronary sinus, can be difficult, and quantification of flow requires accurate recording of temperature and volume of the indicator at the

injection and at the distal site, which can often be problematic and display relatively high variability, also due to frequent incomplete mixing of saline and blood.

3.4.2 Gas Wash-Out Method

This method [96] is also based on the indicator-dilution principle, but uses an inert gas as a tracer (usually argon or xenon). Again, the change of gas concentration in the coronary sinus from the site of injection to that recorded downstream allows calculation of CBF.

The gas, as a radioactive tracer, can also be inhaled at a known concentration over a 5-min period. Analyses of gas concentrations by gas chromatography in arterial and coronary sinus blood samples allow calculation of CBF, as this is proportional to tissue concentration of the gas divided by its mean artery-coronary sinus difference. Alternatively, the gas can be directly injected in the coronary arteries. These methods can allow assessment of regional CBF, based on the scintigraphic detection of activity of the radio-labeled gas. However, the latter approach has major limitations in several clinical conditions.

3.4.3 Intracoronary Doppler Flow Wire

Intracoronary Doppler wires allow direct measurement of CBF velocity in single epicardial arteries, based on the Doppler effect, which establishes that the velocity and direction of blood flow can be derived by determining the frequency shift resulting from the emitted and the returning ultrasound waves, according to Doppler equation [97].

Intracoronary Doppler wires can incorporate a pressure sensor that allows measurement of intracoronary blood pressure. The product of CBF velocity by the section area of the vessel gives a measure of CBF.

Although CBF velocity measurements from Doppler signals are robust, determination of the cross-sectional area of the vessel for calculations of CBF remains problematic even with quantitative coronary angiography. However, this issue is of limited relevance in case of normal coronary arteries, due to the usually limited variations of epicardial vessels during administration of vasodilator stimuli for the assessment of CFR.

Technical problems may also impair the correct acquisition of the signal, including guiding catheter obstruction to flow, poor zeroing/calibration, and signal loss. Additionally, suboptimal guide catheter engagement may result in inadequate delivery of vasodilator agents, thus limiting the accuracy of CFR. Technical artifacts of signal acquisition must be recognized and then minimized to obtain reliable flow data.

Some specific characteristics of the Doppler velocity waveform have also been used to deduce information about microvascular injury. In particular, the

deceleration time of diastolic flow reflects the compliance of the microvascular compartment. Rapid flow deceleration can indeed be regarded as a sign of increased coronary microvascular resistance, suggesting (pre)-arteriolar constriction [98].

Measurement of CVR can easily be added to that of CBF during invasive tests to better characterize coronary microvascular function. CVR can be measured at rest and at peak hyperemia (hyperemic microvascular resistance), thus obtaining a measure of its reduction during maximal vasodilatation [99, 100]. It can be calculated with the formula:

$$\mathrm{MAP} - \mathrm{RAP}\ (\mathrm{mm\,Hg})/\mathrm{CBF}\ (\mathrm{mL}/100\,\mathrm{g}/\mathrm{min})$$

where MAP = mean aortic pressure and RAP = right atrial pressure. However, the calculation can in most cases be reliably simplified as the ratio of coronary diastolic blood pressure over average peak flow velocity.

CVR has also been proposed to be estimated by the index of microvascular resistance measured as distal coronary pressure divided by the inverse of the hyperemic mean transit time, assessed by intracoronary thermodilution [99–101].

To circumvent the issue of cross-sectional area imaging, a similar index of resistance has been introduced, the velocity-based index of microvascular resistance, that is calculated as the ratio between central arterial pressure and Doppler CBF velocity, and is expressed in mmHg cm^{-1} s^{-1} [102].

An increased corrected TIMI frame count of contrast agent during coronary angiography [103], as well as also a higher blush grade [104] have both been considered as a rough, but sufficiently reliable, expression of increased coronary microvascular constriction. These methods provide a semiquantitative categorization of CBF, with the implicit assumption that, in the absence of significant stenosis, a slow flow in epicardial vessels and a lower opacification of myocardium, respectively, would reflect an impairment of coronary microcirculation.

Finally, a direct assessment of coronary microvascular function during catheterization might also be obtained by the use of a first-pass distribution analysis technique. This method measures the absolute CBF on angiographic images through densitometric analysis of spatial and temporal aspects of the contrast propagation through the myocardium [105, 106]. This technique would be an easy method to implement which might also be done in conjunction with routine coronary angiography. The method, however, has until now been applied and validated only in animal models, and, therefore, its reliability in man needs to be addressed before it can be recommended for use in clinical practice.

When performed carefully, invasive methods allow the most accurate assessment of CMD. They indeed allow intracoronary injection of pharmacological stimuli, such as adenosine, with the possibility to achieve maximal coronary microvascular dilatation with appropriate doses without affecting blood pressure, which might instead be reduced with the systemic administration of the vasodilator substance, with consequences on myocardial perfusion and the correct assessment of CFR. Furthermore, only invasive methods allow a reliable assessment of

Table 3.4 Comparative summary of the available methods to investigate coronary microvascular function

	Availability	Cost	Risk	Repeatability	Operator dependency	Full CMV function assessment	Quantitative CBF measure
TTDE	+++	+++	+++	+++	−	−	−
MCE	++	++	+	++	+	+	+
PET	−	−	±	+	++	++	+++
CMR	+	−	−	±	++	++	++
ICD	±	±	±	−	+	+++	++

(−) = poor; (+) = sufficient; (++) = good; (+++) = very good. *CBF* coronary blood flow, *CMV* coronary microvascular, *CMR* cardiac magnetic resonance, *ICD* intracoronary Doppler, *MCE* myocardial contrast echocardiography, *TTDE* transthoracic Doppler echocardiography.

coronary microvascular response to vasoconstrictor stimuli, as they are be integrated with angiography to exclude significant epicardial vasoconstriction.

The most reliable invasive methods to investigate coronary microvascular function are based on intracoronary Doppler recording. An advantage of this method is that it allows a separate assessment of CBF in the different coronary artery territories. The use of intracoronary thermodilution is also reliable, with data relative to the measurement of CFR comparable to those obtained by intracoronary Doppler measures [94].

Invasive methods, however, have inevitable limitations. They are more expensive compared to most noninvasive methods; they are also time-consuming, which is often incompatible with the busy routine activity of most cath labs, cannot easily been repeated serially and portend a possible increase of serious adverse events.

A comparison of the characteristics of the available methods to assess CMD is shown in Table 3.4.

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Part II
Clinical Manifestations of Coronary Microvascular Dysfunction

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

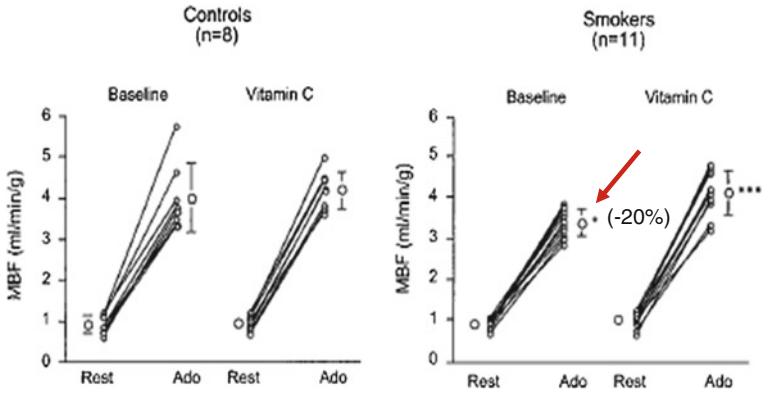

Fig. 4.1 Baseline and hyperemic (adenosine) MBF was measured with PET in two groups of healthy subjects: nonsmoking controls (*left panel*) and smokers (*right panel*). There were no differences in baseline MBF between the two groups. However, compared to nonsmokers, maximum hyperemic MBF was reduced 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].

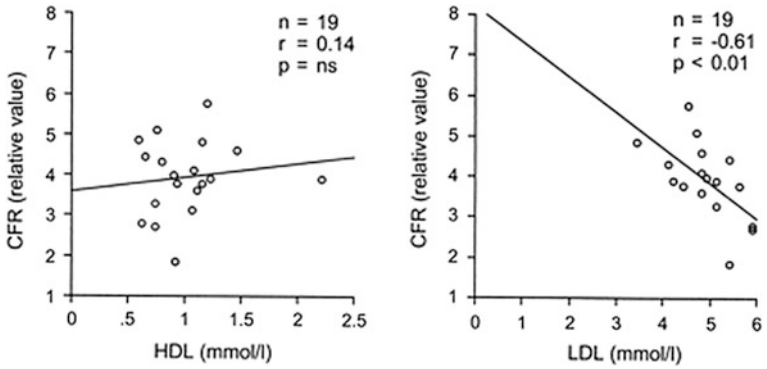

Fig. 4.2 Evidence for a significant inverse relationship between CFR, measured with PET, and LDL cholesterol (*right panel)*, in asymptomatic subjects. By contrast, no relation between CFR and HDL cholesterol (*left panel)* could be demonstrated. Adapted from Kaufmann et al. [31]

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

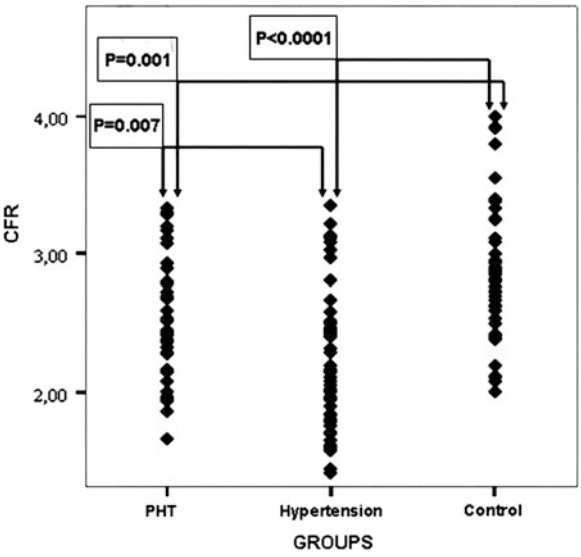

Fig. 4.3 Reduced CFR assessed by TTDE in patients with hypertension and with pre-hypertension (PHT), compared to normotensive controls. Adapted from Erdogan et al. [46]

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].

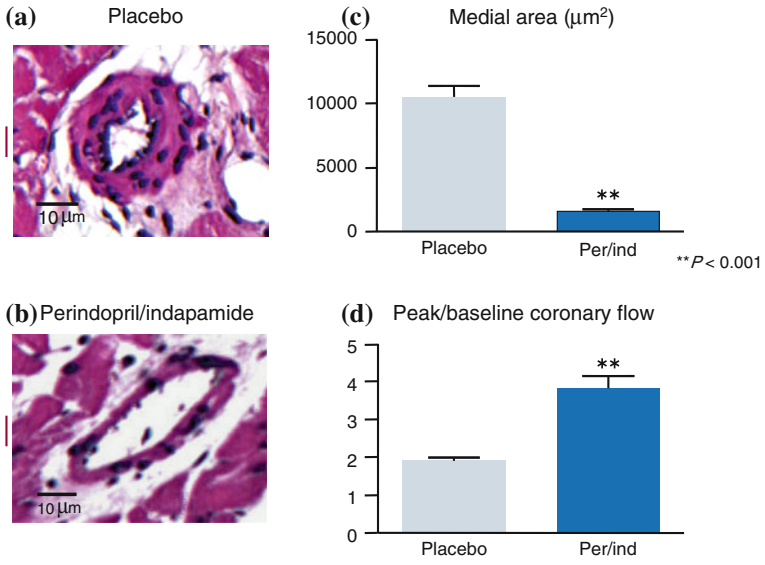

Fig. 4.4 Histological sections (hematoxylin-eosin) of intramural coronary arterioles of spontaneous hypertensive rats (SHR) treated with placebo (**a**) or perindopril + indapamide (**b**). Active treatment led to a decrease in medial wall thickness (**c**) and to an improvement of peak to baseline coronary 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].

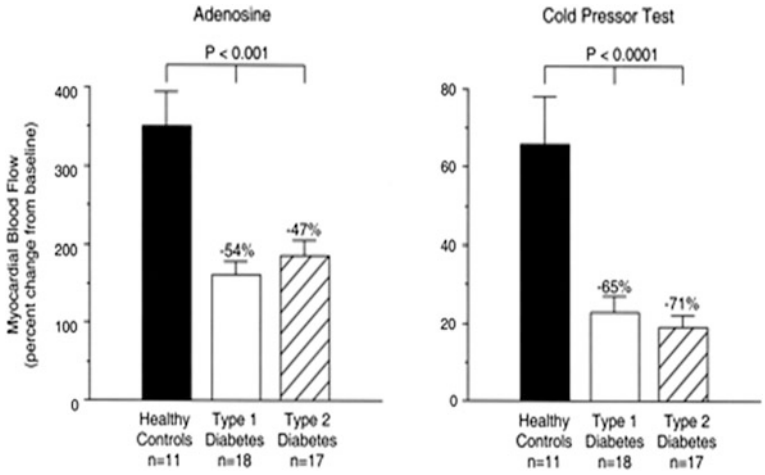

Fig. 4.5 Evidence of reduced CFR in asymptomatic patients with either type 1 or type 2 diabetes mellitus as compared with matched healthy controls in response to adenosine and CPT. Adapted from Di Carli et al. [77]

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

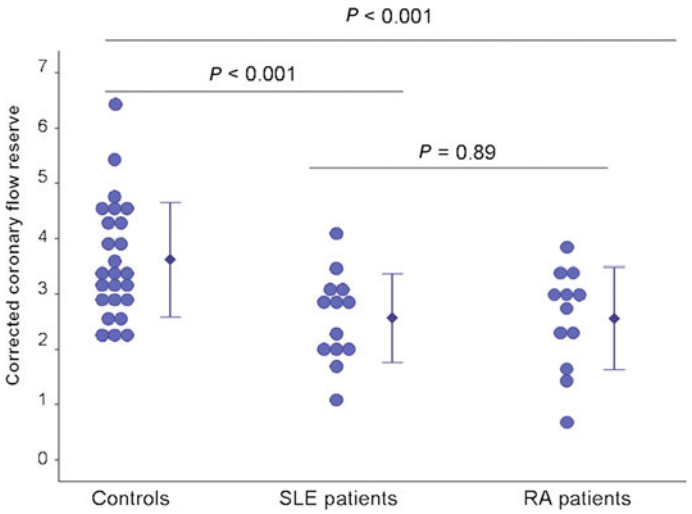

Fig. 4.6 CFR assessed by PET and adenosine in rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE) patients and in controls. Bars represent means ± standard deviations Adapted from Recio-Mayoral et al. [90]

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

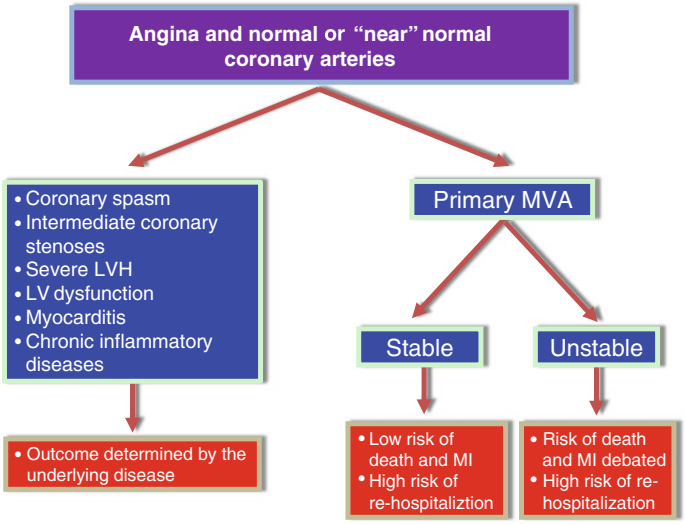

Fig. 4.7 Angina with normal or "near" normal coronary arteries represents a label which identifies a large and heterogeneous group of patients with different causes and mechanisms of angina. Microvascular angina is a well-characterized subset defined by the presence of angina associated with normal coronary 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

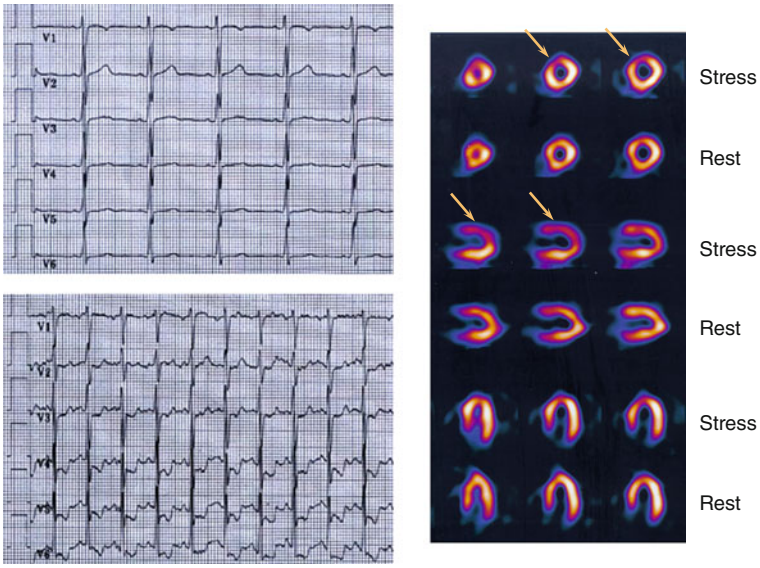

Fig. 4.8 ST-segment depression on the ECG and reversible perfusion defects on myocardial perfusion scintigraphy during exercise stress test in a patient with typical stable MVA (effort angina with normal coronary arteries). Adapted from Lanza et al. [95]

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

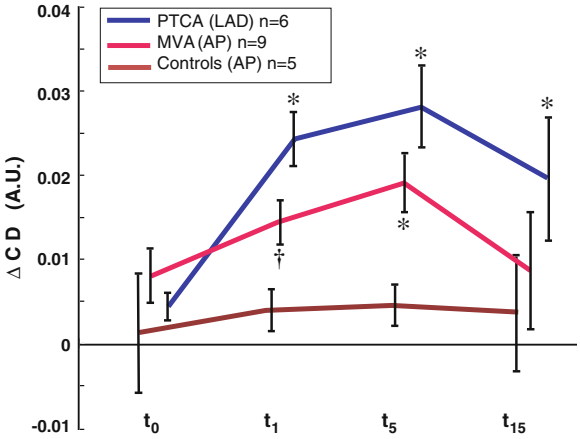

Fig. 4.9 Mean transcardiac arteriovenous conjugated dienes (ΔCDs) in patients with MVA and in controls at baseline (t_0) and 1 (t_1), 5 (t_5), and 15 min (t_{15}) after atrial pacing (AP) and in patients with CAD undergoing coronary angioplasty (PTCA). A consistent and similar increase in cardiac levels 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,

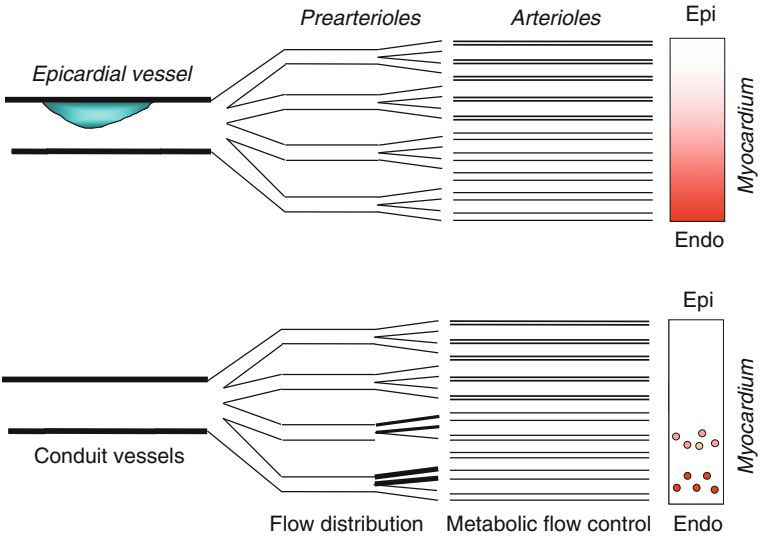

Fig. 4.10 Differences in myocardial ischemia caused by a coronary artery stenosis (*upper drawing*) or coronary microvascular abnormalities (*bottom drawing*). In case of an epicardial stenosis, ischemia involves the myocardial territory subtended by the stenotic vessel and is more severe in the subendocardium (*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).

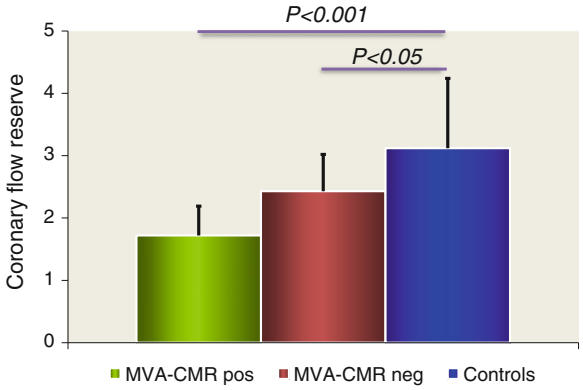

Fig. 4.11 Adenosine CFR, assessed by TTDE in the LAD coronary artery, in 18 patients with MVA and in 10 healthy controls. Patients were divided in two subgroups, based on the presence of reversible regional perfusion defects in the LAD territory at CMR during dobutamine stress test (group MVA/CMR pos, 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

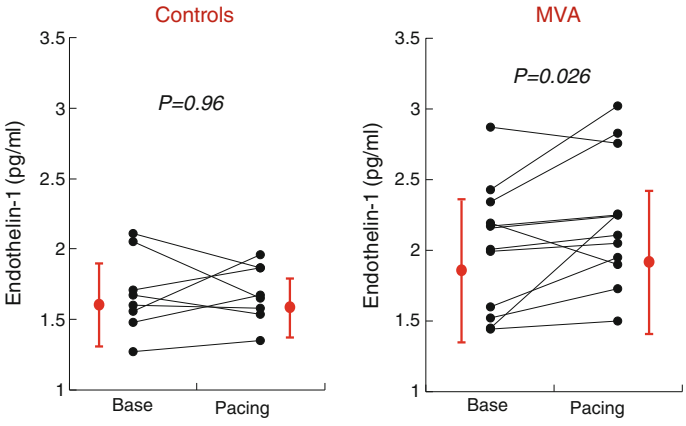

Fig. 4.12 Basal and post-atrial pacing levels of endothelin-1 in the coronary sinus in patients with MVA and in a control group of patients with paroxysmal supraventricular ventricular tachycardia. Adapted from Lanza et al. [154]

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].

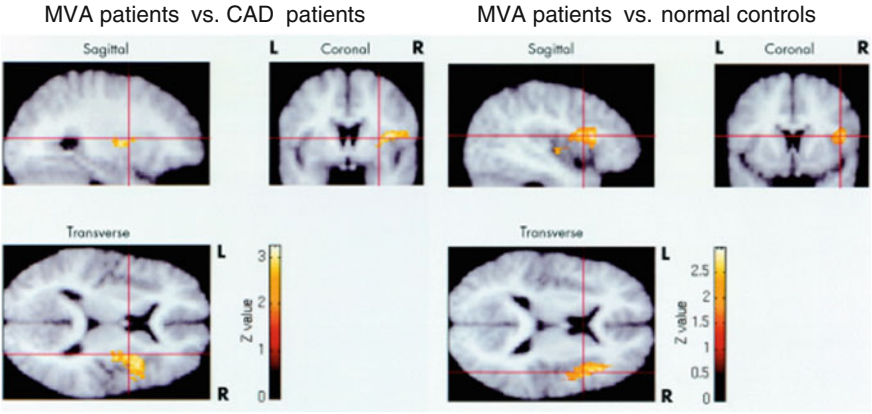

Fig. 4.13 Activation of the right anterior insula during dobutamine-induced chest pain. This feature distinguishes patients with MVA from patients with coronary artery disease *(on the left)* and from normal controls *(on the right)*. The images are obtained by projecting the results derived from the 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.

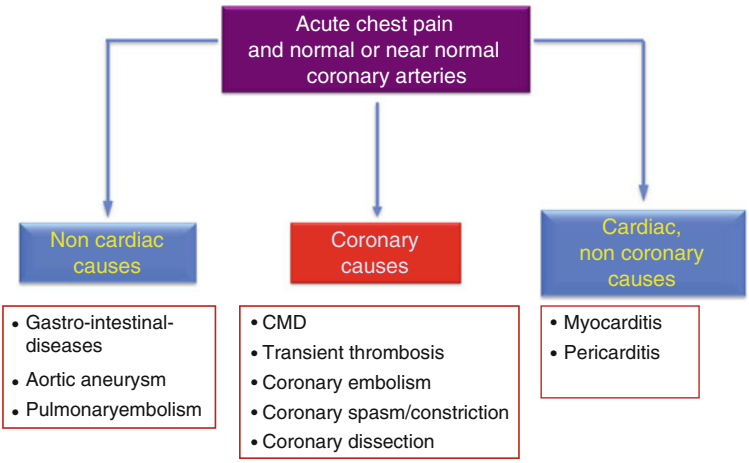

Fig. 4.14 Differential diagnosis of patients with ACS and normal or near normal coronary arteries. These patients constitute a heterogeneous group of patients. Accordingly, the outcome is influenced by the underlying mechanism of disease

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.

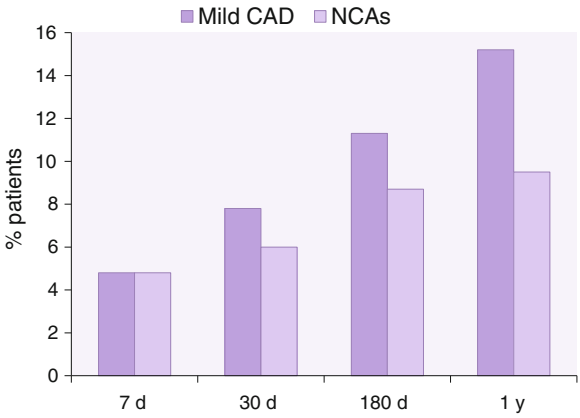

Fig. 4.15 One-year rate of the primary combined cardiovascular end-point (death, myocardial infarction, stroke, coronary revascularization, and re-hospitalization for unstable angina) in patients with normal or near normal coronary arteries enrolled in NSTE-ACS clinical trials. Adapted from Bugiardini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

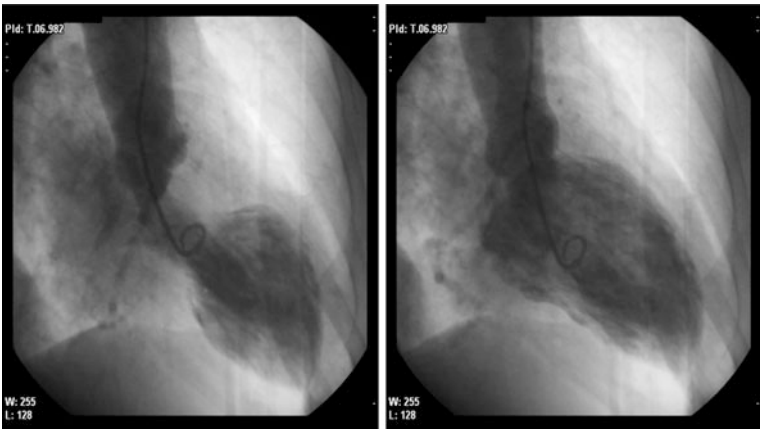

Fig. 4.16 Typical LV angiography in a patient with takotsubo cardiomyopathy. By comparing the end-systolic *(left)* and end-diastolic *(right)* frame, it can be observed a normal contraction of basal LV segments, whereas medial-distal myocardial regions show a severe impairment of contractility, which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

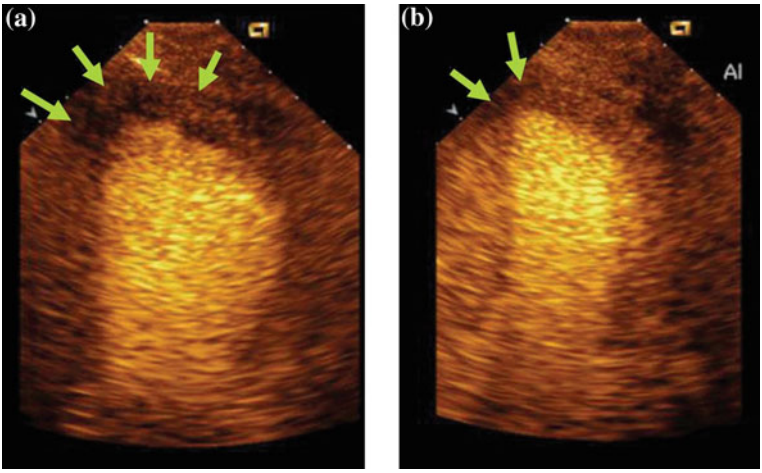

Fig. 4.17 Myocardial contrast echocardiography in a patient with takotsubo cardiomyopathy. **a** A clear perfusion defect is present at baseline within LV apical myocardium (*arrows*). **b** During administration of adenosine, a significant decrease in the extent of the perfusion defect is evident, suggesting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

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CMD in Myocardial Diseases

5

5.1 Hypertrophic Cardiomyopathy

HCM is a heterogeneous genetic heart disease, which is characterized by LVH caused by mutations in genes encoding for components of cardiomyocyte sarcomeres or adjacent Z-discs, mainly β-myosin heavy chain and myosin binding protein C [1, 2]. The pathogenic mutations are transmitted in an autosomal dominant pattern, although sporadic cases occur as a result of de-novo mutations. The prevalence of HCM is about 1 in 500 individuals (0.2 %) [3], although it often goes unrecognized in asymptomatic individuals.

The hallmark of the disease is the presence of LVH in the absence of any known acquired condition. Accordingly, the diagnosis is usually made by 2D-echocardiography, which also allows to define the characteristics of LVH and other typical abnormalities of the disease, including LV outflow tract obstruction (typically present in about two-thirds of patients) and abnormalities of the mitral valve apparatus.

LVH in HCM is usually asymmetric and mainly involves the interventricular septum, with thickness ranging from a mild (13–15 mm) to a severe (>30 mm) increase (Fig. 5.1). A diffuse increase in LV thickness is in fact detectable in about 50 % of patients, but a truly symmetric (concentric) LVH is very rare. On the other side, 10–20 % of patients display a segmental hypertrophy, confined to small regions of the LV chamber, as in the apical region [4, 5]. Histological examination of cardiac tissue in HCM reveals the typical disarray of myocardial fibers and interstitial fibrosis.

Many patients with HCM remain asymptomatic or develop mild symptoms during life, and mortality rate is about 1 % per year, which is not significantly different from that expected in the general adult population. However, HCM can result in major cardiac events, including sudden death and heart failure.

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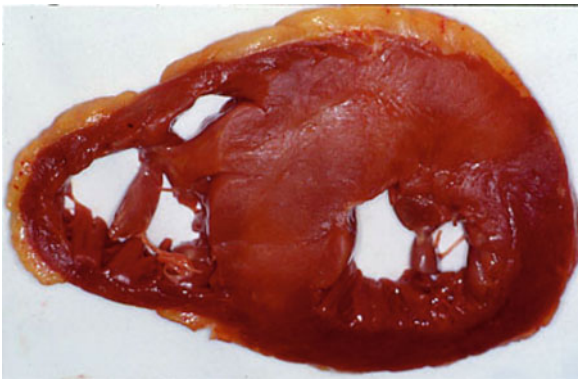

Fig. 5.1 Typical asymmetric LVH, which dramatically involves the interventricular septum, in a patients with HCM deceased due to sudden death. Adapted from Cecchi et al. [15]

Sudden death is a particularly dramatic event in HCM, as it usually hits young patients. HCM is indeed a major cause of sudden death occurring in athletes during sports' activities. The mechanism of sudden death is ventricular tachycardia/fibrillation, and ICD implantation significantly improves survival [6].

Symptoms of heart failure occur in 10–20 % of cases and are more frequent in patients with LV outflow gradient >30 mmHg, significant diastolic dysfunction or development of atrial fibrillation, which also increases the risk of thromboembolic events. Evolution toward a phenotype similar to that of dilated cardiomyopathy occurs in about 5 % of patients and is only predicted by a family history of this complication.

Since its original description, myocardial ischemia has been a recognized, but underappreciated aspect of the pathophysiology of HCM. Symptoms and signs of myocardial ischemia are indeed often found in these patients, despite the usual presence of angiographically normal coronary arteries. Perfusion defects on myocardial thallium-201 single photon emission computed tomography and lactate production in the coronary sinus during pacing stress were indeed convincingly shown in HCM patients many years ago [7].

Moreover, in the past 20 years a number of studies [8–11] have demonstrated that CFR is severely blunted in these patients due to CMD (Fig. 5.2). Notably, CFR impairment is not confined to the hypertrophied interventricular septum, but it concerns also the less hypertrophied LV free wall, in line with the evidence of widespread remodeling of intramural arterioles at autopsy [12, 13].

Notwithstanding the large evidence of data supporting an important pathophysiological role for CMD, the assessment of myocardial ischemia is currently not part of routine clinical diagnostic or management strategies in these patients, which represents a limitation that can significantly impact our capability to achieve a comprehensive evaluation of individual patients with HCM [14]. The severity of CMD in affected patients has indeed been found to be an independent predictor of long-term clinical deterioration and death from cardiovascular causes (Fig. 5.3) [15, 16].

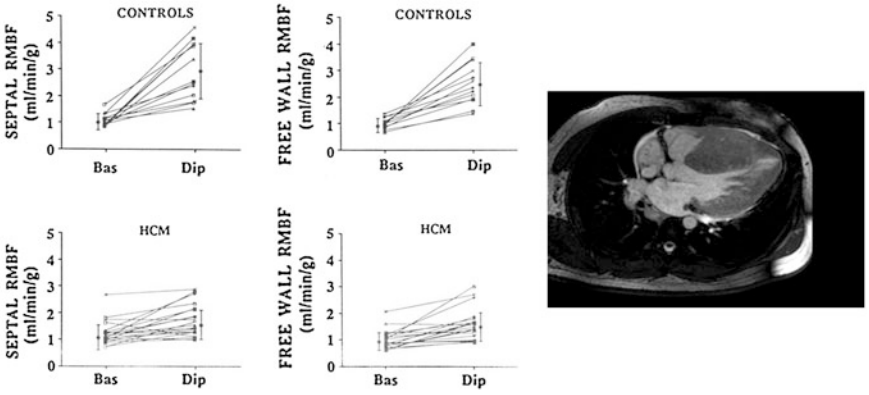

Fig. 5.2 Evidence for a significant reduction of hyperemic MBF (dipyridamole, Dip) in all myocardial regions (septum and LV free wall) in patients with HCM compared to normal controls. RMBF=regional MBF Adapted from Camici et al. [12]

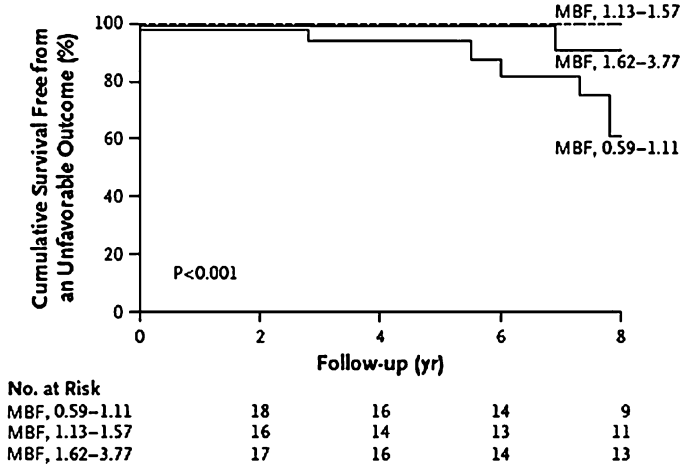

Fig. 5.3 Survival curves of patients with HCM according to hyperemic MBF. Prognosis was significantly worse in those with reduced hyperemic MBF indicating CMD. Adapted from Cecchi et al. [15]

Repeated episodes of focal myocardial ischemia, caused by CMD, might result in a progressive loss of cardiomyocytes and fibrotic replacement of the myocardium [17], which can significantly contribute to some of the severe complications of HCM, including ventricular arrhythmias and sudden death, as well as progressive LV remodeling and systolic dysfunction [18–21], eventually resulting in overt LV dysfunction and failure (Fig. 5.4) [22].

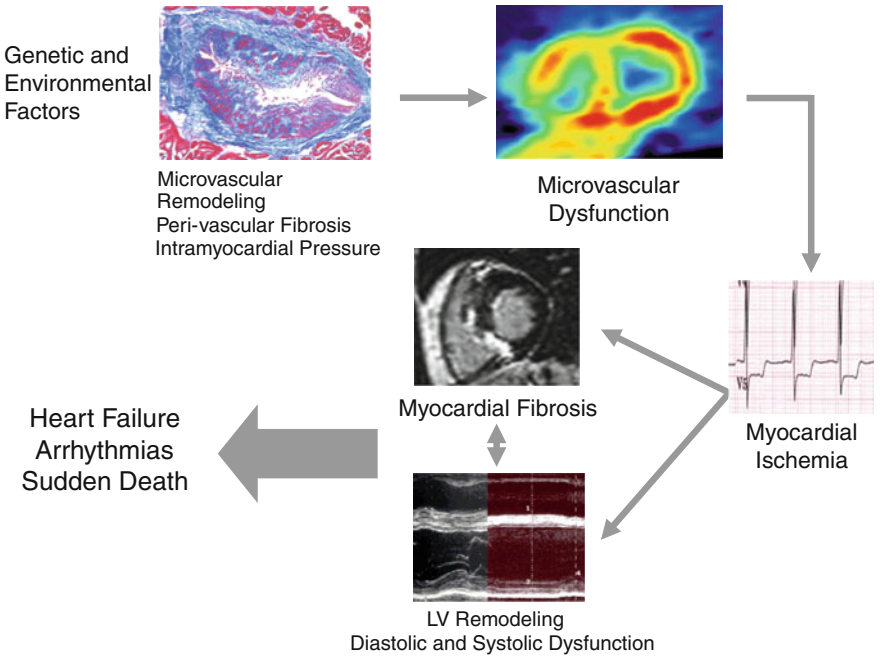

Fig. 5.4 Schematic representation of the relation between CMD and development of myocardial fibrosis, with evolution toward impaired LV function and arrhythmias, in patients with HCM. Adapted from Camici et al. [24]

More recently, several studies using CMR have led to an enhanced understanding of the role that myocardial ischemia and the resulting myocardial fibrosis may play on clinical outcome in patients with HCM. These studies have indeed demonstrated that late gadolinium enhancement, a reliable marker for myocardial fibrosis, at CMR has an outstanding prognostic value in predicting adverse cardiovascular events in patients with HCM. This has also been confirmed by a recent meta-analysis in over one thousand HCM patients, which has shown that late gadolinium enhancement significantly correlated, at an average follow-up of more than 3 years, with the development of heart failure and with all-cause and cardiac mortality, with a trend toward significance also for prediction of sudden death [21, 23–26] (Fig. 5.5).

The presence of sparse areas of fibrosis in the myocardium may indeed favor electrical instability and induction of life-threatening ventricular arrhythmias (see Chap. 4). Based on these studies, extensive late gadolinium enhancement at CMR is now considered among the features that indicate increased risk of sudden death in HCM, together with the classical predictors of familial history of sudden death, unexplained syncope, LV wall thickness >30 mm, recurrent episodes of non sustained ventricular tachycardia during ambulatory ECG monitoring and hypotensive response or attenuated increase in blood pressure during exercise [27].

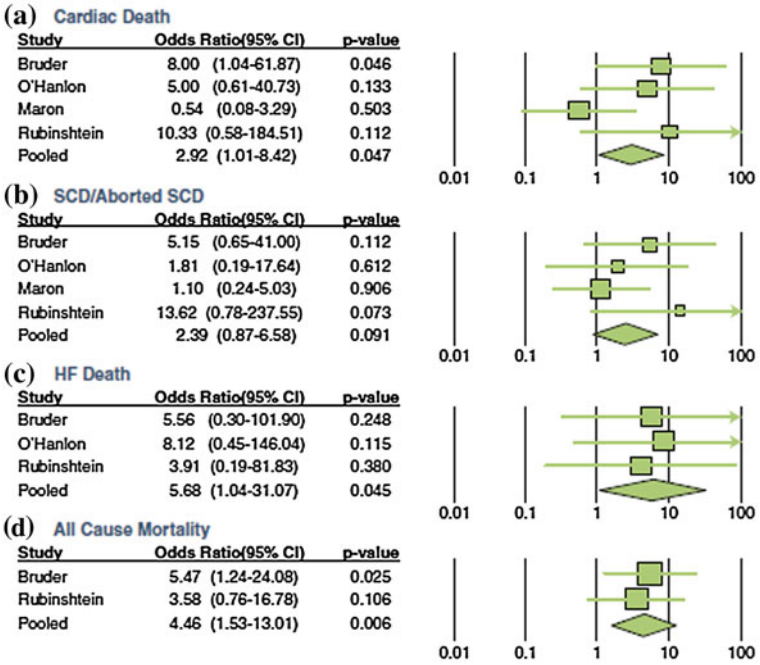

Fig. 5.5 Meta-analysis forrest plots and pooled odds ratios for clinical endpoints in HCM studies assessing the prognostic role of late gadolinium enhancement at CMR. The latter significantly predicted cardiac death, heart failure (HF) death, and all-cause mortality. Furthermore, a trend toward significance was observed for sudden cardiac death (SCD). Adapted from Green et al. [23]

It is worth noting that recent data indicate that [28] patients with evidence of sarcomere myofilament mutations are characterized by more severe CMD and an increased prevalence of myocardial fibrosis, compared with genotype-negative individuals, suggesting a direct link between sarcomere gene mutations and adverse remodeling of the microcirculation, accounting for the increased long-term prevalence of LV dysfunction and heart failure, and possibly arrhythmic events, in genotype positive patients.

5.2 Dilated Cardiomyopathy

Idiopathic dilated cardiomyopathy is a cardiac muscle disease characterized by reduced contractile systolic function with dilatation of the LV or, in some cases, of both ventricles [29]. Dilated cardiomyopathy is a major cause of heart failure, presenting an incidence of about 7 per 100,000 individuals [30]. Despite progress in medical therapy, prognosis remains unfavorable; mortality is indeed 20 % at 5 years [31], with worsening heart failure and ventricular tachyarrhythmias being the most frequent causes of death.

The specific causes of dilated cardiomyopathy remain largely unknown, and include genetic, viral, and autoimmune mechanisms [32]. In particular, an immunological reaction to an initial viral myocarditis, independently of virus persistence in cardiomyocytes, is believed a major cause of the disease, although the hypothesis remains to be proven [33].

The presence of CMD in a significant proportion of patients with dilated cardiomyopathy is suggested by the frequent occurrence of angina, which can sometimes precede the manifestation of symptoms and/or signs of heart failure, and is also supported by the detection of myocardial perfusion defects and/or regional LV wall motion abnormalities during stress tests, despite the evidence of normal coronary arteries at angiography [34].

A severely reduced CFR in patients with dilated cardiomyopathy has been demonstrated in several studies [35–39], and other studies have also shown the presence of impaired endothelium-dependent coronary microvascular dilatation [40].

Interestingly, CMD and MBF abnormalities can be diffuse or mainly localized in some heart regions, which, at PET studies, can also present increased anaerobic glucose metabolism [41, 42] (Fig. 5.6), similarly to the flow-metabolism "mismatch", shown in myocardial "hibernation" of CAD patients, which represents the adaptation of the myocardial tissue to chronic or repetitive ischemia [43]. The question remains open, however, whether CMD is part of the disease or arises late as a consequence of heart failure. In fact, several mechanisms can be involved in determining CMD in dilated cardiomyopathy, including alterations of the coronary microcirculation secondary to significant eccentric LVH and/or dilatation, extravascular compression due to increased LV filling pressure, and MBF downregulation, due to reduced energetic demand [35]. Furthermore, despite the evidence of functional coronary microvascular abnormalities, no structural abnormalities of

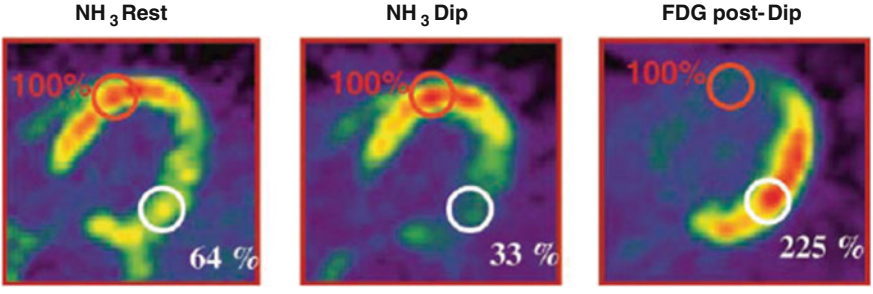

Fig. 5.6 PET scans of MBF and metabolism in a patient with early dilated cardiomyopathy. At baseline (NH_3 rest) there is evidence of reduced tracer uptake (64 % of maximum) in the posterolateral wall of the LV; this MBF defect becomes more severe (33 % of maximum) during pharmacologic stress with dipyridamole (NH_3 Dip). The ^{18}F-fluorodeoxyglucose (FDG) scan shows increased glucose utilization uptake in the hypoperfused region. In the absence of obstructive CAD, this flow/metabolism mismatch suggests myocardial ischemia related to CMD. Adapted from Neglia et al. [41]

arteriolar vessels have usually been found in these patients, although recent data suggest possible changes in arterioles below 50 μm in diameter.

Yet, several findings suggest that small coronary arteries may present functional alterations with a potential causal role in determining the cardiomyopathy, at least in a subset of patients. A reduced CFR can indeed be detected in up to 82 % of patients with early dilated cardiomyopathy (i.e., without any sign of heart failure) [36]. Furthermore, no correlation has been found between impaired peripheral microvascular endothelial function and endothelial CMD, suggesting that the latter can be largely independent of the hemodynamic effects of heart failure [44]; finally, the impairment of MBF in these patients was found to be independent of the extension of myocardial fibrosis, as assessed in explanted hearts of patients with dilated cardiomyopathy [45].

Regardless of whether CMD is a pathogenetic component of the disease or is just a consequence of the abnormal cardiac or systemic effects of the disease, its occurrence can significantly contribute to the evolution of the disease by inducing foci of myocardial ischemia. Accordingly, repeated myocardial ischemia due to CMD might result in areas of necrosis and myocardial fibrosis, which might increase the risk of both progressive myocardial dysfunction and heart failure, but also of electrical instability and sudden death, as discussed above for patients with HCM.

As in the latter patients, indeed, also in those with dilated cardiomyopathy the degree of CMD has been shown to be an independent predictor of cardiac events and is associated with an increased relative risk of death and further progression of heart failure (Fig. 5.7) [46].

A number of clinical parameters are used for risk stratification of patients with dilated cardiomyopathy, including history of syncope, detection of ventricular tachycardia on ambulatory ECG monitoring, induction of ventricular tachyarrhythmias by programmed ventricular stimulation, QRS duration, and several other ECG derived indices, including heart rate variability, baroreflex sensitivity, and heart rate recovery after graded exercise [47].

More recently, CMR has emerged as a very useful tool for risk stratification also in patients with idiopathic dilated cardiomyopathy. Wu et al. [48]. carried out a prospective study in 65 patients with dilated cardiomyopathy with LV ejection fraction $\leq$35 % who underwent CMR before placement of an implantable cardioverter defibrillator for primary prevention of sudden death. Late gadolinium enhancement at CMR was found in 27 patients (42 %); during a 17-month median follow-up, 12 (44 %) of these patients had major cardiac events compared with only 3 (8 %) of those without late gadolinium enhancement. After adjustment for LV volume index and functional class, patients with late gadolinium enhancement had an 8-fold higher risk of experiencing major cardiac events.

Along the same line, Hombach et al. [49] studied a cohort of 141 patients with dilated cardiomyopathy and found that late gadolinium enhancement was detected in 36 patients (26 %). Survival analysis showed that the presence of late gadolinium enhancement, together with a QRS >110 ms, and presence of diabetes

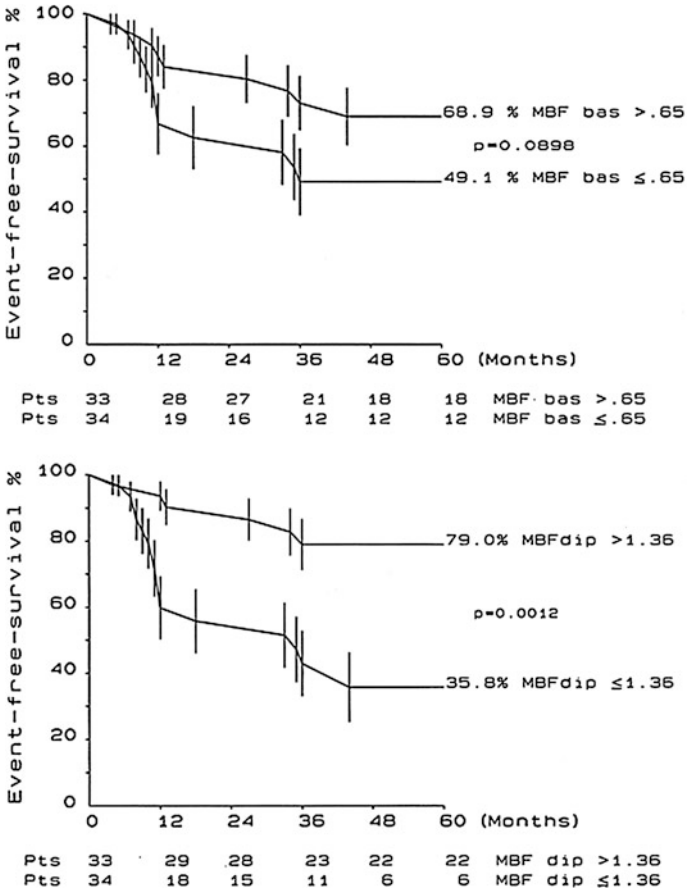

Fig. 5.7 Kaplan-Meier event-free survival plots at 5 years are shown for patients with dilated cardiomyopathy subdivided into groups according to the median value of resting MBF (MBF bas) (*top panel*) or dipyridamole MBF (MBF dip) (*bottom panel*). Adapted from Neglia et al. [46]

mellitus were significant predictors of a worse prognosis, although late gadolinium enhancement lost its predictive value in multivariable analysis.

Finally, Lehrke et al. [50], in a study of 184 patients with dilated cardiomyopathy who received an implantable cardioverter defibrillator, found late gadolinium enhancement in 39 % of patients. Patients with a total late gadolinium enhancement extension $\geq$4.4 % of LV mass had a 3.4-fold higher risk of the composite end point of cardiac death/implantable cardioverter defibrillator discharge/hospitalization for heart failure, as compared to those with less extensive late gadolinium enhancement (Fig. 5.8).

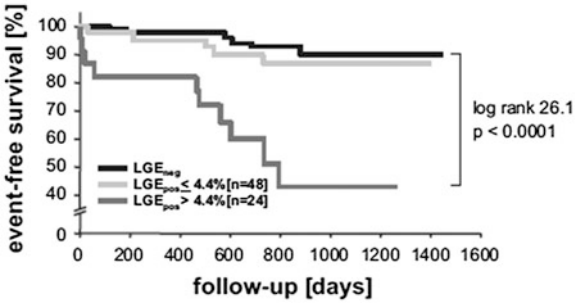

Fig. 5.8 Clinical outcome of patients with dilated cardiomyopathy according to the presence of late gadolinium enhancement (LGE), further stratified into those with an area of enhancement above or below 4.4 % of LV mass; patients with only mild enhancement had a prognosis comparable to those without evidence of enhancement. Adapted from Lehrke et al. [50]

Thus, these early data suggest that late gadolinium enhancement, reflecting the presence of fibrotic areas possibly secondary to microvascular ischemia, may have a relevant prognostic value in dilated cardiomyopathy, although this hypothesis needs confirmation in larger studies.

5.3 Aortic Stenosis

The development of LVH in patients with aortic stenosis is an adaptive response, in that it may reduce wall stress and tension in the LV. Unfortunately, hypertrophy not only provides benefits, but also has many pathological consequences, including myocardial ischemia. Angina episodes are indeed reported by about half of patients with a severe degree of aortic stenosis, and this occurs despite the evidence of normal epicardial coronary arteries at angiography [51]. Of note, the appearance of angina greatly increases the risk of sudden death, as compared to that of asymptomatic patients [52, 53].

CFR is reduced in aortic stenosis [54]. As also discussed in Chap. 2, the mechanisms of CMD in this setting are complex and include the development of severe LVH. Much of our knowledge about CBF in LVH has come from animal models. The experimental animal models, however, differ in many ways from patients with aortic stenosis, and, of course, there is no way to know whether the animal experiences angina. Nonetheless, important mechanistic data have been gleaned from these studies. First, there is a reversal of the normal subendocardial-subepicardial ratio of CBF; in normal conditions this ratio is approximately 1.2:1, appropriate to meet the physiologically higher oxygen demand of the subendocardium, where wall stress is greater than in the subepicardium. It is clear that this ratio is reduced and even reversed in LVH, especially during exercise or pacing [55–57]. Second, as noted above, CFR is impaired in LVH, due to a combination of mechanisms, including: (1) reduced time of diastolic coronary filling during

exercise or pacing-induced tachycardia [55]; (2) increased LV diastolic filling pressure and intramyocardial pressure during diastole, both contributing to impairment of perfusion selectively in the subendocardium [58]; (3) reduced capillary density, with fewer capillaries per unit of myocardial mass perfused [59]; (4) a low coronary perfusion pressure as compared with intra-cavitary pressure; and (5) increased intramyocardial systolic pressure and delay in myocardial relaxation at the end of systole, which further reduces time of coronary filling and perfusion.

Post-mortem studies have confirmed capillary rarefaction in aortic stenosis while, in contrast with hypertension and HCM, they failed to find additional structural alterations which can cause CMD like medial hypertrophy or perivascular fibrosis [60].

Recent studies in patients with aortic stenosis, based on the measurement of MBF by PET, have shed new light on the mechanisms of CMD. Resting total LV MBF has been found to increase proportionally with LV mass. As this occurs in spite of vascular rarefaction, it is likely that the increase in resting MBF is mainly sustained through metabolic vasodilatation in response to the increased myocardial oxygen demand. This is responsible for a partial exhaustion of the autoregulatory capacity of the coronary microcirculation, and therefore contributes to limit CFR. These studies have also confirmed the experimental observation that subendocardial perfusion is severely reduced and have shown that the reduction of CFR is strictly related to aortic valve area and to reduced diastolic perfusion time rather than to the increase in LV mass [61] (Figs. 5.9 and 5.10). Of note, the subendocardial and subepicardial curves correlating CFR and aortic valve area intersect at 0.92 cm^2, a figure that approximates closely to usually applied criteria for clinically severe aortic stenosis (Fig. 5.9).

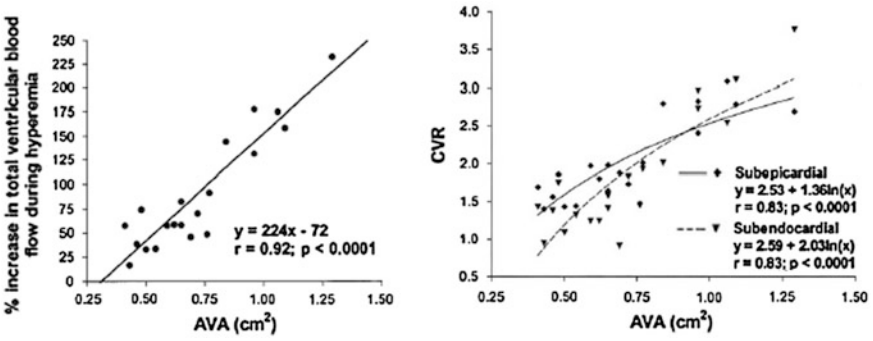

Fig. 5.9 *Left:* relation between aortic valve area (AVA) and hyperemic MBF in patients with aortic stenosis. *Right:* relation between AVA and coronary vasodilator reserve (CVR) in and CFR in subendocardial and subepicardial myocardium; progressive impairment of subendocardial perfusion is evident for decreasing values of aortic valve area. Adapted from Rajappan et al. [61]

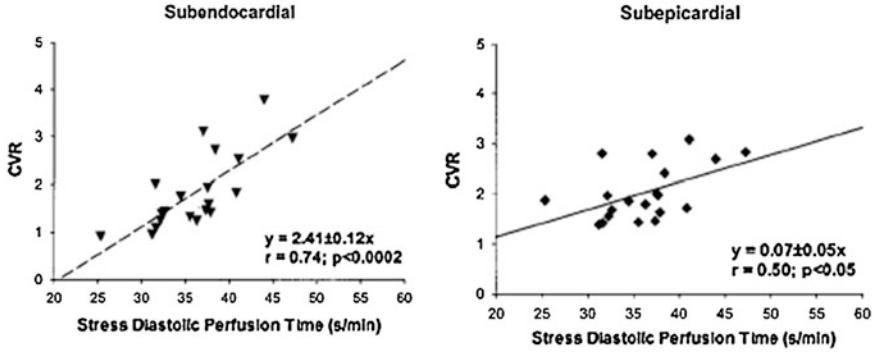

Fig. 5.10 Relation between diastolic time and coronary vasodilator reserve (CVR) in subendocardial *(left panel)* and subepicardial *(right panel)* LV layers in patients with aortic stenosis. Reduction of diastolic time results in severe subendocardial underperfusion. Adapted from Rajappan et al. [61]

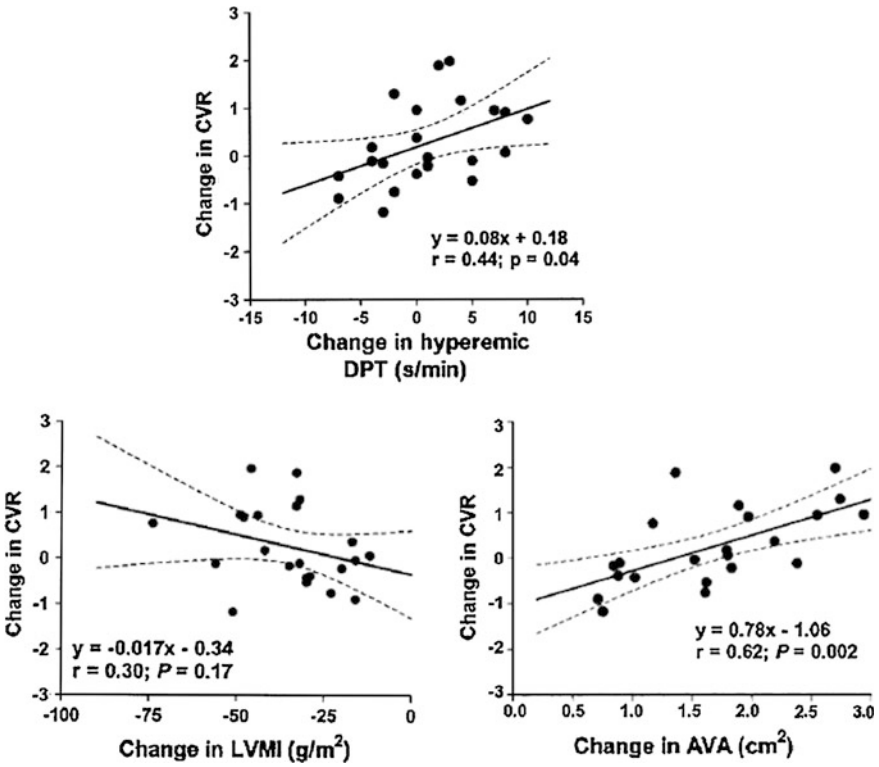

Fig. 5.11 Relation of changes in LV mass index (LVMI) *(left panel)*, hyperemic diastolic perfusion time (DPT) *(top panel)*, and aortic valve area (AVA) *(right panel)* with coronary vasodilatory reserve (CVR) in patients with aortic stenosis after aortic valve replacement. Adapted from Rajappan et al. [62]

Taken together these findings indicate that extravascular mechanisms rather than small vessel disease are responsible for the reduction of CFR in these patients. Accordingly, after aortic valve replacement the increase in CFR is directly related to the increase in aortic valve area and increase of diastolic perfusion time but not to regression of LV mass (Fig. 5.11) [62].

Interestingly, a few studies have shown that, among patients with severe aortic stenosis and normal coronary arteries, those who develop angina, as compared to those who do not develop angina, exhibit: (1) a lower CFR; (2) a higher diastolic and systolic wall stress; and (3) a reduced systolic coronary flow [63] (Figs. 5.12).

The clinical implications of a significant decrease in CFR in patients with aortic stenosis are considerable. First, decreased CFR provides a plausible explanation for why ischemic symptoms such as angina pectoris are often encountered in these patients. Second, these abnormalities provide an explanation for why they often have abnormal electrocardiographic responses to exercise, suggesting myocardial ischemia even when they do not refer angina symptoms; importantly, this

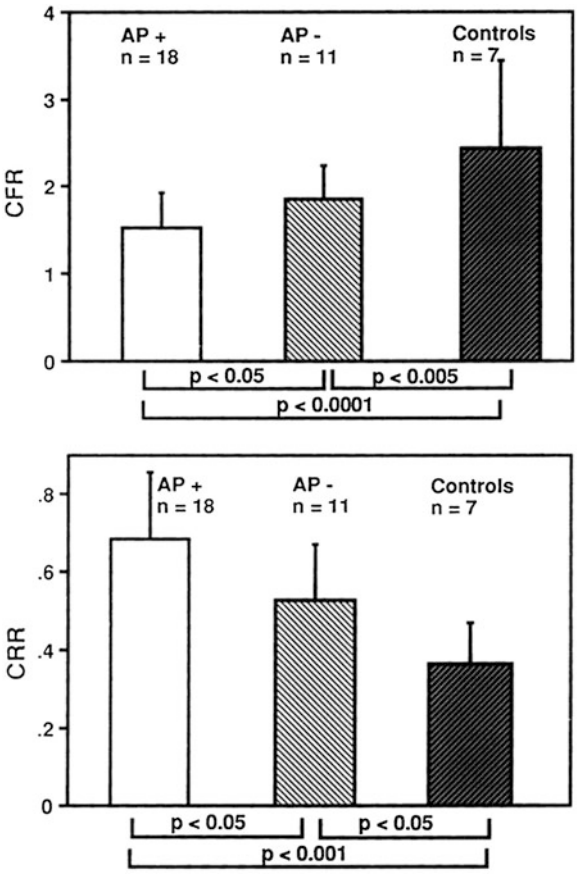

Fig. 5.12 CFR (*top panel*) and coronary resistance ratio (CRR) (*bottom panel*) in patients with aortic stenosis with anginal symptoms (AP+) or without anginal symptoms (AP−) and in control subjects. CFR was significantly reduced in AP+ patients compared with AP− patients or control subjects. Conversely, CRR was significantly increased in AP+ compared with AP- patients and control subjects. Adapted from Julius et al. [63]

significantly impairs the specificity of noninvasive approaches to diagnosing atherosclerotic coronary disease including exercise ECG, exercise nuclear ventriculogram and thallium-201 perfusion scintigraphy. Third, abnormal perfusion, if severe enough, may lead to intermittent episodes of subendocardial ischemia and eventually to diffuse subendocardial fibrosis. This could in turn contribute to the development of diastolic and systolic abnormalities in ventricular function. Although there are other mechanisms that could contribute to the pathogenesis of myocardial failure in hypertrophied ventricles, it is possible that profound alterations in perfusion are the major culprit responsible for the long-term deterioration of LV function often observed in patients with aortic stenosis.

The role played by perfusion diastolic time in causing the observed reduction of CFR and angina in patients with aortic stenosis has also important therapeutic implications. Indeed, drugs that increase diastolic time, like beta-blockers, might help in delaying the ominous onset of ischemia and angina in these patients (see Chap. 9).

5.4 Myocarditis

Recent studies have shown that parvovirus B19 and human herpesvirus 6 are the most common pathogens of viral myocarditis [64] and that the clinical presentation of patients with myocarditis can be related to the type of virus present in the myocardium [65]. Patients with myocardial parvovirus B19 infection, indeed, seem to mainly present with chest pain, whereas patients with myocardial herpesvirus 6 infection or combined parvovirus B19/herpesvirus 6 infection seem to mainly show symptoms of heart failure. These findings suggest that different viruses may have specific pathophysiologic targets, although the reasons for these differences are currently unknown.

It is known, however, that endothelial cells represent specific targets in parvovirus B19-associated myocarditis [66, 67] probably through blood group P antigen [68]. Thus, a causal relationship between parvovirus B19-related myocardial inflammation and/or infection of vascular endothelial cells and CMD can be suspected [69]. In addition, myocardial inflammation in response to viral infection was found to be associated with increased endothelial expression of human leukocyte antigen system and adhesion molecules, and to be correlated with systemic endothelial dysfunction. Taken together, these findings suggest that symptoms of chest pain in patients with parvovirus B19-associated myocarditis without significant CAD may be caused by intense coronary vasoconstriction, as a result of myocarditis-induced coronary endothelial dysfunction and/or direct infection of endothelial cells and/or SMCs. Severe vasoconstriction/spasm of microcirculation might contribute to explain ST-segment elevation in some patients, which can result from sufficiently diffuse myocardial ischemia. Accordingly, in patients with parvovirus B19-associated myocarditis, Yilmaz et al. found that intracoronary acetylcholine administration was associated with severe coronary vasoconstriction [70] in distal segments of epicardial vessels, possibly

extending to the coronary microcirculation (Fig. 5.13). The notion of severe CMD was confirmed in another study showing that myocardial virus persistence and myocardial inflammation were associated with endothelial dysfunction, as assessed by intracoronary administration of acetylcholine. Endothelial dysfunction in patients with myocardial virus persistence occurred independently of myocardial inflammation, although it was more pronounced in patients with concurrent inflammation [71]. Thus, endothelial dysfunction in patients with myocardial virus persistence seems to be mediated by mechanisms other than myocardial inflammatory infiltrates, which seem to also concurrently impair systemic endothelial function [72].

Parvovirus B19-associated CMD might be caused by severe endothelial dysfunction due to a decreased bioavailability of the vasodilator NO [73]. Interestingly, systemic inflammation (induced by vaccination) may cause endothelial dysfunction through reduction of vascular NO bioavailability and increases in oxidative stress [74, 75]. The hypothesis of endothelial dysfunction competes with the view of a coronary smooth muscle cell hyperreactivity as the underlying cause of coronary spasm, as assessed in experimental models [76]. In previous studies,

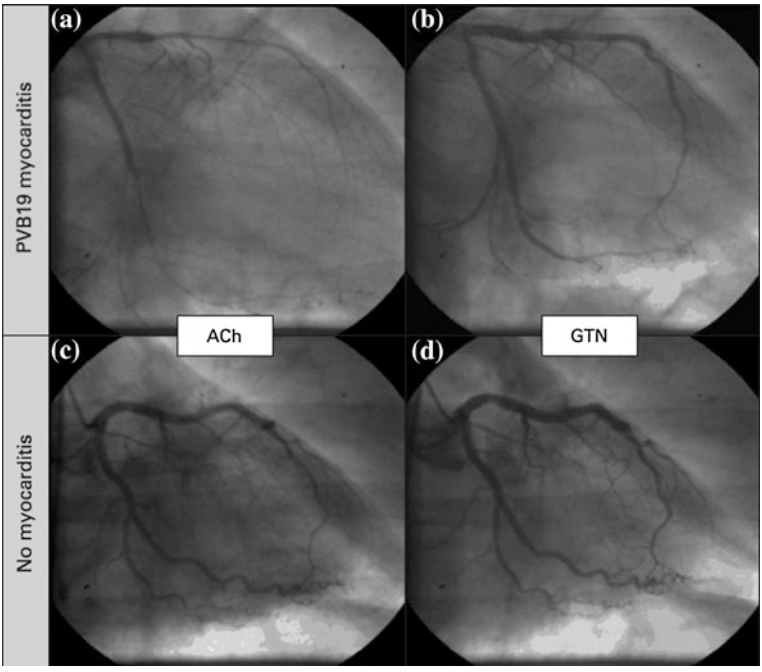

Fig. 5.13 Coronary angiograms of the left coronary artery. In a patient with parvovirus B19 (PVB19) myocarditis significant coronary vasospasm was provoked in the left anterior descending coronary artery and the left circumflex coronary artery in response to acetylcholine (ACh) (**a**), compared with the relaxed state after glyceryl trinitrate (GTN) (**b**). In contrast, no significant vasoreaction was detected in a patient with normal biopsy findings in response to ACh (**c**) when compared with the coronary status after GTN infusion (**d**). Adapted from Yilmaz et al. [70]

an increased intracellular rho-kinase activity was identified as a possible key mechanism for smooth muscle cell hyperreactivity in patients with vasospastic angina [77]. Furthermore, there is evidence that the activation of this kinase may facilitate leukocyte adhesion to arteries, thereby enabling their accumulation in the vessel wall and the spread of inflammation [78]. Therefore, one might speculate that viral infection of distal coronary arteries may be associated with coronary smooth muscle cell hyperreactivity. However, it is currently unknown whether rho-kinase activity is increased in inflamed myocardium. Depending on the severity of virus infection and the individual immune response, a further spread of inflammation to other myocardial regions and layers with the accumulation of interstitial lymphocytes and macrophages can be expected, causing various patterns of myocardial damage.

In this context, increased HLA class II expression reflecting specific antigen-presenting immune cells was seen in the cardiac interstitium surrounding small-sized vessels in some patients. Hence, the infection of coronary endothelial cells with parvovirus B19 may cause a kind of ''coronary vasculitis'', which may constitute a major determinant of the future clinical course and of the myocardial spread of the inflammation.

In conclusion, parvovirus B19-associated myocarditis, with or without virus persistence, may cause severe CMD and angina. Accodingly, parvovirus B19-associated myocarditis can mimic myocardial infarction and persistence of the virus in coronary microcirculation may be responsible for persistent angina [69]. It follows that in patients who present severe rest angina, troponin raise and fall, and ischemic-like ECG changes, and are found to have angiographically normal epicardial coronary arteries, an intracoronary acetylcholine test is indicated in order to establish the presence of distal diffuse coronary vasoconstriction (different from proximal focal spasm observed in vasospastic angina). The diagnosis of myocarditis can then be established by myocardial biopsy confirming the presence of parvovirus B19. Interestingly while in myocarditis CMR typically shows mesocardial or subepicardial late gadolinium enhancement, in patients with positive acetylcholine testing a subendothelial location can be observed perhaps reflecting ischemic necrosis [70].

5.5 Infiltrative Heart Diseases

Infiltrative heart diseases are predominantly characterized by systemic alterations that cause symptoms and signs related to other organs and systems and/or by myocardial alterations responsible for symptoms and signs of heart failure. Notably, in a sizeable proportion of these patients angina is also present and, in a minority of patients, is the initial symptom. In these patients angina is typically caused by CMD; thus the occurrence of MVA, although rather infrequent, can represent the first clue to the diagnosis of a complex systemic disease.

The two infiltrative heart diseases most frequently associated with the evidence of CMD are Anderson-Fabry disease and amyloidosis.

5.5.1 Anderson-Fabry Disease

Anderson-Fabry disease is caused by an X-linked deficiency of lysosomal α-galactosidase A. It has been reported in up to 6 % of men and 12 % of women with late-onset HCM [79]. Lysosomal α-galactosidase A deficiency results in multiorgan damage determined by glycosphingolipid deposition, mainly globotriaosylceramide, with renal, cardiac and cerebrovascular involvement, and premature death [80]. In the heart, glycosphingolipid deposition is accompanied by secondary changes, such as myocyte hypertrophy, which can mimic the morphological and clinical picture of HCM as well as that of other diseases characterized by LVH (Fig. 5.14) [81]. Progressive deterioration of LV function and myocardial scarring occurs in a significant number of patients [82].

A timely diagnosis of Anderson-Fabry disease has relevant therapeutic implications because enzyme replacement and enzyme enhancement therapy have been revealed to be effective in treating the disease. This treatable disease, however, is frequently undiagnosed. Measurement of α-galactosidase A activity in peripheral blood in patients with LVH has been proposed to detect patients with Anderson-Fabry disease; however, this assessment may be unreliable in female carriers and in male patients with specific gene mutations, in whom the nearly normal enzymatic activity and the lack of systemic manifestations, including angiokeratomas, make its identification more difficult [83]. Unfortunately, clinical characteristics and ECG findings do not provide a reliable and definite diagnosis of Anderson-Fabry disease. An echocardiographic binary appearance of LV endocardial border, reflecting endomyocardial glycosphingolipids compartmentalization, has been

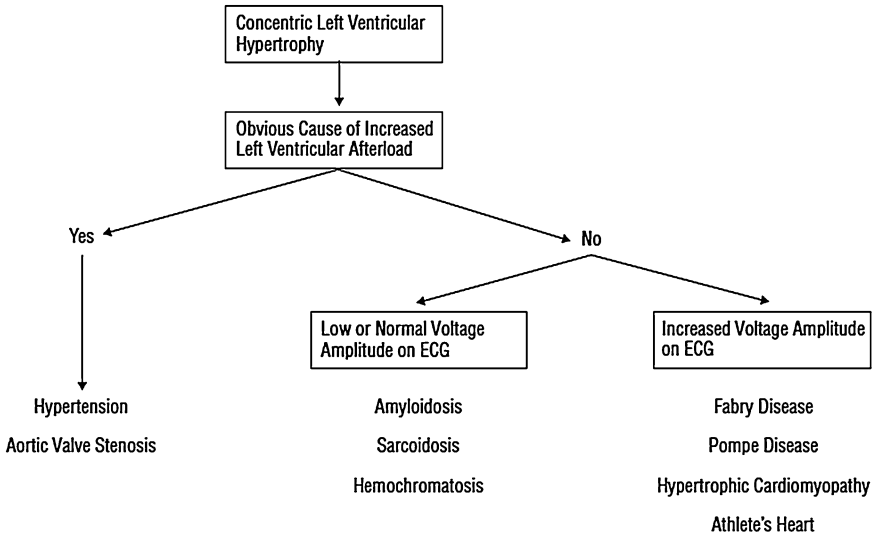

Fig. 5.14 Approach to diagnosis of LVH

proposed as a sensitive and specific diagnostic hallmark of Anderson-Fabry disease cardiomyopathy as it is not observed in other forms of LVH (Fig. 5.15) [84]. Growing evidence suggests that CMR with late gadolinium enhancemet may identify areas of myocardial damage in Anderson-Fabry disease. In particular, one study showed that patients with Anderson-Fabry disease–related LVH exhibit LV late gadolinium enhancement with a typical pattern, characterized by the involvement of the infero-lateral basal or mid basal segments and a by a mesocardial distribution [85].

Chest pain is a common clinical symptom in patients with Anderson-Fabry disease, being reported in up to 60 % of homozygous males and heterozygous females with or without significant LVH. It is often associated with electrocardiographic ST-segment and T wave abnormalities and with severely impaired CFR at PET imaging, suggesting the existence of myocardial ischemia. In the vasculature, glycosphingolipids accumulate in endothelial cells and smooth muscle cells, causing vascular obstruction and reduction of CFR (Figs. 5.16 and 5.17) [86–88]. Hypertrophy and hyperplasia of smooth muscle cells and swelling and proliferation of endothelial cells contribute to CMD [79]. To this regard, recent studies have shown increased concentrations of proliferative factors in plasma, in particular globotriaosylceramide and its metabolites, that can trigger the development of vascular hypertrophy and hyperplasia [89, 90]. Furthermore, patients with Anderson-Fabry disease have been found to have endothelial dysfunction not

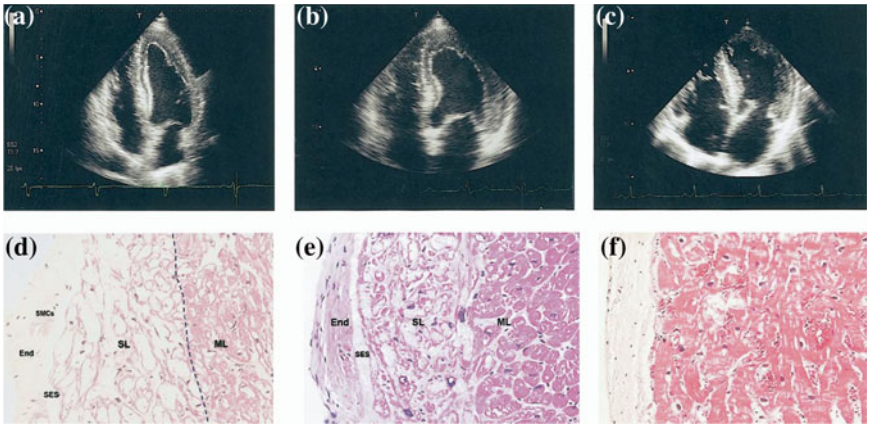

Fig. 5.15 Two-dimensional echocardiography in 4-chamber apical view and LV endomyocardial biopsy from two patients with Anderson-Fabry disease cardiomyopathy (**a, d** and **b, e**, respectively) and a patient with HCM (**c, f**). Comparison of the three echocardiographic frames reveals the presence of a binary appearance of LV endocardial border in the two Anderson-Fabry disease patients (**a, b**). This echocardiographic finding reflects glycosphingolipid compartmentalization involving a thickened endocardium (End) with enlarged and engulfed smooth muscle cells (SMC), a subendocardial empty space (SES), and a prominent involvement of subendocardial myocardial layer (SL), while the middle layer (ML) appears partially spared (**d, e**). The echocardiographic pattern is absent in HCM (c), despite a similar thickening of the endocardium (**f**). Adapted from Pieroni et al. [84]

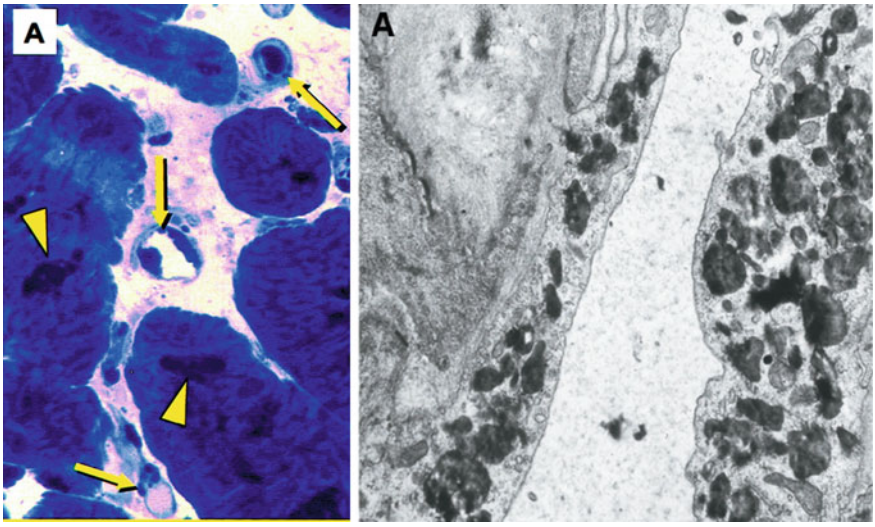

Fig. 5.16 Glycosphingolipids deposition in myocardial small vessels in Anderson-Fabry disease. Adapted from Eng et al. [86] and from Desnick et al. [87]

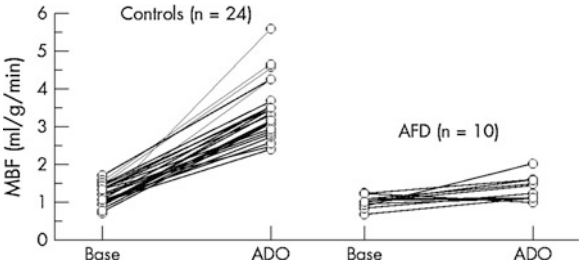

Fig. 5.17 Myocardial blood flow (MBF) at rest (Base) and during adenosine induced hyperemia (ADO) in patients with Anderson-Fabry disease (AFD) *(right)* and controls *(left)*. Adapted from Elliot et al. [88]

involving NO production, as assessed by forearm venous plethysmography, although it is unknown whether similar abnormalities are present in the coronary microvasculature [91]. CMD can be associated with loss of cardiomyocytes as documented by the frequent areas of fibrosis surrounding the most affected vessels . Thus, CMD can be severe enough to cause myocardial cell necrosis which can contribute to progressive LV dysfunction and risk of life-threatening ventricular arrhythmias.

5.5.2 Amyloidosis

Matthias Schleiden, a German botanist, fashioned the word amyloid in 1834 to describe the waxy starch in plants. Today the term amyloidosis is used to describe the infiltration of multiple organs by insoluble deposits composed of fibrillar

protein that arise from a diverse group of disease processes. To date, 24 heterogeneous proteins prone to misfolding have been discovered that comprise amyloid deposits. The misfolded proteins arise secondary to genetic mutations or excess production and form a ß-pleated sheet that aligns in an antiparallel manner. The sheets form insoluble amyloid fibrils that resist proteolysis and cause mechanical disruption and local oxidative stress in various organs. Regardless of which precursor protein causes the disease, the deposits are virtually indistinguishable by light microscopy. This amorphous substance stains pink with Congo red staining, with apple-green birefringence under polarizing light microscopy (Fig. 5.18) [92]. The spectrum of organ involvement can include kidneys, heart, blood vessels, central and peripheral nervous systems, liver, intestines, lungs, eyes, skin, and bones. Amyloid deposition in the heart is a devastating and progressive process that leads to congestive heart failure, angina, and arrhythmias. Of note, in patients with amyloidosis, infiltration of the heart confers the worst prognosis [93–95].

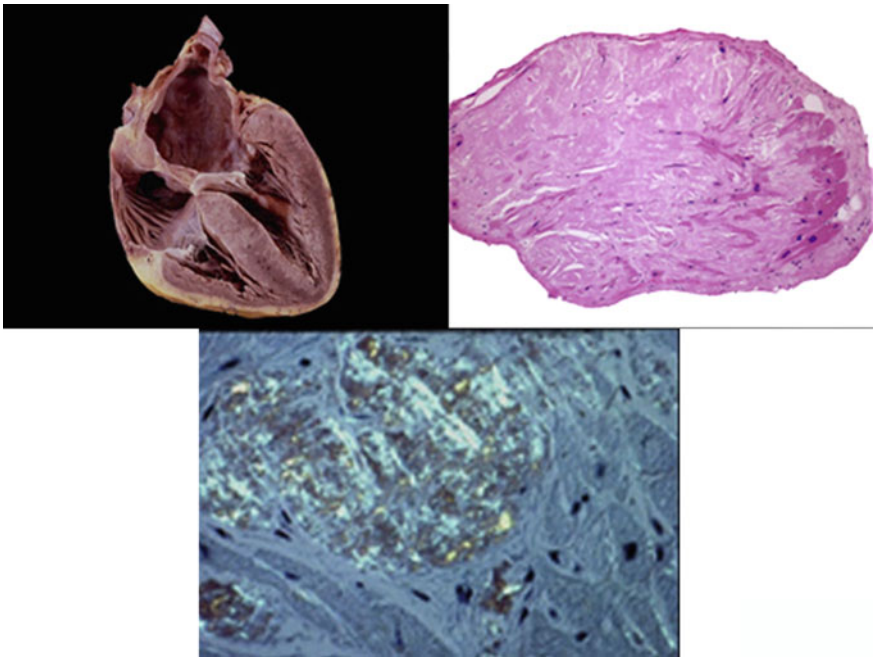

Fig. 5.18 *Left top panel.* Amyloid heart with deposition of lardaceous material causing restrictive cardiomyopathy. Note the biventricular hypertrophy with markedly thickened interventricular septum. *Right top panel.* Hematoxylin–eosin staining of right ventricular tissue shows extracellular amorphous amyloid material. *Bottom panel.* Congo red staining of myocardium shows apple-green birefringence under polarized light, a diagnostic feature of amyloid. Beware that Congo red technique can falsely show birefringence in paravascular and interstitial cardiac connective tissue as a result of its binding with fibrous tissue. Adapted from Kapoor et al. [92]

Cardiac amyloidosis is classified by the protein precursor as primary, secondary (reactive), senile systemic, hereditary, isolated atrial, and hemodialysis-associated amyloidosis. These distinct forms are differentiated by means of immuno-histochemical and genetic testing, and prognosis and therapeutic strategies differ among these subtypes [96].

- In primary amyloidosis, a a plasma cell defect leads to production of amyloidogenic immuno-globulin light-chain proteins, resulting in an aggressive form of amyloidosis. Cardiac involvement in this form is common, with 60 % of patients showing ECG or echocardiographic abnormalities. Death is attributed to cardiac causes (heart failure or arrhythmias) in at least half of these patients. Clinical manifestation of heart failure identifies patients at high risk, with median survival of 4 months. Laboratory data reveal excess light-chain protein production. In one case series, 89 % of patients with biopsy-confirmed primary amyloidosis had monoclonal light chains present at urine or serum protein immunofixation electrophoresis.
- Secondary amyloidosis results from the accumulation of amyloid A fibrils formed from an acute phase reactant, serum amyloid A protein. Secondary amyloidosis can be associated with rheumatoid arthritis, familial Mediterranean fever, chronic infections, and inflammatory bowel disease. Secondary amyloidosis of the heart is typically clinically insignificant.
- Senile systemic amyloidosis, an age-related disease, occurs in the aorta, heart, brain, pancreas, lung, liver, kidney, and a number of other tissues. Wild-type transthyretin, a transport protein synthesized in the liver and choroid plexus, forms the amyloid deposits. Senile systemic amyloidosis affects men usually after age of 70 years, and affects the heart in almost 25 % of people older than 80 years. The disease remains often unrecognized; however, extensive amyloid deposition leads to clinically significant heart failure. The disease course is less aggressive than primary amyloidosis, with a median survival of 75 months [97, 98].
- Hereditary (familial) amyloidosis is an autosomal dominant disease in which genetically mutated proteins form the amyloid fibrils. Mutations in both apolipoprotein I and transthyretin are known to lead to cardiac involvement, but the latter form is more frequent. The prominent feature is peripheral and autonomic neuropathy, a clinical entity also known as familial amyloid polyneuropathy. Mutations causing significant cardiac disease are methionine-for-valine substitution at position 30, serine-for-isoleucine substitution at position 84, and alanine for-threonine substitution at position 60. While less aggressive than primary amyloidosis disease, familial amyloidosis also may result in clinically significant heart failure. Of note, an isoleucine 122 gene mutation of the transthyretin DNA causes a familial amyloidosis primarily involving the heart without neurologic symptoms and is unique to elderly black persons. If tissue sampling confirms the presence of transthyretin in the amyloid deposits, isoelectric focusing of the patient serum can differentiate mutant from normal transthyretin. Genetic testing by restriction fragment length polymorphism analysis can identify the type of mutation.

- Isolated atrial amyloidosis is composed of atrial natriuretic peptide, a protein secreted by atrial myocytes in response to increased wall stretch. The incidence of this form increases with age (>90 % in the ninth decade of life) and in females. The disease also occurs in young patients with valvular heart disease and in patients with chronic atrial fibrillation. Isolated atrial amyloidosis is limited to the heart as thin, linear deposits along and underneath the endocardium. It is unclear whether the disease process has any clinical significance [99–101].
- Patients receiving long-term dialysis can develop cardiac amyloidosis with accumulation of ß$_2$-microglobulin from long-standing uremia. The protein accumulates with declining renal function and is ineffectively cleared with hemodialysis. The clinical effect of deposits occurring in the myocardium, pericardium, and cardiac valves is minimal, and the predominant symptoms are from joint involvement. Renal transplantation normalizes ß$_2$-microglobulin concentrations and improves joint pain. While systemic symptoms of amyloidosis are variable, cardiac findings are dominated by diastolic heart failure resulting from restrictive cardiomyopathy [102, 103].

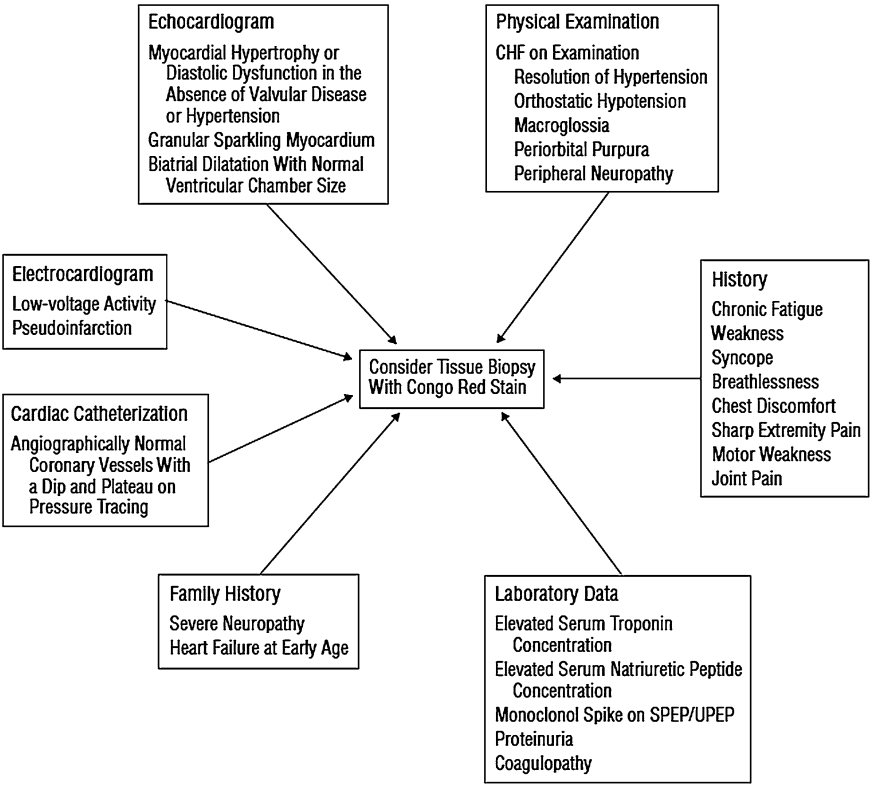

Fig. 5.19 Constellation of symptoms and signs and objective data suggestive of cardiac amyloidosis. CHF indicates congestive heart failure; SPEP, serum protein electrophoresis; and UPEP, urine protein electrophoresis. Adapted from Shah et al. [96]

The diagnosis of cardiac amyloidosis is established indirectly by echocardiographic and CMR findings suggestive of amyloidosis and histologic confirmation of amyloid in noncardiac tissues or directly by endomyocardial biopsy. Several tests, including a 12-lead ECG and cardiac biomarkers, can suggest cardiac amyloidosis, but they are not specific when interpreted in isolation. The 2-dimensional and M-mode echocardiographic features include symmetrical thickening of LV wall and the typical "granular sparkling" appearance of the myocardium [104].

A left interventricular septal thickness >20 mm on echocardiography together with low voltages on ECG have a high sensitivity and very high specificity for cardiac amyloidosis [104]. Indeed, when LV thickening is associated with true LVH (as it is the case for Anderson-Fabry disease) the ECG shows high voltages. Although CMR currently has a limited role in identifying early cardiac involvement, in the advanced stage it demonstrates typical findings of restrictive cardiomyopathy. Diffuse subendocardial late gadolinium enhancement differentiates cardiac amyloidosis from other cardiomyopathies. In addition, patients have abnormal myocardial and blood-pool gadolinium kinetics. Together, these findings have a high accuracy for diagnosing cardiac amyloidosis (Fig. 5.19) [105].

Diagnosis of amyloidosis must be confirmed by histologic analysis of tissues. Congo red staining identifies amorphous pink deposits at light microscopy, which exhibit apple-green birefringence at polarized microscopy. If disease is limited to the heart, as in isoleucine hereditary amyloidosis, examination of endomyocardial biopsy tissue is the only method of diagnosing the disease. Less invasive tissue sampling methods are available for diagnosing systemic amyloid disease. The rectal submucosa has been the traditional biopsy site, with a reported sensitivity of 75 to 85 %, but rectal biopsy can be complicated by bleeding or perforation. Abdominal fat aspiration is without serious complications and is more sensitive for diagnosing systemic amyloidosis. Endomyocardial biopsy specimens should be performed if less invasive methods fail to enable diagnosis of cardiac amyloidosis [106–111]. The distinction among the different types of amyloidosis is based on laboratory and genetic testing as outlined above.

Patients with cardiac amyloidosis mainly complain of symptoms related to right and left-sided heart failure. Indeed, in addition to mechanical disruption, amyloid deposits induce oxidative stress that depresses myocyte contractile function. Amyloid also modulates interstitial matrix composition and tissue remodeling by disabling the balance of matrix metalloproteinases and their inhibitors.

Nevertheless a sizeable proportion of patients with primary cardiac amyloidosis report typical chest pain caused by CMD. Indeed, amyloid deposits typically spare the epicardial vessels, while involvement of the intramural vasculature is present in 90 % of patients with primary cardiac amyloidosis although it is much less frequent in senile amyloidosis [112–115]. Vascular deposition of amyloid first occurs in the media but, with disease progression, it involves the adventitia and the intima. Although severe vascular obstruction is rare, occurring in about 5 % of cases, diffuse involvement leads to numerous endocardial foci of ischemia, microinfarctions, and eventual fibrosis, further contributing to myocardial

dysfunction and, in case of involvement of the conduction system, cardiac electrical disorders.

CMD is mainly caused by amyloid deposits but other mechanisms can play a role. Indeed, a recent study has shown that brief exposure to physiological amounts of light-chain proteins (overproduced in primary amyloidosis) induces endothelial dysfunction in coronary arterioles and increases apoptotic injury in coronary artery endothelial cells, likely as a result of oxidative stress, reduced NO bioavailability, and peroxynitrite production [116].

Thus CMD and microvascular injury are a novel mechanism underlying primary amyloidosis pathobiology and are a potential target for therapy. Clinical studies have confirmed a reduction of CFR in patients with primary amyloidosis and angina noninvasively, using contrast echocardiography [117], and invasively, using a Doppler wire [118].

The impact of CMD on outcome is still poorly known, neither it is known whether therapeutic interventions aimed to reduce amyloid deposition also improve CMD (see Chap. 9). Also, it is unknown whether interventions known to improve vascular function, like statins or drugs active on the renin-angiotensin systems, have the potential to delay the progression of heart failure.

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CMD in Obstructive CAD

6

6.1 Stable Coronary Artery Disease

6.1.1 Pathophysiology of CMD

In 1974, Gould et al. described the effects of progressive coronary artery narrowing on resting and maximal coronary blood flow in a canine model [1]. A reduction in coronary artery diameter of ≥50 % limited maximal coronary vasodilator capacity and a reduction of ≥85 % limited resting coronary blood flow. These laboratory findings were soon transposed into the clinical setting, where a stenosis ≥50 % of luminal diameter was defined as a hemodynamically significant lesion and one ≥85 % as a critical lesion [2]. The notion of "critical coronary stenosis" was then further translated into "ischemia-causing stenosis." Based on this chain of postulates, coronary stenosis gained increasing recognition as a consistent cause of angina.

The results of the experimental findings of Gould et al. have been recently confirmed in patients using PET and quantitative coronary angigography [3, 4]. Of note, these studies have clearly shown that, in patients with stable CAD, there is no reduction in MBF in resting conditions even with coronary stenosis >90 %, likely due to the presence of an effective collateral circulation.

Therefore, when a relatively simple percutaneous technique, such as angioplasty, that could reduce the atherosclerotic obstruction was introduced [5], the cardiology community reacted with enormous enthusiasm and promptly endorsed the methodology.

However, following millions of procedures performed worldwide, outcome analysis does not support the initial enthusiasm, at least in a large subset of patients with stable CAD. Several lines of evidence suggest that the direct relationship between chronic obstructive coronary atherosclerosis and angina has been taken for granted and may represent an overly simplified view. Indeed, many patients with angina and evidence of myocardial ischemia do not have detectable coronary atherosclerosis at angiography, as highlighted in the section on MVA (Chap. 4);

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conversely, some patients with severe coronary atherosclerotic obstructions neither experience angina nor present any evidence of myocardial ischemia [6, 7].

The important role played by CMD in determining symptom severity in patients with obstructive CAD and stable angina was clearly demonstrated in a study, which enrolled patients with stable angina, total occlusion of a single coronary artery and no previous myocardial infarction. All these patients had a remarkable variability in the anginal and ischemic threshold, with angina and ischemia being present at a low heart rate in one occasion and absent, in spite of a much higher heart rate, in another occasion during the same day. As these patients did not have any "dynamic" stenosis in large epicardial arteries, the variability of anginal and ischemic threshold could only be explained by profound dynamic changes of coronary microvascular resistance at the site of prearterioles, arterioles and/or collateral vessels (Fig. 6.1) [8].

In patients with obstructive atherosclerosis of large epicardial arteries, the occurrence of myocardial ischemia during increased oxygen demand is usually attributed to the inadequate flow increase despite maximal vasodilatation of the coronary microvasculature [9]. According to this view, maximal coronary flow capacity and CFR have been proposed as accurate functional descriptors of stenosis severity to identify the need for revascularization [10]. Yet, the clinical correlation between stenosis severity and CFR is widely scattered [3, 4, 11–14]. These findings suggest that other factors might precipitate myocardial ischemia. For instance, the angiographic severity of coronary stenoses can increase during exercise or atrial pacing because of increased tone [15]. More importantly, in

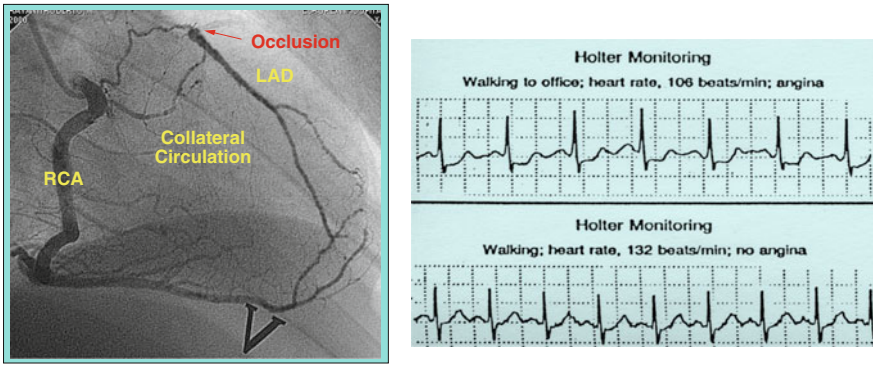

Fig. 6.1 *Left panel*: total occlusion of the *left* anterior descending (LAD) coronary artery which is completely reperfused by collateral vessels from the right coronary artery (RCA) in a patient with stable angina, normal LV function, no evidence of coronary-artery spasm and no other coronary stenoses. *Right panel*: during Holter ECG monitoring a large variability in ischemic threshold was observed, with transient myocardial ischemia (ST-segment depression) being often not observed at heart rate higher (*bottom ECG strip*) than that associated with ST-segment depression in other periods of the day (*upper ECG strip*).This large modulation of ischemic threshold during Holter ECG monitoring could result only from important vasomotor changes of the coronary microcirculation and/or collateral circulation. Adapted from Pupita et al. [8]

experimental studies, an increase in calculated total coronary resistance has been observed during tachycardia in regions supplied by severely stenotic coronary arteries [16]. Thus, it seems conceivable that in CAD, the response of the coronary microcirculation to increased oxygen demand might be more complex than a progressive arteriolar vasodilatation and that changes at the level of coronary stenosis may modulate flow response. To further clarify the possible role of the microcirculation, Sambuceti et al. assessed the resistance of both the stenotic arterial segment and the downstream microvasculature at rest and during pacing-induced ischemia in patients with stable angina. The authors found that tachycardia-induced ischemia was associated with an increase of the resistance of both the stenotic segment and the microvasculature. Interestingly, the infusion of adenosine during pacing reduced microvascular resistance (Fig. 6.2) [17]. This paradoxical behavior of vasomotor tone might reflect the intrinsic control mechanisms of the coronary circulation finalized to the maintenance of the driving pressure in a range of values high enough to perfuse vessels, but low enough to prevent capillary damage (see Chap. 1). Such a control could be as powerful as the metabolic control, although the two may go in opposite directions in this pathological condition. In this line, the response of coronary microcirculation to excessively low perfusion pressure could be a heterogeneous vasoconstriction, able to maintain pressure at the cost of excluding some vascular units. Although somewhat paradoxical and apparently not finalized to avoid or reduce ischemia, this hypothesis agrees with the evidence of both flow heterogeneity during

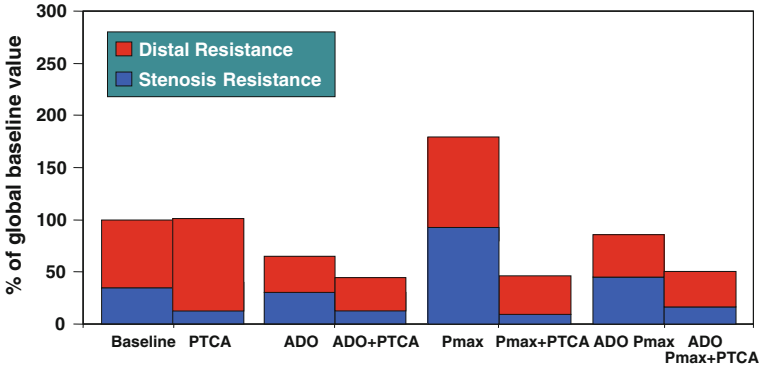

Fig. 6.2 Trend of stenosis, distal and global resistances expressed as percent of global baseline resistance. Stenosis resistance index was calculated as the ratio between mean trans-stenotic pressure gradient and blood flow index. Distal resistance index was calculated as the ratio between distal coronary pressure and flow index. Global resistance = distal + stenosis resistance. Intracoronary adenosine (ADO) markedly reduced distal resistance ($p<0.05$) and, to a lesser extent, stenosis resistance. During maximum atrial pacing (Pmax) an increase in both stenosis and distal resistance was observed ($p<0.05$ compared to baseline). Adenosine administered during atrial pacing markedly reduced distal and stenosis resistance compared to Pmax alone ($p<0.05$). After coronary angioplasty (PTCA), both stenosis and distal resistance remained low during Pmax. Adapted from Sambuceti et al. [17]

hypoperfusion [18] and heterogeneous distribution of the metabolic fingerprints of ischemia in the subendocardial and subepicardial layers of the LV [19]. It is also worth mentioning that this complex microvascular response which is beneficial when microcirculation is intact, as it is the case in canine experimental models, might contribute to ischemia in atherosclerotic patients. Accordingly, in patients with severe epicardial coronary stenoses, adenosine administration during pacing resulted not only in reduction of microvascular resistance but also in reduction of myocardial ischemia, thus confirming that microvascular constriction contributes to negatively modulate the severity of ischemia [20].

The "plaque-centric" hypothesis can also be called into question when the impact of therapeutic strategies based on the removal of coronary atherosclerotic obstructions is considered. Most reports agree that, on a background of medical therapy, revascularization improves symptoms, but in many patients angina recurs after 2–3 years and myocardial infarction and death are not prevented. In the COURAGE trial, which evaluated PCI on top of optimal medical therapy, more than 30 % of patients were still symptomatic with angina 1 year after the percutaneous procedure. Interestingly, at 5-year follow-up, the incidence of angina was not significantly different from that in patients who did not undergo a revascularization procedure (Fig. 6.3) [21]. Moreover, no significant between-group differences were noted for the composite end-point (death, myocardial infarction, and stroke), all-cause mortality, hospitalization for acute coronary syndrome, or myocardial infarction. Similarly, in the RITA-2 trial patients randomized to myocardial revascularization exhibited an initial greater improvement of symptoms and quality of life as compared to patients randomized to medical treatment. Yet, at 3-year follow-up, these differences between the two groups were not significant (Fig. 6.4) [22]. The pathophysiological relevance of obstructive lesions in the genesis of ischemia was further elucidated in the FAME study, where patients with multivessel coronary artery disease were randomly assigned to undergo PCI with implantation of DES guided by angiography alone or guided by FFR

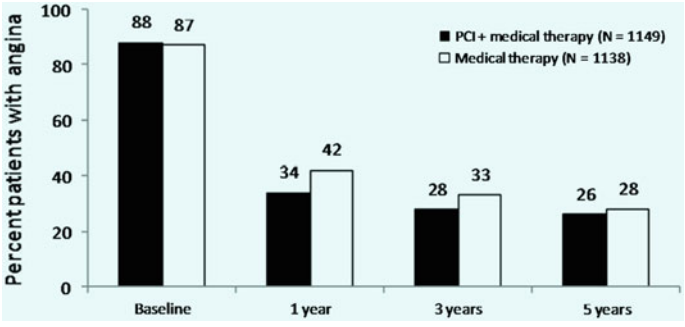

Fig. 6.3 Rate of angina after PCI in the COURAGE trial. Compared to baseline, angina rates decreased in both groups. Significant differences between treatment groups were noted at the 1-year and 3-year time points, but not at 5-year time. Adapted from Boden et al. [21]

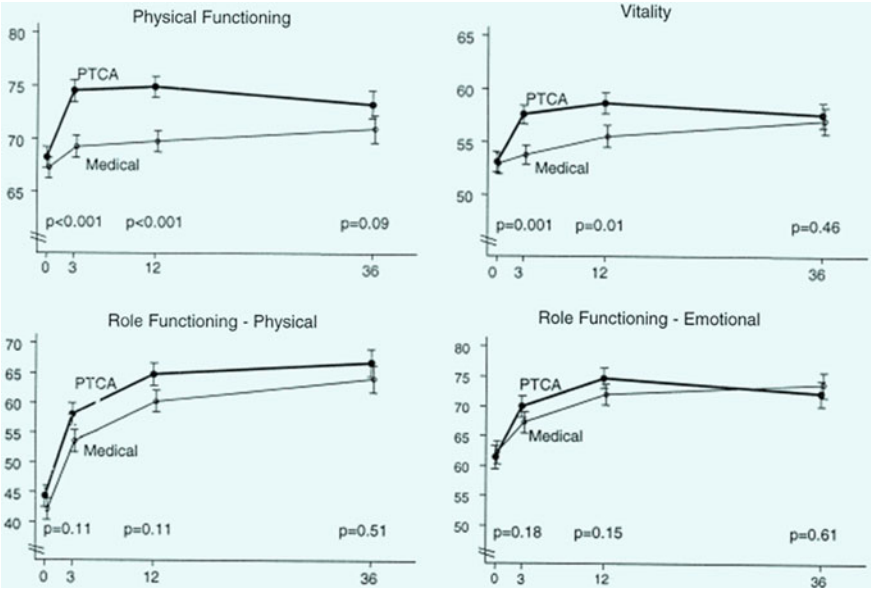

Fig. 6.4 Comparisons of percutaneous transluminal coronary angioplasty (PTCA) and medical therapy in the RITA-2 trial: effects on different dimension of quality of life. The initial benefit observed with PTCA was not maintained at 3–6 year follow-up. Adapted from Pocock et al. [22]

measurements in addition to angiography [23]. Patients assigned to FFR-guided PCI underwent stenting of indicated lesions only if the FFR was ≤0.80, whereas those assigned to angiography-guided PCI underwent stenting of all angiographically significant lesions. The 1-year event rate was significantly higher in the angiography-guided group than in the FFR-guided group (18.3 % vs. 13.2 %), in spite of a smaller number of stents implanted in the former. Importantly, 21 % of patients in the angiography-guided group and 19 % of patients in the FFR-guided group still complained of angina at 1-year follow-up, a figure similar to that observed in the COURAGE trial. The FAME 2 study randomized patients in whom at least one stenosis was functionally significant (FFR ≤0.80) to FFR-guided PCI plus optimal medical therapy or optimal medical therapy alone. Again the incidence of death and myocardial infarction was similar in the two groups. In contrast, the rate of urgent revascularization was higher in patients randomized to optimal medical treatment only and for this reason the study was closed prematurely. However, as FAME 2 was an open label study, a soft end-point like "urgent revascularization" is difficult to interpret [24].

In addition, in the STICH study, in patients with obstructive atherosclerosis and heart failure, no significant difference in all-cause mortality was observed between patients randomized to the medical therapy and those randomized to CABG [25]. Other large clinical trials have consistently shown a lack of mortality and symptomatic benefit in patients with stable angina and low to intermediate risk

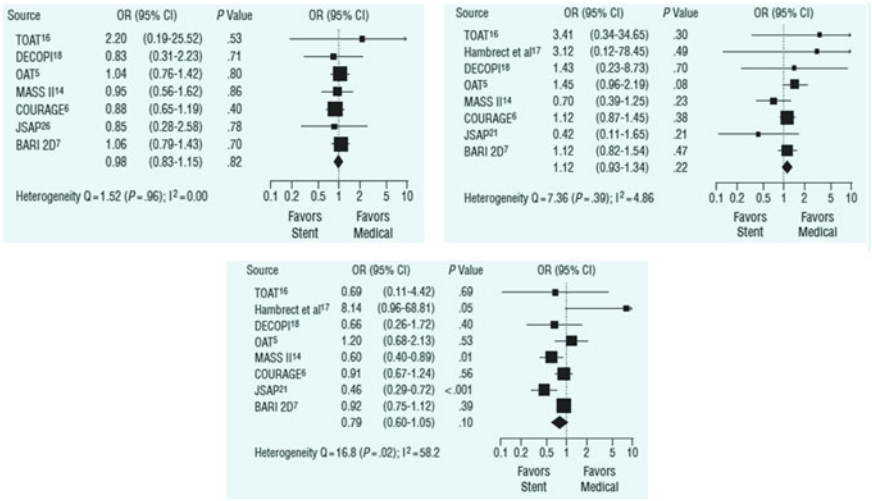

Fig. 6.5 Metanalysis of clinical trials that compared percutaneous coronary intervention with stent implantation with optimal medical therapy. *Top left panel*: death. *Top right panel*: non fatal AMI. *Bottom graph*: persistent angina. Adapted from Stergiopoulos et al. [26]

randomized to stent implantation in addition to optimal medical treatment or to optimal medical treatment alone [26] (Fig. 6.5).

These disappointing results for symptom control in patients with stable angina after coronary revascularization have been attributed to a number of factors, including incomplete revascularization, in-stent restenosis, and patient-related factors. However, in a highly selected cohort of 220 patients in which all possible confounding factors had been excluded, one-third of patients were symptomatic with angina and presented with a positive exercise stress test 1 month after the index procedure [27].

These observations certainly do not deny the usefulness of revascularization in patients with ACS, when coronary revascularization is needed to prevent an impending catastrophe, but they do raise questions about whether revascularization should continue to be regarded as the ultimate treatment for obstructive atherosclerosis in stable patients. The unchanged prognosis and the high recurrence rate of angina clearly suggest that revascularization procedures remove the atherosclerotic obstructions but do not cure the underlying disease. Indeed, obstructive plaque is only one of the causes of stable angina, the other being represented by CMD.

As proof of concept, it is worth mentioning an elegant trial in which patients with stable angina and inducible myocardial ischemia were randomized to percutaneous coronary revascularization or a program of physical training. After 1-year follow-up, major cardiovascular event rate was lower and exercise capacity was better in the latter. This study highlights that physical training-related improvement of microvascular endothelial function and, perhaps, of collateral

circulation function are more important than removal of epicardial coronary stenosis in improving symptoms and outcome in patients with stable angina [28].

Endothelial dysfunction has been shown to play an important role in the development of atherothrombosis through its regulation of vascular tone, platelet activity, leukocyte adhesion, and thrombosis [29]. Endothelial dysfunction is a predictor of cardiovascular events in patients with stable angina with or without obstructive atherosclerosis when assessed in the peripheral circulation, in large epicardial arteries and in coronary microcirculation [30, 31]. In keeping, coronary vasomotor response to acetylcholine has been shown to be an independent predictor of cardiovascular events in women with no, noncritical or critical epicardial stenosis, and suspected ischemia [32]. Accordingly, in a recent follow-up study of women with suspected myocardial ischemia, decreasing levels of CFR assessed by intracoronary adenosine (a nonendothelium dependent vasodilator stimulus) were significantly related to increasing risk of major adverse cardiovascular events (death or hospitalization for nonfatal AMI, congestive heart failure or stroke), with an adjusted hazards ratio of 1.14 per unit decrease in log-transformed CFR [33]. Inflammation is also a prominent part of the pathological process. Monocyte-derived macrophages and T-lymphocytes produce and secrete mediator molecules, such as cytokines, chemokines, growth-factors, proteolytic enzymes, and adhesion molecules, which activate endothelial cells, increase vasoreactivity, and cause smooth muscle cell proliferation. These events can enhance atherosclerotic plaque progression when occurring in large epicardial coronary arteries, while they cause dysfunction when occurring in coronary microcirculation by promoting both functional and structural alterations. In particular, plasma CRP, a prototypic marker of inflammation has been shown to be a risk factor for cardiovascular events in asymptomatic as well as in patients with known obstructive atherosclerosis [34, 35].

Women represent an interesting patient population in whom CMD is likely to play a key role in accounting for angina and myocardial ischemia in the presence of obstructive atherosclerosis [36]. In fact, while presenting with a lower coronary atherosclerotic burden, cardiovascular morbidity and mortality in women is similar to that in men [37]. The morbidity and mortality associated with the disease in this patient population have been a driving force in the exploration of other causes of myocardial ischemia including CMD. In line with these considerations, microvascular dysfunction in chronic angina can almost be considered as a "female gender disease." According to experimental studies, sex plays a relevant role in a number of microvascular mechanisms which may affect microvascular function and disease. Sex-specific differences in microvascular blood flow and vasodilator capacity are observed very early in development.

In summary, a large body of evidence supports the notion that obstructive atherosclerosis is neither a sufficient nor a necessary cause for stable angina, but just one component of a complex pathophysiologic process. In patients with stable angina and obstructive atherosclerosis, the mechanisms responsible for angina are complex and related to both the presence of critical stenoses in large epicardial

coronary arteries and the presence of microvascular dysfunction, which can also affect collateral circulation.

6.1.2 Clinical Implications

A microvascular origin of angina in patients with obstructive coronary atherosclerosis can be suspected in patients who have prolonged angina or angina poorly responsive to sublingual nitrates (clinical features frequently observed in patients with MVA). It can also be suspected in patients in whom angina is more severe than predicted by the severity of coronary stenoses. Finally, it may be suspected in patients in whom the angina threshold is remarkably variable, although this variability can also be accounted for by the presence of "dynamic" stenoses. In the individual patients, however, it is frequently impossible to establish the role played by CMD in causing angina. Therefore, myocardial revascularization should be considered in all patients at high risk (annual cardiovascular mortality rate >2 %) based on the results of stress testing and/or in patients with symptoms refractory to optimal anti-anginal medical treatment [38].

It is predictable, however, that up to 30 % of patients will have persistence of angina and/or evidence of stress-induced ischemia caused by CMD in spite of successful myocardial revascularization. Thus, when the goal of myocardial revascularization is symptom control rather than outcome improvement, it is always worth to test optimal anti-anginal treatment, including drugs targeting CMD, before proposing a procedure of myocardial revascularization.

The use of DES in PCIs has markedly increased during the past few years [39] mainly because they are associated with a significantly lower rate of restenosis compared to bare metal stents [40–42]. However, several studies have shown an increased risk of in-stent thrombosis associated with DES, which makes necessary the use of double anti-platelet drug therapy (aspirin and clopidogrel) for at least 6 months or more [43, 44]. Several factors have been associated with the enhanced prothrombotic effect of DES, including increased tissue factor expression [45] and impaired proliferation and migration of endothelial cells [46]. Accordingly, several studies have reported a significant coronary endothelial dysfunction associated with DES [47]. In particular, a recent study showed that endothelium-dependent vasomotion at adjacent stent segments was preserved after BMS implantation but not after DES implantation probably due to negative vascular effects of drug release [48].

It would be highly desirable to identify patients who have angina and inducible ischemia caused by CMD as opposed to that caused by restenosis. Exercise stress test has a primary role in the diagnosis and prognostic assessment of CAD [38]. However, the test performed after a PCI has been found of limited utility in identifying patients with coronary restenosis. In particular, previous studies showed that, after a percutaneous intervention, exercise-induced ST-segment depression at the ECG may persist, despite complete revascularization, in a proportion varying from 13 to 64 % [49–51].

The causes of ST-segment depression during exercise stress test in this setting, however, remain debatable. Although it is usually considered a false positive result, it might instead reflect myocardial ischemia caused by CMD [52, 53]. Recently, Milo et al. investigated patients with single-vessel LAD artery disease 24 h after successful stent implantation. All patients underwent exercise stress test and investigation of coronary microvascular dilatory function, assessed by measuring the changes in CBF velocity in the LAD coronary artery by TTDE in response to adenosine and to CPT. ST-segment depression during exercise stress test was found in about one-third of patients. No clinical or procedural significant differences were observed between patients with a positive and those with a negative result of exercise stress test. Notably, patients with a positive exercise stress test showed a lower CBF response to adenosine compared to those with negative exercise. At 3-month follow-up, 41 % of patients developed ST-segment depression during exercise stress test. Again, patients with positive exercise stress test showed a lower CBF response to adenosine compared to those with negative test. A low CBF response to adenosine (<2.0) was found in 82 % of patients with a positive test and in 18 % of those with a negative test. At 6-month follow-up, 45 % of patients developed ST-segment depression during exercise stress test. At this stage, a reduced CBF response to adenosine was present in all patients with a positive test whereas it could be detected in 6 % only of those with a negative test (Fig. 6.6). Of note, CBF response to CPT also was lower in patients with positive, compared to those with negative, exercise test up to 6-month follow-ip [54].

Finally, El Tamimi et al. [55] found that 50 % of patients treated by successful balloon angioplasty had a positive exercise stress test 1 week after the procedure; of note in all patients the test became negative after administration of sublingual nitrates. In the same patients intracoronary ergonovine failed to cause coronary spasm of epicardial arteries. They concluded that the cause of stress-induced ischemia was inappropriate vasoconstriction of coronary microcirculation.

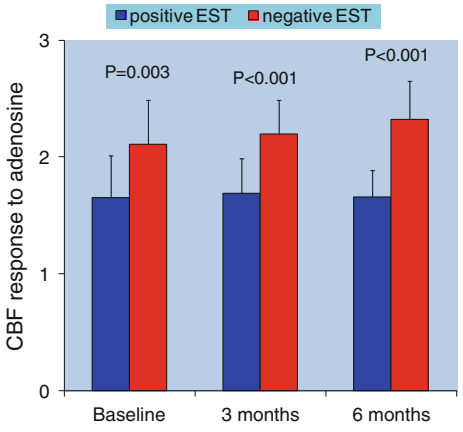

Fig. 6.6 Coronary blood flow (CBF) response to adenosine in patients with positive vs. negative exercise stress test (EST) 24 h (baseline) after a percutaneous coronary intervention and at 3-month and 6-month follow-up. Adapted from Milo et al. [54]

The results of the above-mentioned studies do not allow us to discern whether CMD responsible for the positive response to exercise stress testing early after successful angioplasty was caused or just unmasked by the procedure. Furthermore, the results of these studies clarify that a positive result of an exercise stress test can be caused by either restenosis or by CMD and that no distinctive feature can separate between these two possibilities, although a positive result early after stent implantation is likely to be caused by CMD, while a negative test which becomes positive after months is more likely to reflect restenosis, although progressive microvascular dysfunction cannot be excluded. Imaging techniques as well appear inadequate to discriminate between CMD and restenosis. In one study in patients with stable angina and one-vessel disease who had undergone successful stent implantation, early adenosine thallium-201 scintigraphy showed transient perfusion normalities in the region supplied by the treated coronary artery branch in about half of patients [56].

A more direct noninvasive assessment of coronary anatomy would be desirable in this setting, which might be achieved by multislice computed tomography coronary angiography. Yet, this technique still has important limitations in the assessment of in-stent restensosis; furthermore, it is associated with a significant radiation exposure and does not allow assessment of functional coronary abnormalities.

Thus, with the exception of invasive coronary angiography, all noninvasive techniques are unable to reliably discriminate between angina and myocardial ischemia caused by CMD vs restenosis.

Taken together, a large body of evidence gathered in the past 10–15 years indicates that among patients with stable angina both symptoms and myocardial ischemia are caused by both epicardial stenoses and CMD: their relative clinical relevance probably varies in different patients and varies over time in the same patient. In patients in whom myocardial revascularization is not dictated by a poor outcome related to a large area of myocardium at risk of ischemia, but rather by the need to improve invalidating anginal symptoms, the main goal is optimal medical anti-anginal treatment based on drugs which reduce myocardial oxygen demand and improve myocardial perfusion operating at the site of both large epicardial vessels and coronary microcirculation. Lack of appreciation that symptoms can originate from CMD can expose to unnecessary revascularization procedures. This is particularly important in patients who have persistence of symptoms and/or of evidence of inducible ischemia after successful myocardial revascularization.

Because of the lack of information on how to identify the contribution of epicardial stenoses and of CMD to anginal symptoms in the single patient, in patients with stable angina who do not have a large area at risk of myocardial ischemia, the main goal of treatment should be global risk factor control and anti-anginal treatment targeting both large epicardial coronary arteries and coronary microcirculation.

6.2 Acute Coronary Syndromes

6.2.1 Pathophysiology of CMD

The pathophysiology of CMD in ACS has not fully been elucidated. In the vast majority of patients, ischemic attacks are associated with reduction in CBF and occlusion of a major coronary branch attributed to thrombosis.

In contrast, coronary spasm due to smooth muscle hyperreactivity is the predominant cause of myocardial infarction in patients with a history of vasospastic angina, although this event is less common. However, coronary vasoconstriction and thrombosis are deeply interrelated [57–59].

On the one hand, occlusive coronary spasm and distal blood stagnation are known to cause a transient several-fold increase of fibrinopeptide A in systemic blood [60, 61]. On the other hand, serotonin, a substance released by activated platelets, is known to produce occlusive spasm in patients with variant angina and myocardial ischemia caused by distal vessel constriction in patients with chronic stable angina [62]. This vicious cycle, at least partially, mediated by serotonin, thromboxane A2, and thrombin, may have an important role in the setting of ACS where unstable coronary plaques, frequently showing a preserved smooth muscle, are in contact with activated platelets [63]. Furthermore, several findings sustain the possibility of smooth muscle hyperreactivity in unstable angina. Indeed, ergonovine injection causes occlusive spasm much more often in unstable than in stable angina (38 % vs. 4 %), a difference similar to that observed in patients with recent infarction compared with patients with old infarction (20 % vs. 6 %) [59]. It is also known that unstable plaques are more reactive to the stimuli of exercise and CPT than stable plaques [64]. Furthermore, Zeiher et al. [65] have demonstrated greater endothelin-1 immunoreactivity in unstable coronary plaques compared with that found in stable plaques obtained by directional atherectomy. This observation may provide a clue to the mechanisms of segmental coronary hyperreactivity frequently observed in patients with unstable angina [64, 65]. Indeed, endothelin-1 is not only a potent vasoconstrictor itself, but it also potentiates the effects of other vasoconstrictor stimuli such as catecholamines, serotonin, and angiotensin II [66].

A growing body of data indicates that plaque inflammation may play a key role in the pathogenesis of ACSs, as the cytokines secreted by activated inflammatory cells have the potential to activate the endothelium, transforming its antiadhesive and anticoagulant properties into adhesive and procoagulant properties. Furthermore, they may reduce matrix synthesis and increase its degradation, thus favoring plaque rupture. Finally, they may increase endothelin-1 synthesis in endothelial cells and macrophages and endothelin-1, in turn, can enhance smooth muscle reactivity to other constrictors. Hence, plaque inflammation may account for the multiple mechanisms so far proposed as being directly responsible for ACSs.

Thus, over the last two decades, the working hypothesis has been that ACSs are primarily an epicardial or a large vessel event as a result of plaque rupture or

erosion [67]. At the time of infarction, the angiographic display of an occluded epicardial artery with intra-luminal thrombus and slow or even absent coronary flow that persists after recanalization led to the widely accepted opinion that the coronary microcirculation is an innocent bystander in the initial phase of the acute coronary event [68].

According to these classical concepts, a sudden focal increases in epicardial coronary artery resistance should be associated with compensatory vasodilatation at the level of microcirculation [69]. However, experimental studies have shown that this is not the case during prolonged severe ischemia [70, 16]. Moreover, clinical studies suggest the occurrence of a microvascular vasoconstriction during transient myocardial ischemia in patients with stable angina [20, 71] and Wilson et al. observed intense symptomatic microvascular constriction after angioplasty of acute thrombotic coronary lesions [72]. Accordingly, elegant studies documented that substances released during platelet aggregation can constrict coronary microvasculature, particularly in presence of atherosclerotic endothelial dysfunction [73]. These observations emphasize the need for a better understanding of the role of microcirculatory vasomotor tone during ACS. To this purpose, simultaneous evaluation of blood flow changes together with proximal and distal coronary pressures are required. This information can be obtained in humans by measuring CBF velocity using an intracoronary Doppler wire and a pressure wire with the positioned distal to the culprit stenosis [74]. Using this approach, Marzilli et al. found that, in these patients, transient myocardial ischemia was associated with paradoxical vasoconstriction of both stenotic arterial segment and downstream microcirculation [75] (Fig. 6.7). These findings do not agree with the traditional view of a maximal compensatory vasodilatation in ischemic myocardium.

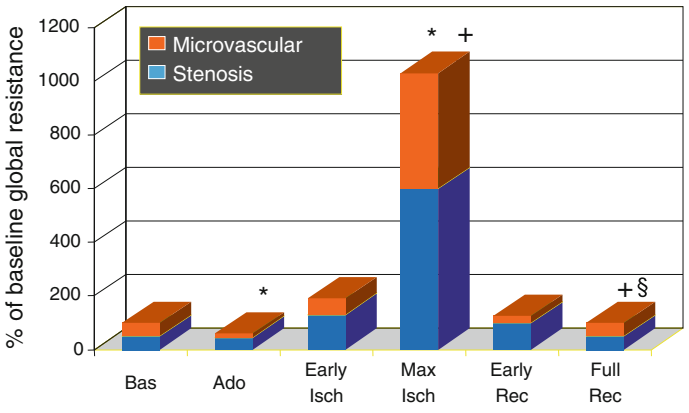

Fig. 6.7 Trends of total coronary resistance and the contribution of stenosis (*blue* columns) and microvascular resistance (*orange* columns). Coronary resistance was not calculated during balloon coronary occlusion. During ischemia, both coronary stenosis and distal microcirculation showed a significant increase in resistance to flow (*$p < 0.05$ vs. baseline, +$p < 0.05$ vs. adenosine; § 5 $p < 0.05$ vs. max ischemia). Adapted from Marzilli et al. [75]

By contrast, they strongly support the hypothesis that spontaneous ischemia can be associated with microvascular constriction and suggest that abnormalities in distal coronary vasomotion can contribute to the precipitation and maintenance of ischemia in unstable angina. Along this line, intermittent ischemia might reflect mural thrombosis and release of substances able to constrict coronary microvessels [76, 77]. Alternatively, vasoactive signals not linked to coronary thrombosis might be responsible for coronary vasoconstriction. Actually, endothelial dysfunction impairs microvascular adaptation to ischemia [78], and a constrictor response to reduced intraluminal pressure has been described in isolated microvessels [79]. Similarly, ischemia mediated by stimulation of postsynaptic alpha-2-receptors has been documented in anesthetized dogs [80]. Potent coronary vasoconstrictors such as neuropeptide-Y [81] and endothelin-1 [82] are more effective on coronary microcirculation than on large epicardial arteries arteries.

Identifying the mechanisms of the altered control of vasomotor tone, during ischemia, might allow a more accurate identification of patients who will develop an acute coronary disease and the development of more specific forms of anti-ischemic therapy. At present, the most used vasoactive drugs are most effective on large epicardial arteries; in fact, direct arteriolar vasodilators may precipitate ischemia by coronary steal. The identification of the mechanisms underlying this paradoxical microvascular constriction and thus of specific substances able to prevent it, might provide a more efficient pharmacologic strategy especially for those patients who cannot benefit from coronary revascularization.

Interestingly, Marzilli et al. found that abciximab, a GP IIb/IIIa antagonist, immediately improved MBF in patients with ACSs, mostly because of the beneficial effect on coronary microcirculation (Fig. 6.8) [83]. In agreement with other published reports, these data suggest that GP IIb/IIIa antagonism might prevent MVO, thus increasing the amount of myocardial mass reached by perfusion. These observations offer an alternative explanation for the clinical benefits of anti-platelet agents in patients with ACS.

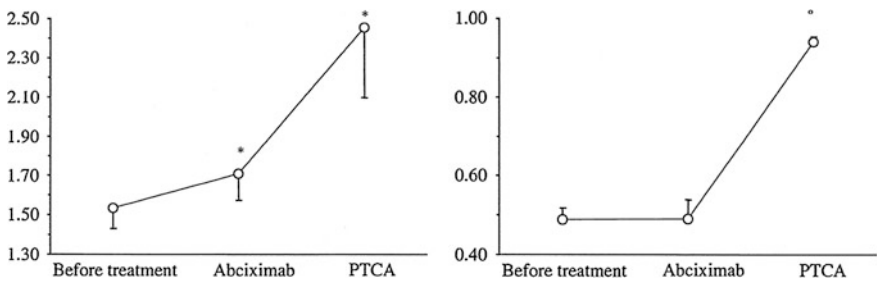

Fig. 6.8 The coronary flow reserve (CFR) (*left panel*) and fractional flow reserve (FFR) (*right panel*) responses to abciximab and percutaneous transluminal coronary angioplasty (PTCA). Abciximab improved CFR but not FFR, indicating a greater effect of the drug on coronary microvascular function than on stenosis severity. Data are shown as average values SEM. *p 0.05 vs. baseline. °p 0.01 vs. baseline and abciximab. Adapted from Marzilli et al. [83]

Taken together, these data suggest that, besides changes in plaque structure and morphology, microvascular phenomena might contribute to precipitating ischemia in unstable patients. Although the mechanism(s) of the paradoxical constriction of the coronary microcirculation during ischemia are largely unknown, some reports suggest that platelets might interfere with microvascular regulation of CBF. Platelets may be activated by exposure to thrombus, injured endothelium, and collagen while crossing the stenotic segment [84]. Activated platelets can affect microvascular resistance by microembolization and/or release of constrictive, pro-adhesive, and pro-inflammatory factors. Along this line, ACSs are often associated with evidence of microvascular obstruction [85]. Although this phenomenon is generally attributed to microembolization from the epicardial thrombus, it has been documented that interaction with adhesion molecules prevents MVO in experimental models of ischemia without coronary thrombosis [86].

Thus, at the time of an acute coronary event: (1) CMD, characterized by paradoxical vasoconstriction, seems to play an important modulatory role; (2) antiplatelet drugs known to improve clinical outcome appear to improve CMD.

6.2.2 Relations Between CMD and Plaques Instability

The temporal association between events occurring in large epicardial vessels (plaque erosion or fissure associated with thrombus formation) and in the microcirculation (paradoxical vasoconstriction) does not allow to establish what is the causal relation between these two events. It is widely believed that epicardial events precede and cause microvascular events. Yet this assumption is based on studies that were not designed to answer this question and is challenged by several clinical observations. Indeed, it has to be taken into consideration that plaque ruptures can remain clinically silent. Although the exact prevalence is unknown, autopsy studies do outline that healed ruptures are not infrequently encountered upon histopathological review of coronary arteries of sudden cardiac death patients [87, 88]. In fact, in one intravascular ultrasound-based study, almost one quarter of all ruptured plaques was encountered in patients with stable angina or no symptoms at all [89] and similar findings have recently confirmed using optical coherence tomography [90]. Moreover, by serial coronary angiography, one study suggested a delay of at least 3 days from plaque rupture and thrombus formation to the classical clinical presentation of acute myocardial infarction [91]. Furthermore, patients with similar coronary "patho-anatomy" may present with unstable angina rather than acute myocardial infarction or even sudden cardiac death. Hence, there is a fairly broad spectrum in the clinical presentation of an epicardial event, which has remained largely unexplained. While systemic factors such as thrombotic-fibrinolytic balance and local factors such as collateral blood flow have to be taken into consideration, one may also want to question the coronary microcirculation as a potential modulating factor.

Thus, one may postulate the presence not only of the vulnerable plaque but also of the vulnerable coronary microcirculation. A more extreme view is that, at least in a proportion of patients, a primary CMD might play a causal role in determining thrombus formation in epicardial coronary arteries. Several lines of evidence support this working hypothesis.

For instance, the fact that CBF is reduced by 50 % in the nonculprit coronary arteries in patients with acute myocardial infarction both before and after a PCI points to global rather than regional myocardial microcirculatory impairment [92].

Moreover, in patients without obstructive CAD and evidence of coronary epicardial and microvascular endothelial dysfunction during invasive cardiac evaluation, future cardiovascular events, including ACS, occurred more frequently in those with a reduction of CBF in response to vasodilator stimuli, indicating CMD [93]. Thus, Britten et al. who followed patients with angiographically normal or minimally diseased coronary arteries over an average of 6.5 years, noted a more than threefold higher cardiovascular event rate in patients in the lowest compared with the highest tertile of CFR with about one-third of all events related to ACSs [94]. Marks et al. followed patients with chest pain and normal coronary angiograms over a mean period of 8.5 years and noted a nearly threefold higher mortality for those patients with an abnormal CFR [95]. Hence, the presence of CMD is a significant predictor of clinical outcome, including future acute coronary events, even in the absence of hemodynamically significant epicardial disease [96]. These findings have recently been confirmed in a large cohort study of 11,223 Danish patients referred for coronary angiography because of stable angina pectoris and 5705 asymptomatic patients found to have angiographically normal coronary arteries Main outcome measures were major adverse cardiovascular events, defined as cardiovascular death, myocardial infarction, stroke or heart failure, and all-cause mortality. Significantly, more symptomatic women (65 %) than men (32 %) had non obstructive CAD. Notably, the multivariable adjusted risk of major cardiovascular events was 52 % higher for symptomatic patients with angiographically normal coronary arteries and 85 % higher for patients with diffuse non obstructive CAD compared with the reference population. In particular, the risk of all-cause mortality was 29 and 52 % higher, respectively [97]. Similar findings were observed in another study which compared clinical outcome of 540 women with non obstructive CAD enrolled in the WISE study (symptomatic women referred for clinically indicated coronary angiography because of angina or suspected ischemia) with those of 1,000 age and race-matched women enrolled in the WTH Project (asymptomatic, community-based women with no history of heart disease). Five-year annualised event rates for cardiovascular events were 16.0 % in WISE women with nonobstructive coronary disease, 7.9 % in WISE women with normal coronary arteries, and 2.4 % in asymptomatic WTH women after adjusting for baseline risk factors [98].

PCI can be considered as a iatrogenic form of plaque rupture and allows assessment of the significance of the myocardial microcirculation in a more defined setting. In this regard, it is important to notice that clinical studies of PCI pointed out that patients with pre-procedural CFR impairment were more likely to

have post-procedural CFR impairment and procedure-related myocardial injury as well as worse long-term outcome [99, 100]. These data suggest that pre-existing impairment of coronary microcirculation yields greater vulnerability to myocardial injury and thereby imply a primary role of CMD, at least in PCI-related myocardial injury.

Inflammation may be a common link between macrovascular and microvascular disease. Indeed, Neri Serneri et al. demonstrated an acute inflammatory process involving coronary microvessels but not cardiomyocytes in unstable angina patients [101]. Accordingly, in patients with normal coronary angiograms, a significant inverse correlation was noted between CRP serum concentrations and MBF responses to cold pressor test measured by PET [102]. Based on these latter findings, one could plausibly speculate that the inflammatory mechanisms linked to plaque rupture also cause CMD.

Further support to this argument may be derived from previous retrospective and prospective randomized trials, which demonstrated a reduction in the incidence and extent of myocardial injury with PCI by pre-treatment with statins, known to improve microvascular function [103–105]. Even more, a recently published study highlighted a 74 % reduction in the incidence of MVO with primary PCI among patients who were taking statins before admission for anterior acute myocardial infarction, suggesting that chronic statin treatment could preserve the microvascular integrity [106] (see Chaps. 10 and 11).

Taken together, there is a growing body of multilayered evidence to suggest that the integrity of the coronary microcirculation plays an integral role in the evolution of ACS. In line with the concept of the primary significance of the myocardial microcirculation, pre-existing transient or permanent microcirculation dysfunction may contribute to the development and prognosis of ACS via reduction of CBF, leading to an alteration of shear stress and thereby aggravation of endothelial dysfunction in epicardial level as well as aggravation of thrombus formation in an extension of 'Folts' coronary thrombosis model [107]. Coronary thrombus formation as a primary or secondary event in acute myocardial infarction has been debated quite extensively in the past, and some authors would argue that reduction of flow is the primary factor and intracoronary thrombus develops after the onset of myocardial ischemia (Fig. 6.9) [108].

A limitation of the working hypothesis that CMD may play a primary role in the pathogensis of ACS relates to the question how microvascular function and basal CBF could deteriorate so acutely and so extensively to contribute to acute coronary thrombosis, especially because the majority of patients with acute myocardial infarction apparently do not display CMD at the time of assessment. Yet, acute deterioration in microvascular function and myocardial perfusion has been demonstrated in diabetic patients postprandially [109]. A dysfunctional endothelium is also increasingly sensitive to catecholamines, which may explain the sudden increase in cardiac events with stressful life events [110]. Accordingly, in healthy individuals, endothelium-dependent vasodilatation by forearm venous occlusion

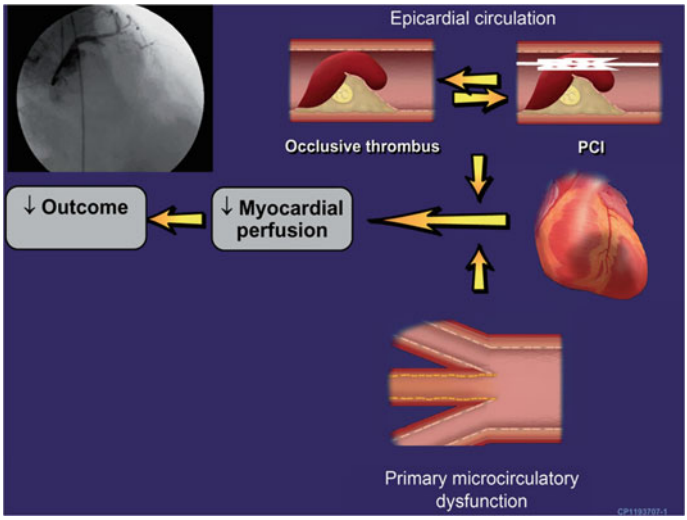

Fig. 6.9 A nontraditional concept of the mechanisms of ACS centers on the vulnerable patient, taking into account primary dysfunction of the microcirculation of a vulnerable myocardium in addition to the vulnerable plaque, which contributes to the clinical presentation and outcome. Adapted from Lerman et al. [108]

plethymography is lower in the evening than in the morning hours and thought to counteract potentially harmful diurnal patterns of sympathetic tone and coagulability [111]. However, in patients with angiographically proven obstructive CAD, this diurnal variation in endothelium-dependent vasodilatation was noted to be absent, conferring a potentially greater risk [111]. Finally, an excellent example of sudden intense microvascular constriction able to cause severe myocardial dysfunction in the absence of obstructive coronary atherosclerosis is represented by the takotsubo syndrome which is discussed elsewhere (see Chap. 4).

Although the hypothesis of a primary role of CMD is fascinating, a major limitation to argue for or against this notion is the lack of tracing data on microvascular function and CBF just prior to the acute coronary event. Thus, future studies should take these possibilities into account in the design of a novel clinical approach for the treatment of ACS. If indeed microcirculatory dysfunction is ever demonstrated to be one of the major contributors to the evolution and not just the consequence of an acute coronary event, this could substantially alter future research directions and approaches to therapy. The paradigm that an ACS may be initiated at the level of coronary microcirculation and results in thrombus formation at a site of a nonocclusive epicardial artery may not, however, change clinical practice, which is to restore CBF and myocardial perfusion. Nonetheless, it could exert an influence upon the selection of adjuvant therapy prior and/or following the revascularization procedure or even a novel design for DES.

6.3 Coronary Microvascular Obstruction

6.3.1 Definition and Clinical Relevance

In the setting of STEMI, a specific pathophsysiological condition is represented by CMD, which occurs after recanalization of the infarct-related artery. Prompt referral for mechanical reperfusion by urgent primary PCI represents the pivotal step in the current management of STEMI [112]. Yet, in a sizable proportion of patients primary PCI achieves epicardial coronary artery recanalization, but not myocardial reperfusion, a condition known as "no-reflow" and currently more commonly defined MVO [113].

Although the existence of MVO was initially debated, a large amount of experimental and clinical data has nowadays convincingly shown that it occurs after reperfusion with a variable prevalence, ranging from 5 % to 50 %, according to the methods used for the diagnosis and the population under study [114].

In 1993, at the climax of the thrombolytic era, Lincoff and Topol wrote a provocative editorial wondering whether reperfusion was just an illusion [115]. At that time, they estimated that only "25 % or less" of patients treated by thrombolysis had an optimal reperfusion, defined as a rapid, complete, and sustained coronary recanalization with adequate myocardial tissue perfusion. What is this figure after 15 years at the climax of primary PCI era? As shown in Fig. 6.10, a reasonable estimate of the proportion of patients who get optimal myocardial reperfusion, among those without cardiogenic shock undergoing primary PCI, is about 35 % [116].

A series of consistent data have clearly shown that MVO has a strong negative impact on outcome, negating the potential benefit of primary PCI [117–122]. Indeed, patients with MVO exhibit a higher prevalence of: (1) early post-infarction complications (arrhythmias, pericardial effusion, cardiac tamponade, early congestive heart failure); (2) left adverse ventricular remodeling; (3) late re-hospitalizations for heart failure; and (4) mortality (Fig. 6.11).

Therefore, detection, prevention, and treatment of MVO are likely to have an important impact on the outcome of primary PCI.

6.3.2 Time-Course and Pathogenetic Components

Kloner et al. described MVO for the first time in a canine model, demonstrating that it occurs after prolonged (90 min) coronary occlusion followed by reperfusion [123]. The consequences of coronary ligation of a non atherosclerotic coronary artery, however, cannot be directly extrapolated to the human situation where myocardial infarction is caused by occlusive coronary thrombosis superimposed to an atherosclerotic unstable plaque [124].

Galiuto et al. using sequential measurements of myocardial perfusion by myocardial contrast echocardiography have shown that in man MVO detected

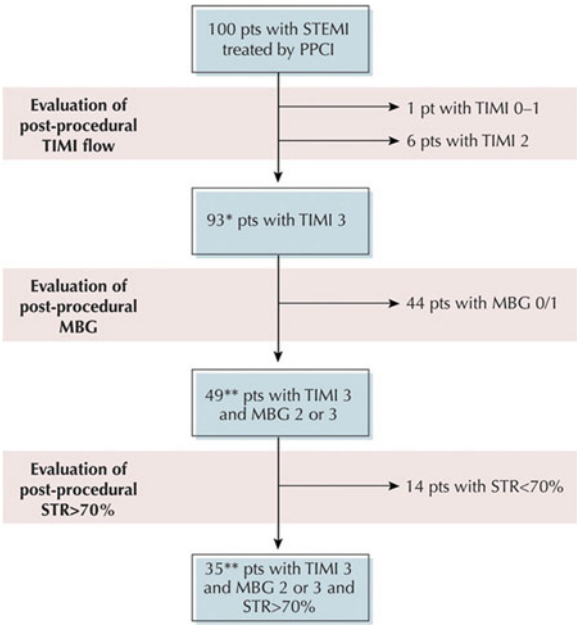

Fig. 6.10 Prevalence of myocardial MVO. Estimate of the number of patients (pts) receiving optimal reperfusion according to Thrombolysis In Myocardial Infarction (TIMI) flow grade, myocardial blush grade (MBG), and ST-segment resolution (STR) of 100 patients without cardiogenic shock treated by primary percutaneous coronary intervention (PPCI). *Estimation derived from 20 randomized trials comparing standard percutaneous coronary intervention with thrombectomy or distal protection. **Estimation derived from core laboratory analysis of the CADILLAC trial. Adapted from Niccoli et al. [116]

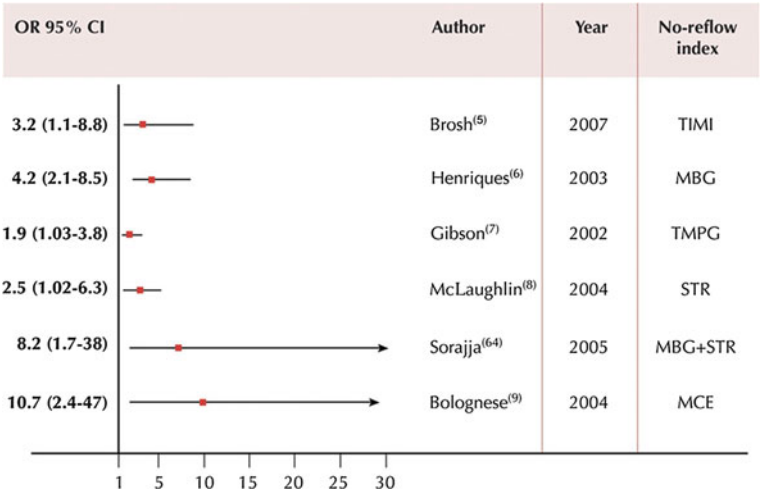

Fig. 6.11 Prognostic value of MVO according to angiographic, electrocardiographic, and echocontrastographic indexes. The end point was cardiac death or total mortality. Data are presented as odds ratio (OR) and 95 % confidence interval. Adapted from Niccoli et al. [116]

24 h after successful PCI spontaneously improves over time in about 50 % of patients. Thus, MVO can be categorized as sustained or reversible. Sustained MVO is probably the result of anatomical irreversible changes of coronary microcirculation, while reversible MVO is the result of functional and, thus reversible, changes of microcirculation. Interestingly, while patients with sustained MVO undergo unfavorable LV remodeling, patients with reversible MVO maintain their ventricular volumes unchanged over time [125]. Similar findings were shown by Hoffman et al. by analyzing changes of myocardial blush grade over time. In this study, also the evolution of MBG was a potent predictor of left ventricular remodeling [126].

In man, MVO is caused by the variable combination of four pathogenetic components: (1) distal atherothrombotic embolization; (2) ischemic injury; (3) reperfusion injury; and (4) individual susceptibility of coronary microcirculation to injury (Fig. 6.12). As a consequence, appropriate strategies to prevent or treat each of these components are expected to reduce the prevalence of sustained MVO.

Distal atherothrombotic embolization can originate from epicardial coronary thrombus and from fissured atherosclerotic plaques, in particular during primary PCI [127]. Experimental observations have shown that, MBF decreases irreversibly when microspheres obstruct more than 50 % of coronary capillaries [128]. Okamura et al. used a Doppler guide wire in man to detect high-intensity transient signals, which allowed counting the number of embolic particles. The average number of emboli throughout primary PCI was 25. Thus, this small number of emboli is unlikely to affect CBF [129]. Yet, large emboli (>200 μm diameter), can obstruct pre-arterioles causing infarctlets (Fig. 6.13) [130].

Ischemic injury mainly affects endothelial cells. Changes of endothelial cells, visible after prolonged ischemia, are represented by endothelial protrusions and membrane-bound bodies, which often fill the capillaries up to luminal obliteration. Furthermore, large endothelial gaps with extra vascular erythrocytes are common [131]. Morphological findings are accompanied by a reduction of regional MBF within the previously ischemic region [132]. Moreover, myocardial cell swelling associated with interstitial edema may cause microvascular compression [133].

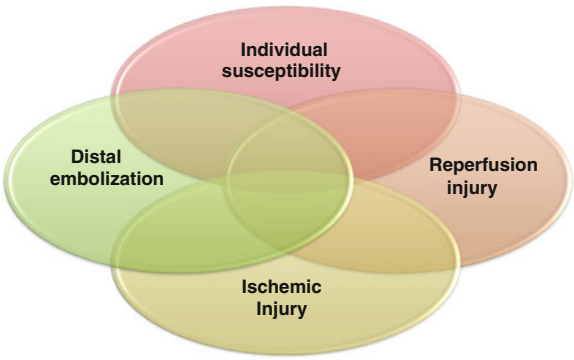

Fig. 6.12 Pathogenetic mechanisms of MVO. Adapted from Niccoli et al. [116]

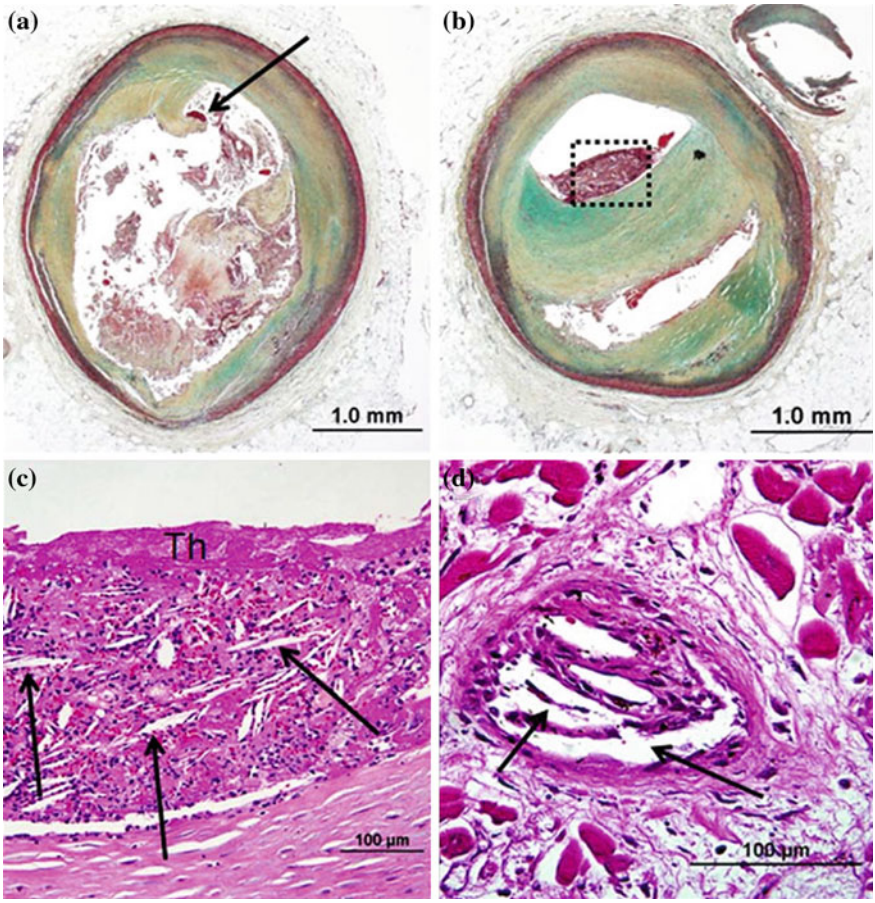

Fig. 6.13 Representative micrographs of distal microembolization of plaque material from ruptured atheroma. **a** Low-power (Movat's pentachrome) view of rupture site (arrow) showing luminal fibrin and cholesterol clefts. **b** Adjacent distal segment to rupture site demonstrates nonocclusive thrombus composed of necrotic core material. **c** High-power image demonstrating cholesterol clefts (arrows) with superimposed thrombus (Th) (hematoxylin and eosin). **d** High-power image of intramural coronary artery atheroembolus consisting of cholesterol clefts (arrows) and surrounded by healing myocardium in apatient who underwent percutaneous coronary intervention for acute myocardial infarction. Adapted from Bekkers et al. [130]

Reperfusion injury is characterized by a massive infiltration of coronary microcirculation by neutrophils and platelets occurring at the time of reperfusion [134]. Indeed, reintroduction of neutrophils in post-ischemic myocardium results in their activation, with subsequent adhesion to the endothelial surface and migration in the surrounding tissue. Activated neutrophils, in turn, release oxygen free radicals, proteolytic enzymes, and pro-inflammatory mediators, which can directly cause tissue and endothelial damage. Neutrophils also form aggregates

with platelets which plug capillaries, thus mechanically blocking flow [135, 136]. Finally, vasoconstrictors released by damaged endothelial cells, neutrophils, and platelets contribute to sustained vasoconstriction of coronary microcirculation [137].

From a molecular point of view, inflammatory mediators are involved in the complex interaction between platelets, neutrophils and endothelium. In particular, TNF-alpha expression is induced by reperfusion and can impair endothelium-dependent CFR [138]. Furthermore, interleukin-1β has recently been associated with ischemia–reperfusion injury since interleukin-1β knock-out animals exhibit marked reduction of ischemia induced inflammation [139]. Selectin expression on cell surfaces is also important for mechanical plugging of the microcirculation [140]. Finally, the balance between NO and superoxide is tipped in favor of superoxide within minutes of reperfusion of ischemic tissues, due to increased production of xanthine oxidase by neutrophils, endothelial cells and cardiac myocites, which leads to an exacerbation of the inflammatory state [141].

Reperfusion may also cause irreversible injury to myocytes [142]. During ischemia, the intracellular content of Na^+ increases due to accumulation of H^+ that is exchanged by the Na^+/H^+ exchanger. The subsequent exchange of Ca^{++} with Na^+ by sarcolemmal Na^+/Ca^{++} exchanger produces calcium overload, which triggers uncontrolled hypercontraction and stimulates opening of the mithocondrial permeability transition pores, which further enhances calcium overload. Furthermore, Na^+ extrusion trough Na^+/K^+ ATP-ase is impaired and together with Ca^{++} accumulation leads to myocite cell swelling, which contribute to subsequent rupture of the cell membrane when the extracellular osmolality is rapidly normalized by reperfusion. Of note, cyclosporine, which blocks the mithocondrial permeability transition pores has been recently shown to reduce infarct size by 20 %, when administered intravenously in patients undergoing primary PCI [143]. Of note, IPC also reduces infarct size by blockade of mithocondrial permeability transition pores [144].

Natriuretic peptides may modulate ischemia–reperfusion injury. Atrial natriuretic peptide may suppress the renin angiotensin-aldosterone system and endothelin-1 which increase infarct size and negatively affects MVO and cardiac remodeling [145]. Accordingly, Hayashi et al. showed that infusion of atrial natriuretic peptide in patients with their first anterior AMI was associated with lower concentrations of endothelin-1, angiotensin-II and aldosterone [146]. Notably, B-type natriuretic peptide limits infarct size when administered prior to and during coronary occlusion acting through a K-dependent ATP channel, which requires nitric oxide synthase activity [147].

A fourth pathogenetic component of MVO is individual susceptibility of coronary microcirculation to injury. This notion is supported by the observation that in man, MVO is occasionally observed during elective percutaneous coronary procedures [148], while it can be absent following primary PCI carried out several hours after coronary occlusion. Predisposition may be genetic and/or acquired. In particular, diabetes has been associated with impaired microvascular reperfusion after primary PCI and hypercholesterolemia in the animal model aggravates

reperfusion injury by enhancing endothelial oxidative stress [149, 150]. Finally, IPC appears to have a beneficial effect on microvascular function [151] (Fig. 6.14).

6.3.3 Predictors of the Different Pathogenetic Components of MVO

The role played by these four pathogenetic mechanisms of MVO can be predicted, to some extent, in the individual patient by specific markers. This is important in order to develop a personalized treatment of MVO (Chap. 10).

Some angiographic findings predict the risk of distal embolization. Yip et al. proposed a score to assess thrombus burden [152] based on the following features: (1) an angiographic thrombus with the greatest linear dimension more than three times the reference lumen diameter; (2) cutoff pattern (lesion morphology with an abrupt cutoff without taper before the occlusion; (3) presence of accumulated thrombus (>5 mm of linear dimension) proximal to the occlusion; (4) presence of floating thrombus proximal to the occlusion; (5) persistent contrast medium distal

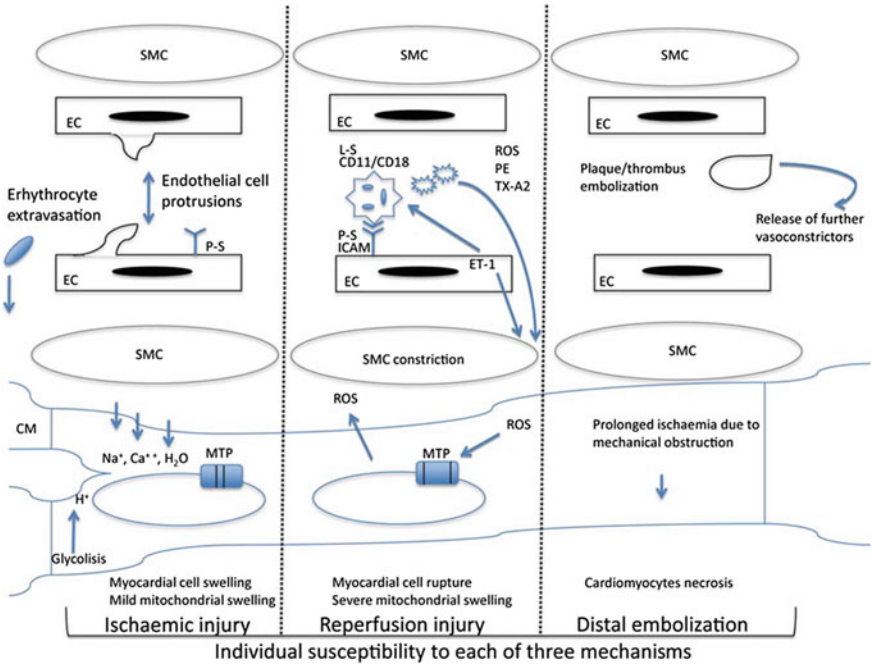

Fig. 6.14 A comprehensive illustration showing multiple mechanisms involved in the pathogenesis of MVO that might be targeted by appropriate therapy. CM=cardiomyocyte; EC=endothelial cell; ET = endothelin; L-S=L-selectin; MPT MTP=mitochondrial transition pore; PE=proteolytic enzymes; P-S=P-selectin; ROS=reactive oxygen species; SMC=smooth muscle cell; T×A2 = thromboxane-A2. Adapted from Niccoli et al. [116]

to the obstruction; and (6) reference lumen diameter of the infarct related artery >4.0 mm. All these features were independent predictors of MVO in 800 patients undergoing primary PCI. The relevance of high thrombus burden at the site of the culprit artery in predicting distal embolization has been confirmed by Limbruno et al. Indeed, in a series of patients with STEMI undergoing primary PCI with distal filter protection, they found that the Yip's score was an independent predictor of total debris volume captured in the filter's basket [153].

An important predictor of ischemia-related injury is a longer time from symptom onset to reperfusion, being a longer time associated with a higher prevalence and a larger extent of MVO [154]. Interestingly, Turschner et al. showed that prolonged ischemia followed by reperfusion is associated with increased thickness of the myocardium due to tissue edema and hemorrhage, which eventually contributes to MVO due to mechanical effects [155].The extent of the ischemic region is another important determinant of MVO, as demonstrated in animal models. This is confirmed in man by the association of ECG and echocardiographic indexes of the extent of ischemic region, such as QRS score and wall motion score index, respectively, with the prevalence of MVO [156, 157]. The higher prevalence of MVO when the LAD coronary artery is the infarct-related artery, as compared to other epicardial coronary artery branches, confirms that a larger extent of the ischemic area is an important predictor of MVO.

With regard to predictors of reperfusion-related injury, a promptly available clinical predictor of MVO is neutrophil count, which has been recently associated with microvascular injury after primary PCI [158]. Platelets also play an important role in MVO. Accordingly, platelet reactivity on admission, as assessed by the platelet function analyser-100 method, is associated with an increased prevalence of MVO and adverse LV remodeling [159]. Furthermore, Huczek et al. demonstrated that mean platelet volume on admission is an important predictor of impaired reperfusion [160]. Interestingly, early data indicate that plasma levels of thromboxane-A2 and increased CD41 platelet expression predict MVO [161]. Increased oxidative state contributes to reperfusion injury. Accordingly, Matsumoto et al. found that levels of antioxidants vitamin C, vitamin E, and glutathione peroxidase obtained from coronary sinus before primary PCI are significantly lower in patients exhibiting MVO than in patients exhibiting myocardial reperfusion [162]. Endothelin-1 released by activated endothelium plays a key role in MVO, depending on its strong vasocostrictive effect, exerted on small-resistance coronary arteries, on the enhancement of neutrophil adhesion to the endothelium and on the induction of elastase release, which may also mediate tissue injury and oedema. Accordingly, in patients who developed MVO, endothelin-1 levels on admission were found increased and to be an independent predictor of MVO [163]. Importantly, endothelin-1 is a possible therapeutic target and this notion is supported by the beneficial effect of its selective inhibition in animal models of ischemia–reperfusion [164].

Thus, the severity of reperfusion injury can be predicted using laboratory predictors such as neutrophil count, mean platelet volume, platelet reactivity,

thromboxane-A2, and endothelin-1 levels, which might also become therapeutic target.

Genetic and acquired susceptibility to MVO may play an important role in the modulation of MVO. Interestingly, a recent study suggested that the 1976T > C polymorphism of the adenosine 2A receptors gene is associated with a higher prevalence of MVO [165]. Furthermore, patients with MVO show a more compact fibrin network possibly suggesting a genetically mediated resistance to lysis [166].

Baseline reactivity of inflammatory cells also might modulate the severity of MVO. Yet, no correlation between CRP serum levels measured within 6 h of chest pain onset and the prevalence of MVO was found in one study [167]. In contrast, peak CRP reflecting necrosis extent has been associated with MVO [168].

Acquired risk factors such as diabetes and hypercholesterolemia may predispose to MVO as suggested by observations carried out in man and in animal models. Recent studies have also shown an association between acute hyperglycaemia and MVO, which was independent of previous glycemic control evaluated by HbA1c levels, and may suggest a direct detrimental effect of hyperglycemia on reperfusion injury [169]. Finally, pre-infarction angina may have a protective effect as it induces IPC [170], which, in contrast, is abolished by binge drinking known to be associated to a worse outcome after an acute myocardial infarction [171].

Several therapeutic strategies have been tested for the prevention and treatment of MVO with inconsistent results, possibly because applied indistinctively to all patients (See Chap. 10). It is conceivable that the relevance of each pathogenetic component of MVO is different in different patients. Therefore, the assessment of the multiple mechanisms of MVO may guide in the development of personalized forms of treatment. Thus, it is possible to envision a personalized treatment of MVO, which stems from the assessment of the predictors of the four pathogenetic components of the phenomenon.

6.3.4 Diagnosis

The diagnosis of MVO can be assessed at the time of primary PCI or subsequently using noninvasive approaches (Fig. 6.15).

MVO can initially be demonstrated by assessing the TIMI flow grade [172]. Indeed, TIMI flow 0–2, observed in 5–10 % of patients, is predictably associated with MVO. The latter, however, occurs also in a sizeable proportion of patients with apparent successful large epicardial vessel reopening resulting in TIMI 3 grade. Thus, the sensitivity of TIMI flow assessment in the detection of MVO is rather low. At the time of primary PCI, MVO can be inferred more efficiently by assessing MBG, which describes the relative "blush," or intensity, of the radiopacity of myocardial tissue achieved with an epicardial coronary injection of contrast medium, and the rapidity which this enhancement clears with. The more intense is myocardial blush and the faster its clearance, the better is microvascular

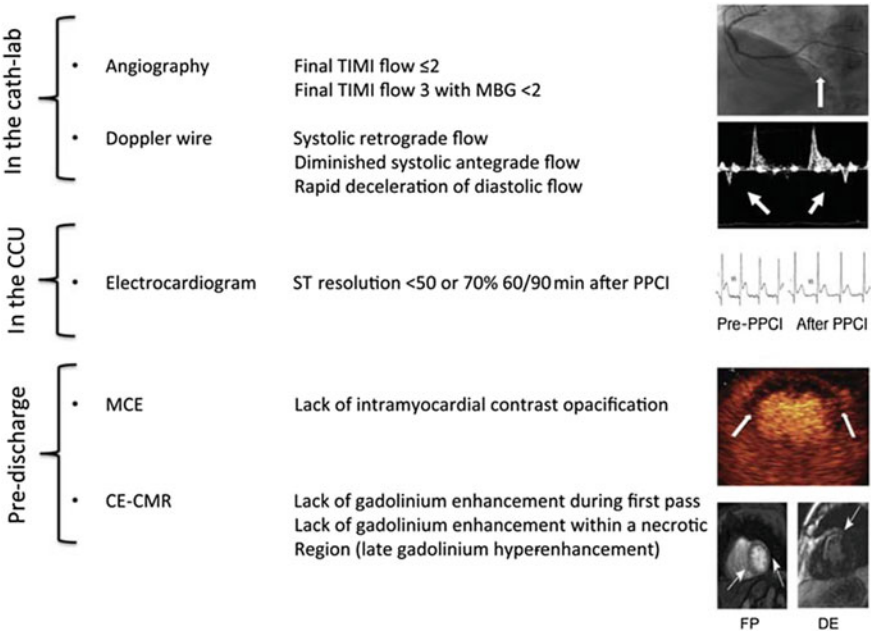

Fig. 6.15 Diagnosis of MVO. CCU, coronary care unit; CE-CMR, contrast-enhanced magnetic cardiac resonance; MCE, myocardial contrast echocardiography; TIMI, thrombolysis in myocardial infarction; MBG, myocardial blush grade; PPCI, primary percutaneous coronary intervention

perfusion. MBG is scored on a scale of 0–3, with higher scores indicating better perfusion. MBG 0–1, suggestive of MVO, is observed in as high as 50 % of patients with TIMI flow grade 3 [173]. Taken together, angiographic MVO can be defined as a TIMI flow <3 or a TIMI flow 3 with a MBG 0–1.

Largely used in the clinical arena and in clinical trials is the measurement of ST-segment resolution at 60–90 min after primary PCI. Different methods have been proposed to measure ST-segment resolution. An ST-segment reduction lower than 50 or 70 %, compared to admission ECG, is considered an established marker of MVO; the predictive value of this finding was indeed demonstrated during the pharmacological era of coronary reperfusion and has been confirmed in the contemporary era of mechanical reperfusion [174]. However, it should be observed that about one-third of patients with TIMI flow grade 3 and MBG 2–3 do not exhibit significant ST-segment resolution [175].

As TIMI flow grade, MBG and ST-segment resolution may be obtained from routine management of STEMI patients, are inexpensive, and provide additional prognostic information, their assessment should become current clinical practice. Notably, the integration of MBG and ST-segment resolution has been shown to improve patient risk stratification. Indeed, one study in patients treated by either primary PCI or pharmacological reperfusion [176], reported very good outcome in

patients with a MBG 2–3 and ST-segment resolution >70 %, very poor outcome in patients with MBG 0-1 and ST-segment resolution <70 % and intermediate prognosis in patients with discordant results of angiographic ad ECG indexes of MVO.

Although easily available in the clinical arena, neither MBG nor ECG resolution provide a direct assessment of myocardial perfusion. In contrast, noninvasive imaging techniques such as MCE and CMR provide a more direct assessment of myocardial perfusion.

Contrast echocardiography utilizes ultrasound to visualize contrast microbubbles that freely flow within patent microcirculation. Such microbubbles are injected in the peripheral circulation, safely pass the pulmonary circulation and reach intact coronary bed. They have a rheology similar to that of red blood cells and thus freely flow within coronary microvessels, as the only one pure intravascular tracer (Chap. 3). Lack of intramyocardial contrast opacification is due to [177, 178]. In the AMICI study, the extent of MVO at contrast echocardiography was demonstrated to be the best predictor of adverse LV remodeling after STEMI, being superior to ST-segment resolution and to MBG among patients exhibiting TIMI 3 flow grade.

CMR utilizes gadolinum to assess regional myocardial perfusion. MVO can be diagnosed as either lack of gadolinium enhancement during first pass or lack of gadolinium enhancement within a necrotic region, identified by late gadolinium hyper-enhancement [179]. In particular, very good correlation has been found between gadolinium enhancement during first pass and MBG, thus suggesting that both parameters reflect the degree of microvascular integrity within the infarct zone [180]. Studies performed by CMR have confirmed that MVO is a powerful predictor of LV remodeling and of patient survival [181].

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Iatrogenic Coronary Microvascular Dysfunction

7

7.1 Percutaneous Interventions

Percutaneous coronary revascularization has become a widely used and effective treatment for CAD. Severe acute complications are rare, but a mild and asymptomatic release of biochemical markers of myocardial necrosis is frequently observed after otherwise technically successful interventions. Both impairment of flow in coronary side branches following stent deployment and distal embolization of atheromatous material contribute to myocardial necrosis during PCI. Occlusion of small side branches is associated with necrosis in small myocardial regions adjacent to the territory supplied by the stented coronary artery. Distal necrosis in the dependent vascular territory occurs, instead, when atheromatous plaque is embolized during the percutaneous procedure (Fig. 7.1) [1, 2]. Distal embolization is more extensive following PCI in saphenous vein grafts than in native coronary arteries and is more frequent following PCI in unstable patients than in stable patients (Fig. 7.2) [3, 4]. Notably, Prati et al. found that in unstable patients a considerable amount of the lumen enlargement obtained after stenting was attributable to plaque reduction associated with distal embolization and a proportional rise of myocardial necrosis markers (Fig. 7.3) [5].

Based on these and other observations, the last version of the universal definition of myocardial infarction suggests that, by arbitrary convention, myocardial infarction related to PCI (type 4) should be diagnosed when troponin values >5 times the upper normal limit during the first 48 h after the procedure are detected, occurring from a normal baseline troponin value, together with (1) evidence of prolonged ischemia (≥20 min) as demonstrated by prolonged chest pain, or (2) ischemic ST changes or new pathological Q waves, or (3) angiographic evidence of a flow-limiting complication, such as loss of patency of a side branch, persistent slow-flow or no-reflow, embolization, or (4) imaging evidence of new loss of viable myocardium or new regional wall motion abnormality [6].

The clinical relevance of distal embolization during PCI is considerable. In a recent comprehensive meta-analysis, Testa et al. have assessed the occurrence and the prognostic impact of Tn elevation in patients with normal baseline levels

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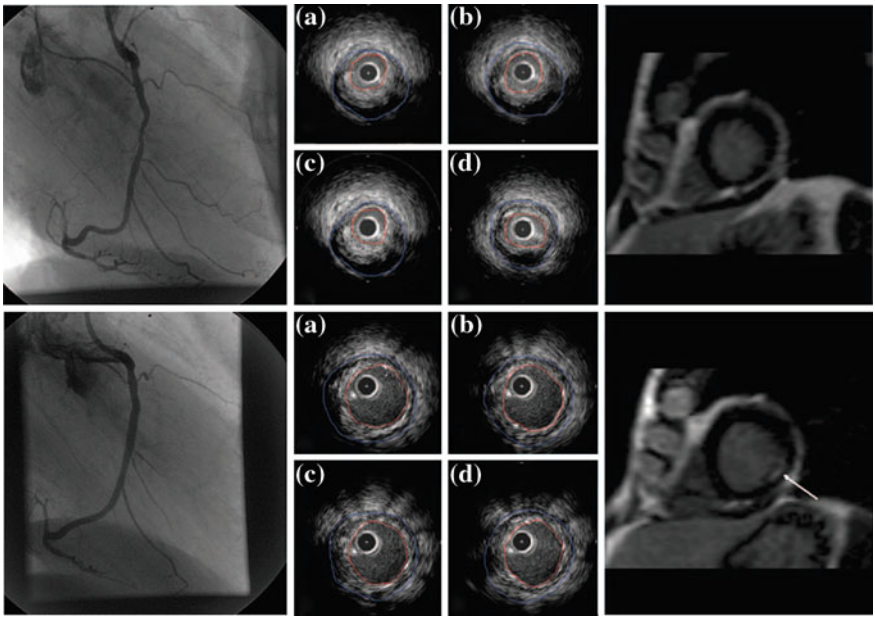

Fig. 7.1 *Top panel. Left:* pre-procedural angiogram of the right coronary artery showing a 60–70 % mid-vessel stenosis; *middle:* Intravascular ultrasound (IVUS) examination (4 slices taken at 1-mm distance in the middle of the plaque, with red lines depicting the borders of lumen area, blue lines the external elastic membrane area, and with the difference being the plaque area) shows a large plaque burden with hypo-echogenic features, suspected for a large necrotic core; *right:* late gadolinium enhancement CMR shows no evidence of pre-existing myocardial necrosis. *Bottom panel. Left:* angiogram after stenting shows a good result from the PCI; *middle:* IVUS examination confirms the good post-procedural result, showing a significant reduction of plaque burden; *right:* Late gadolinium enhancement CMR, however, shows a focal area of endocardial hyper-enhancement in the infero-lateral segment (*arrow*), suggesting a small myocardial necrosis caused by distal embolization of plaque material during the stenting procedure. The calculated mass of the new necrotic tissue was 2 g. Adapted from Porto I et al. [1]

undergoing PCI. Tn elevation after PCI occurred in about one-third of patients. At 18 months follow-up periprocedural Tn elevation was associated with a 50 % increased risk of subsequent major cardiovascular events, a twofold increased risk of death, a threefold increased risk of myocardial infarction, and a 50 % increased risk of re-PCI (Fig. 7.4) [7].

Although this meta-analysis could not assess the relation between amount of enzyme raise and outcome, this issue has been carefully assessed in a multicenter prospective cohort study, which evaluated the influence of post-procedural elevations of CK-MB on long-term mortality. CK-MB elevation was detected in 16 % of patients (Fig. 7.5) [8]. At 2 years follow-up periprocedural CK-MB elevation was associated with a twofold increased risk of death. A multivariable logistic regression analysis showed that CK-MB elevation independently predicted the risk of death with a linear relationship with the adjusted probability of death.

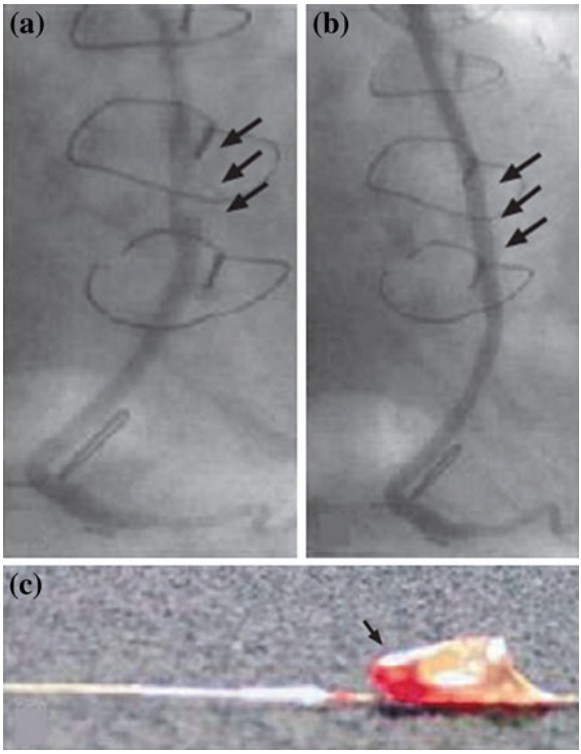

Fig. 7.2 *Panel A:* coronary angiogram obtained in a 76-year-old patient with an acute coronary syndrome treated for an ulcerated lesion in a saphenous vein graft to the lower circumflex–marginal branch (*arrows*). A stent was placed in the lesion, with an excellent final result and good distal flow (*Panel B*, *arrows*), after distal positioning of a filter basket similar to that shown in *Panel C* (*arrow*). Adapted from Kornowski R et al. [4]

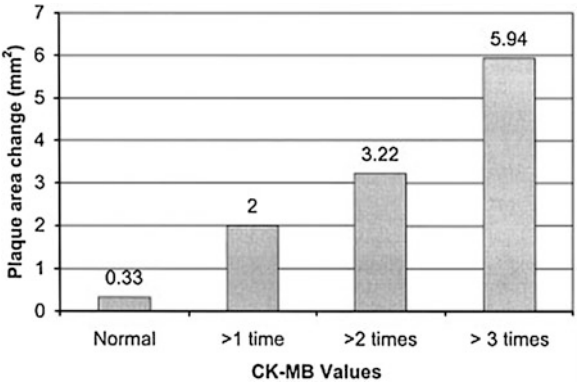

Fig. 7.3 Relation between CK-MB increase after PCI and change in plaque area after stenting assessed by intravascular ultrasound examination. These findings suggest that a considerable amount of the lumen enlargement obtained after stenting is attributable to plaque reduction associated with distal embolization. Adapted from Prati F et al. [5]

Importantly, when the patients with baseline CK-MB levels above the upper reference limit or procedural complications were removed from the analysis, the CK-MB raise retained a similar independent predictive value. These findings are important because they show that even in patients with apparently successful PCI, a subclinical increase of markers of myocardial necrosis is associated with a higher risk of death at medium long-term follow-up.

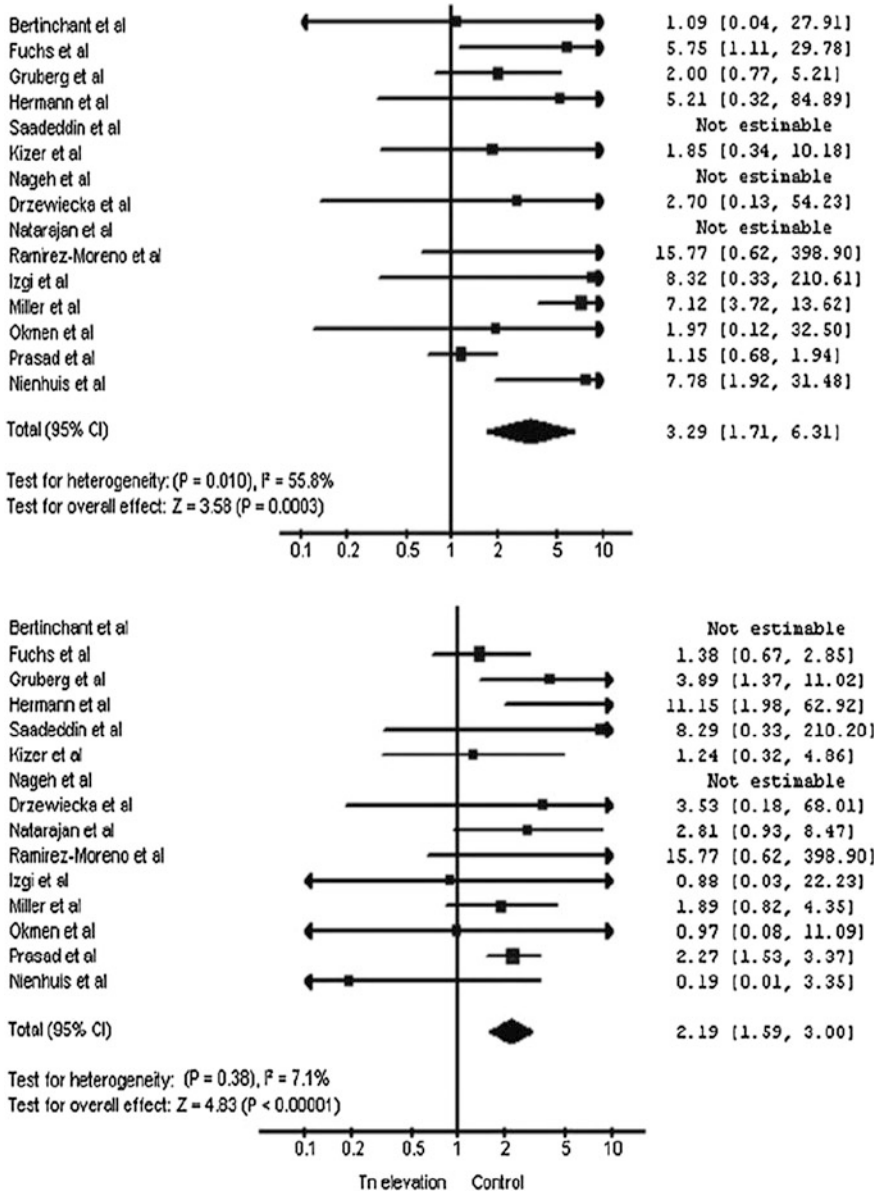

Fig. 7.4 Meta-analysis of studies assessing the impact of troponin raise after PCI on clinical outcome. *Top panel*. Individual and summary odds ratios (95 % confidence limits) for re-infarction. *Bottom panel*. Individual and summary odds ratio (95 % confidence limits) for all-cause death. Any troponin raise was associated with a threefold increase of the risk of re-infarction and a twofold increase of the risk of all-cause death. Adapted from Testa L et al. [7]

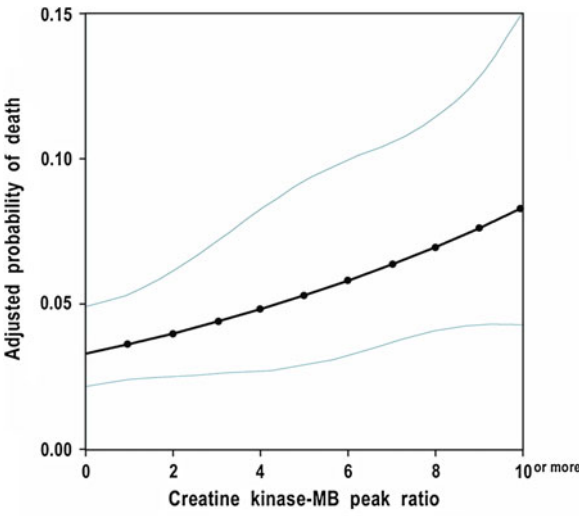

Fig. 7.5 CK-MB peak ratio after PCI and adjusted probability of death 2 years after the procedure. Adapted from Cavallini C et al. [8]

It is only possible to speculate as to why procedural myocardial necrosis marker elevations influence long-term mortality. One potential mechanism may be related to the myocardial damage per se, which might lead to increased mortality as a result of electrical instability or of persistent myocardial ischemia associated with CMD. Alternatively, raised necrosis marker levels after PCI may signal a more active atherosclerotic process associated with an adverse prognosis due to a higher risk of cardiovascular events. It is interesting to note that antithrombotic drugs such as platelet glycoprotein IIb/IIIa receptor inhibitors, which have consistently been shown to reduce post-procedural myocardial damage, also reduce long-term mortality especially in high-risk subsets of patients [9, 10]. This observation supports the notion of a direct effect of periprocedural myocardial necrosis on mortality. It might be speculated that CMD might favor thrombogenic mechanisms in the proximal epicardial coronary arteries (see Chap. 6).

It is worth noting that CMD associated with PCI is characterized not only by distal embolization but also by functional alterations. Indeed, Gregorini et al. found that after stenting CFR transiently decreases in the myocardium supplied by the stented coronary artery branch. She also found that α_2-adrenergic blockade by yohimbine normalized CFR [11]. Several mechanisms can be hypothesized to play a role in the periprocedural CFR decrease observed during coronary stenting. In particular, ischemia induced by balloon inflations and the stretch of the artery may elicit a reflex [12] sympathetic increase of α-adrenergic constrictor tone, as observed both in animals and in humans [13–15]. Both α_1- and α_2-adrenergic receptors are present in the human coronary circulation, with α_2-adrenergic receptors being predominant in the microcirculation [14–18].

Accordingly, selective blockade of α_1 and α_2-adrenergic receptors has different effects on conduit and resistance vessels [19–21]. Notably, Gregorini et al. found that α_2-adrenergic receptor blockade, rather than α_1 blockade normalized CBF

after PCI, thus supporting the notion that this alteration was mediated by coronary microvascular constriction [11].

Taken together, the information on the coronary microvascular effects of PCI shows that while, on the one hand, improvement of myocardial perfusion related to removal of epicardial stenoses is beneficial, on the other hand, the functional and, more importantly, structural microvascular alterations may substantially limit these advantages. Accordingly, in patients with stable angina associated to small or moderate amount of myocardium at risk of myocardial ischemia, stenosis removal by PCI does not improve the outcome. In a recent meta-analysis initial stent implantation for stable CAD showed no evidence of benefit compared with initial medical therapy for prevention of death, nonfatal MI, unplanned revascularization, or angina [22] (see Chap. 6).

The failure of stent implantation to reduce the risk of death or infarction compared with medical therapy in stable CAD reinforces current concepts of the underlying pathophysiologic characteristics of atherosclerosis as a diffuse arterial inflammatory disease that gives rise to vulnerable plaques, the disruption of which leads to coronary thrombosis, myocardial infarction, and death. Lesions most prone to rupture tend to be those of the least hemodynamic consequence, whereas the obstructive lesions that are stented to treat angina or ischemia are paradoxically less prone to rupture [23]. These findings fail to support theories suggesting that PCI might reduce mortality by stabilizing vulnerable plaques [24, 25].

Notably, over 400,000 PCI procedures are performed for the treatment of stable CAD in the United States each year [26]. Despite publication of clinical trials and guidelines supporting the initial use of optimal medical therapy prior to PCI, 44 % of stable patients only receive optimal medical therapy before deciding to perform PCI [27], while at the other extreme approximately 50 % of patients with STEMI do not receive a primary PCI [28]. This resistance to adhere to recommendations derived from high quality evidence is multifactorial. It has been suggested that financial rewards for physicians and hospitals to perform PCI in the fee-for-service health care environment of the United States may contribute to the persistent use of PCI in settings where it has been shown to offer no clinical benefit. In support of this concept, rates of PCI for stable coronary artery disease in Ontario, Canada, where a single-payer government regulates system controls, the annual volume of cardiac procedures, are less than half what they are in the New York State [29]. In the context of controlling rising health care costs, several studies suggest that up to 76 % of patients with stable CAD can avoid PCI altogether if treated with optimal medical therapy [30]. At the other extreme, PCI clearly improves the outcome in patients with ACS. In this setting the benefit of limiting the impending risk of loss of a large amount of myocardium is clearly superior to the detrimental effects of PCI on coronary microcirculation.

7.2 Surgical Interventions

Surgical trauma and cardiopulmonary bypass contribute to a systemic inflammatory response measurable by circulating cytokines [31–35]. This can be the result of many factors, including contact of blood with the bypass circuit, myocardial ischemia during bypass, aortic cross clamping, and reperfusion injury [36–39]. Perioperative myocardial infarction results in further elevation of inflammatory markers [40, 41]. Substantial biomarker elevations after CABG have been shown to have significant prognostic implications [42–45] and usually represent CABG-related myocardial infarction [46–48]. Identifying CABG-related infarction using conventional ECG and biochemical methods, however, can be difficult. Troponins are particularly sensitive biomarkers introduced predominantly for risk stratification in patients with acute coronary syndrome and are the gold standard for identifying myocardial necrosis. However, there is uncertainty about what absolute level of biomarker elevation reflects myocardial infarction after CABG. Furthermore, there are little data on whether an early measurement of biomarkers (at 1 h or less after surgery) can provide any diagnostic or prognostic relevant element. One study using late gadolinium enhancement at CMR imaging and TnI measurement found that about one-third of patients undergoing CABG had new myocardial infarction and that a cut off of TnI of 5 μg/L (upper normal limit 0.6 μg/L) at 1 h had 67 % sensitivity and 79 % specificity for detecting the new infarction. In this study the predictive value of CK-MB for the diagnosis of myocardial infarction was lower than that of TnI: using a cut off of CK-MB of 25 μg/L (upper normal limit 4.8 μg/L) at 1 h had, indeed, 44 % sensitivity and 89 % specificity for detecting the new infarction [49] (Fig. 7.6). Based on these and other observations the last version of the universal definition of myocardial infarction states that by arbitrary convention, myocardial infarction with bypass surgery (type 5) should be diagnosed for troponin values >10 times the upper normal limit during the first 48 h following surgery, occurring from a normal baseline troponin value. In addition, either (1) new pathological Q waves or new left bundle branch block, or (2) angiographically documented new graft or new native coronary artery occlusion, or (3) imaging evidence of new loss of viable myocardium or new regional wall motion abnormality, should be documented for the diagnosis of a CABG-related myocardial infarction [6].

Thus, elevations of biochemical markers of myocardial damage, CK-MB and troponins are common after CABG and have been associated with increased in-hospital and short-term mortality [43, 44, 50, 51]. However, few studies have assessed long-term mortality, especially in relation to troponin peak. Sorras et al., assessed the impact of both CK-MB and TnT on mortality after bypass grafting over 6 years follow-up. They enrolled 1,350 consecutive patients undergoing isolated on-pump coronary bypass grafting and measured CK-MB and TnT at 7, 20 and 44 h postoperatively. Both peak CK-MB and peak TnT independently predicted long-term mortality when analyzed in separate multivariate Cox models, adjusting for baseline demographic characteristics and perioperative risk factors.

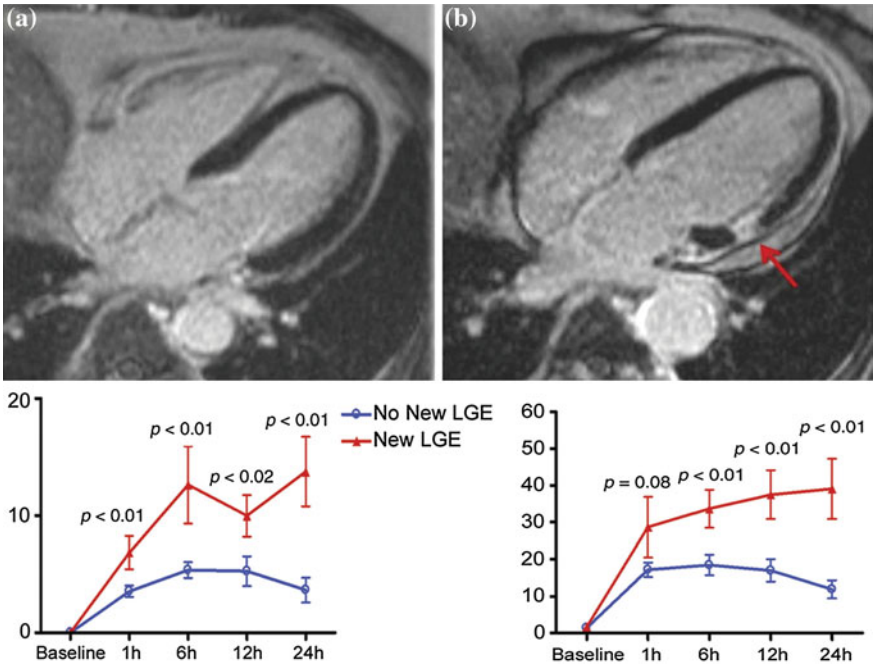

Fig. 7.6 *Top panel.* **a** CMR before CABG. **b** New hyper-enhancement is shown on CMR after CABG (*arrow*). *Bottom panel.* Comparison of curves of troponin I release *(left)* and CK-MB release *(right)* after CABG in patients with the evidence of new areas of late gadolinium enhancement (LGE, *triangles*) vs. patients without new LGE areas (no new LGE, *circles*) at CMR. The error bars are mean standard errors. Adapted from Lim CC et al. [49]

However, when analyzed simultaneously in the same Cox model, TnT only was a significant predictor. They concluded that both CK-MB and TnT were predictors of mortality after CABG surgery, but TnT appeared to be a better predictor of long-term mortality [52].

Domanski et al. reported a meta-analysis of 18,908 patients enrolled in 7 studies that examined the prognostic significance of CK-MB or TnT elevation within 24 h after CABG. They found a strong, graded and independent association of elevation of CK-MB and TnT levels with mortality following CABG. The mortality rate more than doubled at a CK-MB ratio of 4.4. Qualitatively similar results were seen for TnT elevation. Importantly, myocardial enzyme elevation within 24 h after CABG continued to be prognostically important for events at 1 year among individuals who had survived 30 days after the procedure [53].

A comparison with studies of enzyme elevations following PCI offers an intriguing parallel with the relation of enzyme elevation to prognosis following CABG. As noted above, elevation of CK-MB following PCI also is associated with reduced long-term survival and mortality increases with increasing enzyme elevation. The infarcts (biomarker elevations) that occur following PCI are related mainly to embolization and to functional microvascular alterations leading to CMD.

The potential mechanisms of myocardial necrosis are many and different in the setting of CABG and include air embolism, graft or native artery closure, global ischemia with suboptimal cardioplegia and low postoperative flow. The fact that different mechanisms of injury following PCI and CABG have similar prognostic implications suggests that patient prognosis is eventually driven by the extent of necrosis regardless of the mechanisms responsible for its occurrence. The reasons why small infarcts are associated with reduced survival and result in a monotonically increasing, nearly exponential relationship of biomarker elevation (extent of myocardial injury) and mortality rate remain to be understood. An improved understanding of the mechanism linking small amounts of post-CABG and post-PCI enzyme elevations with outcome would be an advance, and future studies examining this issue would be useful. It should be incidentally observed here that the impact of biomarker elevations in other settings, such as valve surgery, is not known.

The prognostic impact of myocardial damage assessed by biomarker elevation has at least two important implications. The first is that post-procedural enzyme elevation is a potentially important surrogate end-point for clinical trials. Also of significance is the potential use of these biomarker elevations as a measure of procedure quality, including the comparison of different centers and even of individual operators. Important in this regard will be standardizing the post-procedure time when biomarker levels should be determined. Future effort should be directed to achieving a better understanding of the mechanisms that contribute to procedural myocardial necrosis, particularly those that are under the control of the operator and thus potentially amenable to easy correction.

Finally, as noted above for PCI, the increased risk of mortality, associated with even modest CABG–related cardiac biomarker raise and the attendant CMD strongly suggest to perform CABG in stable patients only if they exhibit refractory angina or a large area of myocardium at risk of ischemia.

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Part III
Therapeutic Approaches to Coronary Microvascular Dysfunction

Treatment of Primary CMD

8

8.1 Primary CMD Caused by Cardiovascular Risk Factors

Control of cardiovascular risk factors has been the main form of intervention that has allowed a reduction of cardiovascular mortality in the last decades. Accordingly, appropriate treatment of risk factors should be implemented independently of any evidence of vascular abnormalities. However, identification of early impairment of vascular function, and in particular of CMD, might suggest a more aggressive approach to treatment. Some studies have indeed suggested that the presence of CMD in patients with cardiovascular risk factors can be predictive of future development of macrovascular atherosclerosis [1], and some data also suggest an association between CMD and cardiovascular events at follow-up [2].

Treatment of CMD obviously reflects treatment of individual cardiovascular risk factors, and several studies have assessed whether treatment of specific risk factors does improve CMD. These studies, however, present some pitfalls that should be taken into account. First, they have usually been conducted on small groups of patients. Second, in most studies the state of coronary anatomy was unknown, and therefore the lack of significant obstructive CAD was only based on the absence of angina and a low risk profile for CAD. Third, they have usually assessed the effects over short-term follow-up periods. Finally, no study assessed whether improving CMD in patients with cardiovascular risk factors portends a prognostic benefit.

8.1.1 Hypertension

A large number of studies assessed the effect of pharmacological therapy on CMD in patients with hypertension. On the whole, these studies show that anti-hypertensive drugs are able to improve CMD in patients with hypertension, although they suggest that some differences among classes of medications might exist.

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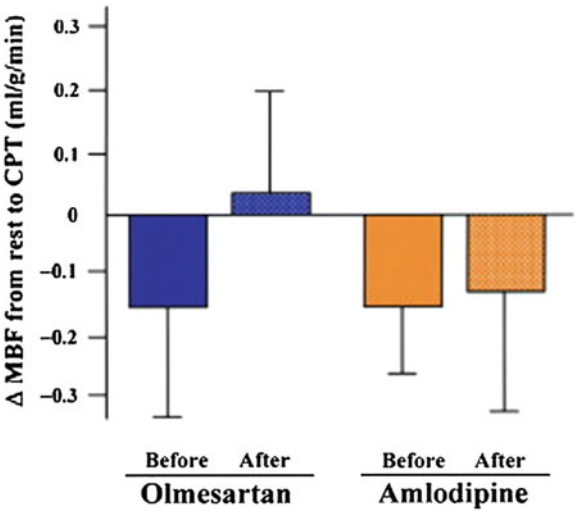

Fig. 8.1 Effect of olmesartan and amlodipine on CFR in patients with arterial hypertension. Adapted from Naya et al. [10]

Overall, ACE-inhibitors and angiotensin II receptor blockers, with rare exceptions, have been shown to improve or normalize endothelium-independent coronary microvascular function [3, 4]. In contrast, dihydropyridine calcium-antagonists (i.e., amlodipine, nifedipine) have consistently been found to have no significant effects [5], while verapamil, a nondihydropyridine calcium antagonist, showed positive results in one study [6].

Among ß-blockers, nebivolol [7], which is known to have beneficial effects on the endothelial function through ß-3 stimulation, and carvedilol [8], which also exhibits α-blocking effects, have shown favorable effects on CMD, whereas no effects have been observed with metoprolol [8] and atenolol [9].

The effects of antihypertensive therapy on endothelium-dependent CMD has been investigated in a limited number of studies. In one study [10] olmesartan, but not amlodipine (Fig. 8.1), was found to improve the response of MBF to CPT, as assessed by PET, whereas in another study [6] verapamil, but not enalapril, was found to improve MBF during atrial pacing, in spite of a similar reduction of systemic blood pressure. These findings suggest that the improvement of CMD can be largely independent of the reduction of blood pressure determined by drugs.

The favorable effects of antihypertensive drugs on CMD, therefore, likely mainly depend on other mechanisms, including direct effects on vascular smooth muscle cells, an improvement of oxidative state, endothelial function and diastolic function, as well as effects on autonomic nervous system. Accordingly, agents like dihydropiridines might fail to improve CMD due to reflex sympathetic activation, whereas some ß-blockers might have detrimental effects on diastolic relaxation.

Of note, several studies have also clarified how the impairment of CFR in hypertensive patients is largely independent of the presence and degree of LVH [11], suggesting that CMD is mainly a consequence of vascular remodeling or of functional alterations of endothelial cells and/or smooth muscle cells [12, 13] (see Chaps. 2 and 4).

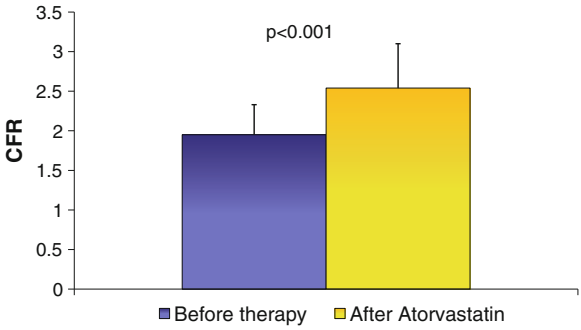

Fig. 8.2 Effect of atorvastatin on CFR in patients with hypercholesterolemia. Adapted from Caliskan et al. [14]

8.1.2 Hypercholesterolemia

Cholesterol-lowering therapy with statins has been shown to improve endothelium-independent coronary microvascular function in patients with high cholesterol levels [14], although with some discrepancies (Fig. 8.2). Notably, despite several studies showing that statins significantly improve endothelium-dependent vasomotion of large conductance coronary arteries, as well as of peripheral arteries, a significant effect on endothelium-dependent CMD, as assessed by acetylcholine intracoronary Doppler measures, has only been demonstrated in a small study with pravastatin [15].

It is still controversial whether the beneficial effects of statins on endothelial function is entirely mediated by the cholesterol lowering effects or also by their pleiotropic, in particular anti-inflammatory, effects.

8.1.3 Diabetes

In contrast with hypertension and hypercholesterolemia, only very few studies investigated the effect of glycemic control on CMD in diabetic patients. A combination of gliburide or glimepiride with metformin was reported to improve CMD in type 2 diabetes mellitus, but contrasting effects were noticed with regard to the relation between glycemic control and the increase of CFR. Acute administration of insulin also was shown to improve CFR in type 1 diabetics, but its long-term effects remain unknown [16] (Fig. 8.3).

8.1.4 Other Cardiovascular Risk Factors

Weight loss in obese patients has recently been reported to improve CBF response to dipyridamole, and the improvement was found to correlate with the increase in adiponectin levels [17, 18].

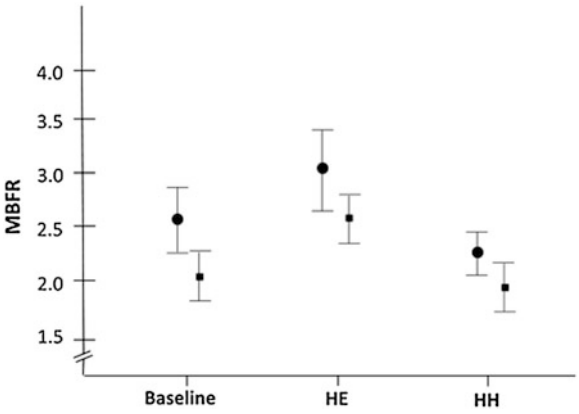

Fig. 8.3 MBF reserve (MBFR; mean ± SD), at baseline and during hyperinsulinemic euglycemia (HE) and hyperinsulinemic hypoglycemia (HH), in type 1 diabetes mellitus patients and in healthy control subjects (●). Adapted from Rana et al. [16]

Finally, the reduction of CFR related to smoking has been shown to be normalized by administration of the antioxidant vitamin C, lending support to the notion that the detrimental effects of smoking on coronary microcirculation can be explained, at least in part, by an increased oxidative stress [19].

8.2 Primary Stable MVA

The main goal of treatment of stable MVA is the control of symptoms, as major cardiac events are not increased in these patients [20, 21] (see Chap. 4). The response to treatment, however, is unpredictable, and drug therapy is therefore empirical and requires an optimal interaction between the physician and the patient. Anti-ischemic drugs remain the mainstay form of medical therapy, but their efficacy is limited in several patients. For this reason several alternative forms of therapy have been proposed for unresponsive patients.

Studies assessing the effects of therapy in MVA have several limitations, including the usually small number of patients enrolled, the lack of appropriate controls and the short-term follow-up period.

8.2.1 Classical Anti-ischemic Drugs

Anti-ischemic medications, alone or in combination, constitute the first pharmacological approach to patients with stable MVA [22]. The main results of studies that investigated the effects of classical anti-ischemic drugs in these patients are summarized in Table 8.1.

8.2.1.1 Beta-Blockers

ß-blockers may have several beneficial effects in patients with stable MVA. They reduce myocardial oxygen consumption, in particular during exercise and stress

Table 8.1 Main results of studies assessing the effects of traditional anti-ischaemic drugs in patients with cardiac syndrome X

	Drug	Angina	QoL	EST	Holter	NTG use	Other
Beta-blockers							
Fragasso [24]	Atenolol	↑		↑			Improved diastolic function
Lanza [25]	Atenolol	↑					
Leonardo [26]	Atenolol	↑		↑			Improved diastolic function
Romeo [27]	Acebutolol			↔			
Ferrini [28]	Propranolol			↔			
Bugiardini [29]	Propranolol				↑		
Calcium-antagonists							
Cannon [30]	Verapamil, Nifedipine	↑		↑		↓	
Cannon [30]	Lidoflazine	↑		↑	↔		Severe arrhythmic adverse effects
Ozçelik [31]	Nisoldipine	↑		↑		↓	
Romeo [27]	Verapamil			↔			
Montorsi [32]	Nifedipine sl	↑		↑			↑ CBF
Montorsi [34]	Nifedipine sl						Variable coronary vasomotor response
Bugiardini [29]	Verapamil				↔		
Lanza [25]	Amlodipine	↔					
Ferrini [28]	Diltiazem			↑			
Sütsch [33]	Diltiazem						↔ CFR
Nitrates							
Lanza [37]	sl ISDN			↓			
Radice [38]	sl NTG			↓			
Bugiardini [40]	i.c. ISDN						↓ CBF
Lanza [25]	ISMN	↔	↔				

NTG nitroglycerin, *QoL* quality of life, *ISDN* isosorbide dinitrate, *ISMN* isosorbide mononitrate, *CBF* coronary blood flo, *CFR* coronary flow reserve, *sl* sublingual, *i.c.* intracoronary, *EST* exercise stress test

conditions, but may also improve coronary perfusion by prolonging diastolic time and improving left ventricular dynamics. On the whole, ß-blockers are particularly useful in patients who show evidence for increased adrenergic activity, including those with increased heart rate at rest, a rapid increase of heart rate and/or blood pressure during exercise, abnormal heart rate circadian rhythm, and sympathovagal imbalance as assessed by heart rate variability [23].

The few studies that assessed the effects of ß-blockers on symptoms in MVA patients have all used atenolol and have all concordantly reported significant beneficial effects, as compared to placebo or other drugs [24–26]. Data are less consistent when exercise test endpoints are considered; indeed, an improvement of ischemic and angina threshold was reported in some studies [24, 26], but not in others [27, 28]. In a study, however, propranolol, but not verapamil, reduced the number of episodes of ST-segment depression during 24-h ECG Holter monitoring [29].

8.2.1.2 Calcium Antagonists

Calcium antagonists are powerful vasodilator drugs and are therefore used in the attempt to improve the reduced vasodilatory capacity of coronary microcirculation; furthermore, they also reduce cardiac afterload. In addition, nondihydropyridine calcium-antagonists reduce myocardial oxygen consumption due to negative chronotropic and inotropic effects. However, calcium-antagonists, in particular dihydropyridine drugs, may rapidly reduce blood pressure, and this effect causes a reflex increase in adrenergic activity, which may antagonise their favorable vasodilatatory effects.

Beneficial effects on chest pain symptoms in MVA have been reported in several studies [27, 30–32]. Furthermore, favorable effects of calcium-antagonists have also been reported on exercise-induced angina and ST-segment depression, as well as on exercise tolerance [28, 30, 32] (Fig. 8.4).

However, no significant improvement of angina symptoms were observed with amlodipine in a study [25], and verapamil failed to reduce spontaneous episodes of ST-segment depression during daily life as assessed by ambulatory ECG Holter monitoring in another study [29]. Disappointing results have also reported in the assessment of the effects of calcium antagonists on CBF. No effects of diltiazem on CBF response to dipyridamole were shown in a study [33]; in another study sublingual nifedipine improved myocardial perfusion, but was associated with a worsening of exercise-induced angina and ECG changes in a few patients [34].

In summary, nondihydropyridine calcium antagonists constitute a valid therapeutic first-line option, alternative to ß-blockers, particularly in patients in whom the prevailing mechanism of angina appears to be an increased microvascular constriction, as in patients who also report angina at rest.

8.2.1.3 Nitrates

The anti-ischemic effects of nitrates are mainly related to their capacity to reduce cardiac work through a reduction of preload, although they also have coronary

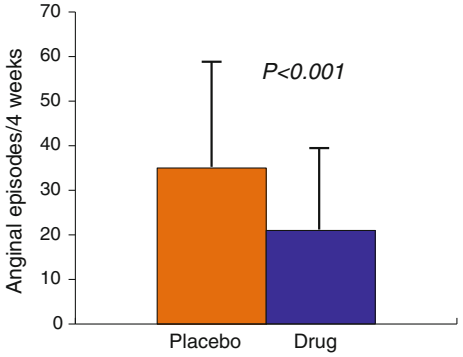

Fig. 8.4 Effect of verapamil or nifedipine (drugs) on episodes of angina in patients with MVA. Adapted from Cannon et al. [30]

dilator effects. However, the effects of nitrates on the coronary microcirculation seem to be variable and rather limited [35].

As in patients with obstructive CAD and in those with epicardial spam, sublingual short-acting nitrates are the first-choice drugs to treat angina attacks also in patients with MVA. However, the efficacy of sublingual nitrates seems less consistent in these patients, as a complete effect seems to be achieved in only about a half of patients [20, 36].

This is in agreement with the poor, or even negative, effects of short-acting nitrates on ischemic threshold assessed at exercise stress test [37, 38]. Of note, a significant relationship was recently found in MVA patients between the coronary microvascular dilator effect of sublingual nitroglycerin and time to ischemic threshold during exercise test performed after nitrate administration, thus suggesting that it may be beneficial in a subset of patients responsive to its vasodilator effect (Fig. 8.5) [39]. The reasons for the unsatisfactory effects of acute nitrates in MVA patients, in addition to a limited effect on CMD, are not fully known, but may include myocardial hypoperfusion caused by hypotension and reflex adrenergic activation, with an increase in heart rate and, possibly, coronary vasoconstriction. Paradoxical reduction of CBF was indeed observed after intravenous and/or intracoronary short-acting nitrate administration in a study [40].

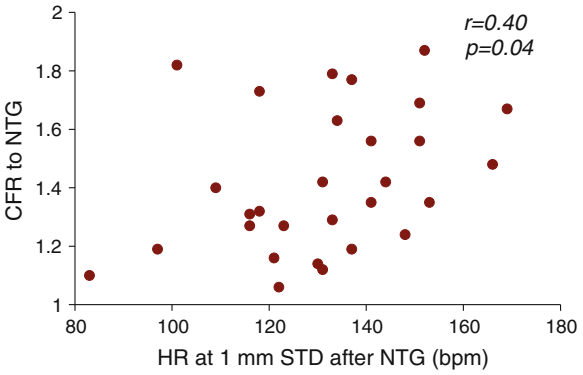

Fig. 8.5 Relationship between heart rate (HR) at 1 mm ST-segment depression (STD) during nitrate exercise stress test (*y* axis) and coronary blood flow velocity reserve (CFR) to nitroglycerine (NTG) (*x* axis) in patients with MVA. See text for more detail. Adapted from Russo et al. [39]

There are no data concerning the effects of chronic oral nitrate therapy in CSX patients, with the exception of a small study in which the administration of isosorbide-5-mononitrate (40 mg) failed to improve symptoms and quality of life over a period of 4 weeks [25].

8.2.2 Other Anti-ischemic Drugs

Several other forms of therapy, shown to have anti-ischemic effects, have been assessed in patients with stable MVA and can be prescribed in addition to classical anti-ischemic medications. The main clinical results obtained with these drugs are summarized in Table 8.2.

8.2.2.1 Xanthine Derivatives

The beneficial effects of xanthines in MVA can be related to two different mechanisms [41]. First, xanthines inhibit the arteriolar dilator effects of adenosine, through antagonism on vascular A_2 receptors on smooth muscle cells. This effect in nondysfunctional coronary microvessels may favor CBF redistribution toward myocardial areas with CMD, where the release of adenosine is increased. Second, xanthines stimulate presynaptic α-1 sympathetic receptors; this results in enhanced noradrenaline concentrations in the synaptic space, which, again, causes a more significant microvascular constriction in nondysfunctional areas, thus favoring CBF toward dysfunctional microvessels. Furthermore, xanthines may also have, in addition, an "analgesic" effect, as they antagonize the stimulation of cardiac nerve pain fibers by adenosine, which is a major mediator of ischemic pain [41]. This effect can be particularly important in patients with a reduced pain threshold [42].

A reduction of exercise-induced angina symptoms and/or ischemic ECG changes by acute intravenous administration of aminophylline, a nonspecific A_1/A_2 adenosine receptor antagonist, in MVA patients was reported in two small controlled trials [43, 44]. A single oral dose of aminophylline (400 mg) [38] was also reported to significantly improve ischemic ST-segment depression and angina pain induced by exercise stress test in a study.

In an uncontrolled trial, however, intravenous aminophylline failed to improve exercise induced angina and ST-segment changes [45], and, in a small randomized placebo-controlled trial, intravenous administration of bamiphylline (300 mg) [46], a specific adenosine A_1-receptor antagonist, had no effect on exercise-induced ST segment changes, although reduced the severity of exercise-induced chest pain.

Only one study assessed the effects of chronic oral xanthine therapy on spontaneous angina attacks [47]. In this randomized crossover study 13 MVA patients received either aminophylline (225–350 mg twice daily) or placebo for 3 weeks. In the 10 patients who completed the trial, aminophylline failed to significantly improve angina episodes; furthermore, the drug was found to improve exercise

Table 8.2 Main results of studies assessing the effects of alternative kinds of drugs with potential anti-ischaemic effects in patients with cardiac syndrome X

	Drug	Angina	QoL	EST	Holter	NTG use	Other
Xanthines							
Emdin [43]	Aminophylline	↑		↑			
Yoshio [44]	Aminophylline	↑		↑			↑ LVEF at rest but not at peak EST
Radice [38]	Aminophylline	↑		↑			
Lanza [45]	Aminophylline	↑		↔			
Lanza [46]	Bamiphylline			↔			
Elliott [47]	Aminophylline	↑		↑	↔		
ACE-inhibitors							
Kaski [50]	Enalapril			↑			
Nalbantgil [51]	Cilazapril			↑			
Ozcelik [31]	Ramipril	↑		↑			
Pizzi [52]	Ramipril		↑	↑			↓ Oxidative stress
Chen [53]	Enalapril			↑			↑ CFR and endothelial function
Alpha-antagonists							
Camici [49]	Doxazosin	↑		↑			↑CFR
Rosen [54]	Doxazosin						↔ CFR, chest pain and ECG changes after dipyridamole.
Bøtker [56]	Doxazosin			↔			
Galassi [57]	Prazosin			↔	↔		

(continued)

Table 8.2 (continued)

	Drug	Angina	QoL	EST	Holter	NTG use	Other
Nicorandil							
Yamabe [60]				↑			↑ Perfusion defects at scintigraphy
Chen [61]		↑		↑	↔		
Trimetazidine							
Leonardo [26]		↔		↔			↔ Diastolic function
Ranolazine							
Mehta [65]		↑	↑				↑ Perfusion defects at CMR
Villano [66]		↑	↑	↑			↔ CFR and FMD
Ivabradine							
Villano [66]		↑	↑	↔			↔ CFR and FMD
Statins							
Fábián [69]	Simvastatin			↑			↑ FMD
Kayikcioglu [70]	Pravastatin			↑			↑ FMD
Pizzi [52]	Atorvastatin		↑	↑			↑ FMD; ↓ oxidative stress
Estrogens							
Rosano [76]	17-ß-oestradiol	↑		↑			
Albertsson [77]	17-ß-oestradiol	↑		↑			

LVEF left ventricular ejection fraction, *CMR* cardiovascular magnetic resonance, *FMD* flow mediated dilation; Other abbreviations as in Table 8.1

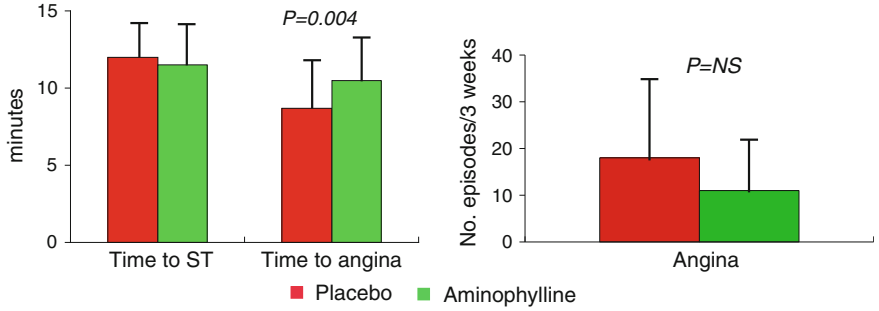

Fig. 8.6 Effect of aminophylline on exercise test (*left panel*) and on the number of episodes of angina (*right panel*) in patients with MVA. See text for more detail. Adapted from Elliott et al. [47]

induced angina, but not exercise induced ST-segment change nor episodes of ST-segment depression on ECG Holter monitoring (Fig. 8.6).

Thus, although data suggest that xanthines may improve exercise-induced angina in MVA patients and pharmacodynamics suggests their utility in case of increased pain sensitivity, their effects on spontaneous angina episodes during continuous therapy need further assessment.

8.2.2.2 ACE-Inhibitors

ACE-inhibitors have been proposed as therapeutic agents in MVA due to their lowering effects of serum and tissue angiotensin II. Although there is no evidence of a major role of angiotensin II in the CMD of these patients, local tissue angiotensin II, in particular, is involved in the regulation of coronary microvascular structure and function, exerting, when increased, several potentially deleterious effects, including vasoconstriction, increased oxidative stress, and degradation of nitric oxide [48]. Furthermore, angiotensin II enhances the effects of sympathetic nervous system on coronary microvascular tone and may also favor structural microvascular changes by stimulating cell growth [48]. Accordingly, enalapril has been found to improve CMD through increase of NO availability and reduction of oxidative stress in MVA patients [49].

The favorable clinical effects of ACE inhibitors in stable MVA were suggested by a small randomized placebo-controlled trial [50], in which enalapril prolonged time to ischemic threshold. Similar results have subsequently been obtained with the use of cilazapril [51]. Moreover, an improvement of angina symptoms, as well as of exercise capacity, has been reported with the use of ramipril [31, 52, 53].

8.2.2.3 Alpha Antagonist Drugs

The increased sympathetic activity shown in MVA patients might result in increased microvascular constriction through stimulation of vascular α-receptors. Accordingly α-blocking agents might have favorable effects.

Doxazosin, a postsynaptic α-1 receptor blocker, was found to improve CBF response to dipyridamole in an uncontrolled study [54]; however, this effect was not confirmed in a placebo-controlled trial [55], and doxazosin also failed to improve exercise-induced angina symptoms and ischemic ST-segment changes in a small placebo-controlled cross-over study [56]. In agreement with the latter results, prazosin, which has similar effects of doxazosin, and clonidine, which reduces central α-adrenergic outflow, failed to variably improve exercise capacity and reduce chest pain episodes or ischemic episodes at Holter monitoring in other studies [57, 58].

The inconsistent results of peripheral α-blockers can, at least in part, reside in the development of tolerance, which occurs frequently with this kind of drugs.

8.2.2.4 Nicorandil

Nicorandil is an adenosine triphosphate (ATP) potassium channel opener, which also has nitrate-like effects. Nicorandil has been shown to have direct dilator effects on coronary resistance vessels, but might also modulate the response of these vessels to sympathetic stimulation [59]. In a noncontrolled study of 11

Table 8.3 Main results of studies assessing alternative forms of therapy for patients with cardiac syndrome X with refractory chest pain episodes

	Angina	QoL	EST	Holter	NTG use	Other
Imipramine						
Cannon [57]	↑					
Cox [80]	↑	↔				
Spinal cord stimulation						
Eliasson [82]	↑		↑			
Lanza [83]	↑	↑			↓	
Sgueglia [84]	↑	↑	↑		↓	
TENS						
Chauhan [86]						↑ CBF
Sanderson [87]						↓ CBF; ↑ coronary resistance
EECP						
Kronhaus [89]	↑					↑ Myocardial perfusion at scintigraphy
Psychological interventions						
Potts [32]	↑					Improvement in anxiety and depression scores and EST tolerance

patients with MVA, intravenous administration of nicorandil decreased the extension and severity of exercise-induced ST-segment depression at the ECG and of myocardial perfusion defects on thallium myocardial scintigraphy [60]. Furthermore, in a randomized placebo-controlled trial, oral nicorandil improved both symptoms and exercise ECG results over a 2-weeks treatment [61]. Accordingly, where available, nicorandil should be taken into account in the treatment of MVA patients, in particular as an alternative to nitrates.

8.2.2.5 Trimetazidine

Trimetazidine has been suggested to improve tolerance to myocardial ischaemia by switching cell metabolism from free fatty acid toward glucose oxidation.

Trimetazidine has shown discordant results in patients with MVA. In a double-blind placebo-controlled study [62], indeed, the drug improved exercise capacity and time to 1 mm ST segment depression. In another placebo-controlled trial, however, trimetazidine failed to show significant effects on symptoms and exercise tolerance [26].

8.2.2.6 Ranolazine

Ranolazine is an anti-ischemic drug which seems to act by inhibiting the inward late Na^+ current, thus reducing intracellular Ca^{2+} overload in cardiomyocytes during ischaemia and, therefore, improving myocardial relaxation and left ventricular diastolic function [63].

Ranolazine has been shown to be useful in patients with stable angina and obstructive CAD [64]. In a recent small randomized, controlled crossover trial of 20 women with MVA and evidence of ischemic perfusion defects on adenosine CMR imaging, ranolazine resulted in significantly higher Seattle Angina Questionnaire scores, compared to placebo; furthermore, ranolazine significantly improved the myocardial perfusion reserve index at CMR in the subgroup of patients with CFR < 3.0 [65].

In another study, in which 45 patients with MVA were randomized to ranolazine, ivabradine or placebo for 4 weeks, ranolazine improved both angina status and exercise stress test results more significantly than both ivabradine and placebo (Fig. 8.7) [66].

Although further data, on larger samples, are warranted, these studies suggest that ranolazine can be helpful in clinical management of MVA patients.

8.2.2.7 Ivabradine

Ivabradine is a pure anti-bradycardic agent, which selectively reduces the activity of the sinus node through the inhibition of the pacemaker I_f current, which involves both Na^+ and K^+ flows. While ivabradine has been shown to improve symptoms and signs of myocardial ischemia in patients with obstructive CAD [67, 68], its effects on MVA have only been assessed in one study, in which the drug showed favorable results, compared to placebo, thus suggesting that it can be helpful in the control of symptoms (Fig. 8.7) [66].

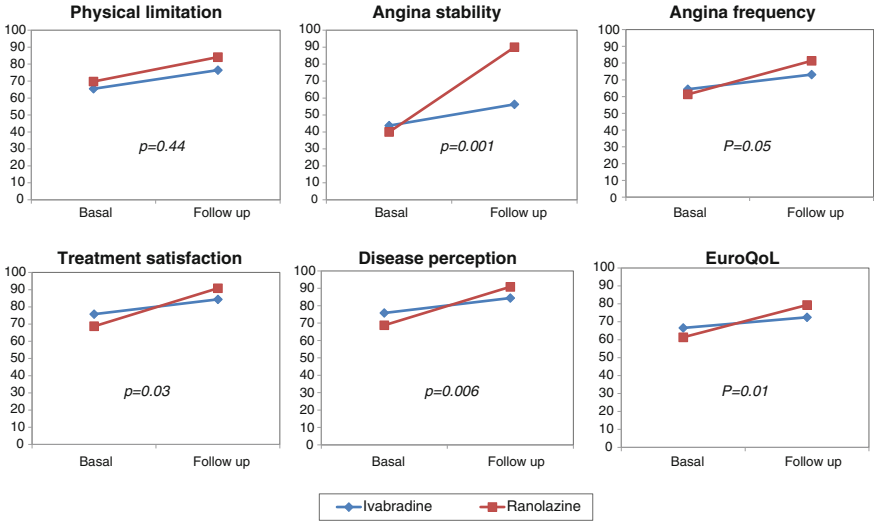

Fig. 8.7 Comparison of the effects of ranolazine and ivabradine on Seattle Angina Questionnaire items and on the EuroQoL score (quality of life) in stable MVA patients. Adapted from Villano et al. [66]

8.2.2.8 Statins

Statins might have beneficial effects on CMD through their powerful antioxidant and anti-inflammatory, as well as cholesterol-lowering effects, all of which can result, in particular, in an improvement of endothelial function.

In small randomized, placebo-controlled trials simvastatin and pravastatin were both found to significantly increase endothelial function and time to 1 mm ST-segment depression on exercise stress testing in MVA patients with mild hypercholesterolemia [69, 70]. Furthermore, in a randomized placebo-controlled trial of 45 MVA patients [52], a combination of ramipril (10 mg) and atorvastatin (40 mg) for 6 months significantly reduced oxidative stress and improved endothelial function, together with improvement of quality of life and exercise capacity.

Thus, data suggest that statins can be useful in MVA, in particular in patients with high cholesterol levels, evidence for inflammatory activity and increased oxidative stress.

8.2.2.9 Estrogens

Patients with stable MVA are predominantly women often in the peri- and postmenopausal state [71], suggesting that a deficiency of estrogens might constitute an important pathogenic factor. Estrogen deficiency is, in fact, associated with vasomotor abnormalities, including an impairment of endothelial function [71, 72]. Accordingly, estrogen administration improves endothelial function [73]. Of note, estrogen deficiency may also induce adrenergic activation [74], which can be reduced by estrogen therapy [75].

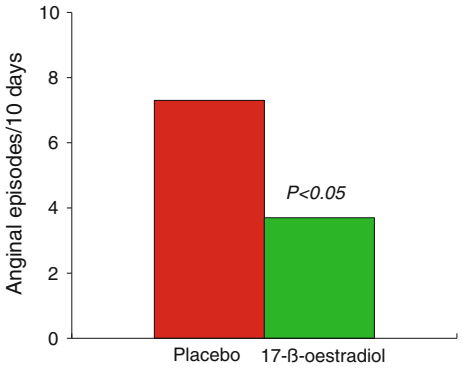

Fig. 8.8 Effect of 17-ß-estradiol on episodes of angina in patients with MVA. Adapted from Rosano et al. [76]

In a small placebo-controlled cross-over study [76], transdermal administration of 17-ß-estradiol (100 μg/24 h) reduced spontaneous episodes of chest pain in postmenopausal women with MVA, although no significant effects were observed, as compared to placebo, on exercise-induced myocardial ischemia and on ischemic episodes during ECG Holter monitoring (Fig. 8.8). Another randomized placebo-controlled trial, however, showed a significant improvement in time to angina and to ST segment depression during stress testing, together with exercise capacity, after 7 days of treatment with transdermal estrogen [77].

On the whole, these results suggest that estrogens may be helpful for management of women with MVA who show clinical evidence of estrogen deficiency. An issue, however, is that long-term therapy may portend some increased risk of serious adverse clinical events [78]. Furthermore, some data suggest that the initial benefits of estrogens may reduce or disappear over long-term treatment [79].

8.2.3 Drugs Modulating Pain Perception

As mentioned in Chap. 5, an enhanced painful perception of cardiac stimuli is often present in patients with stable MVA and can significantly contribute to a severe symptomatic state and impaired quality of life [20, 21]. Accordingly, the administration of drugs able to inhibit cardiac pain transmission and perception, might be helpful in these patients.

Several medications may include this mechanism in their antianginal effects. ß-blockers, through their negative inotropic effect, might reduce mechanical stimulation of cardiac pain fibers. Xanthine derivatives may inhibit stimulation of cardiac afferent pain fibers by adenosine.

The pure visceral pain inhibitor imipramine has been assessed in two placebo-controlled trial in patients with MVA. In a first trial, imipramine, during a period of 3 weeks [58] (Fig. 8.9), reduced spontaneous chest pain attacks by 52 ± 25 %, whereas no significant effects were observed with placebo or clonidine. This beneficial effect was confirmed in another trial [80], in which, however,

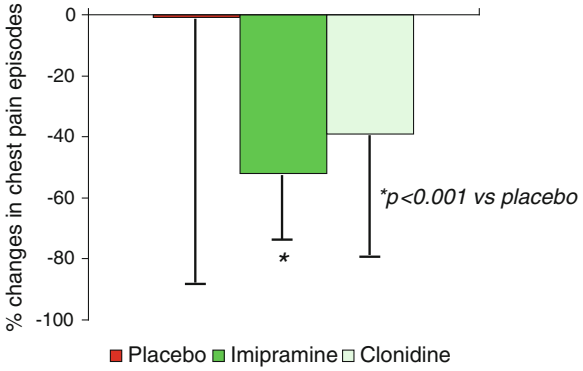

Fig. 8.9 Effect of imipramine and clonidine on episodes of chest pain in patients with angina and normal coronary arteries. Adapted from Cannon et al. [58]

imipramine failed to improve quality of life, likely due to a significant occurrence of side effects.

Thus, although imipramine seems useful to prevent episodes of chest pain the frequent occurrence of side effects can significantly limit its use.

8.2.4 Nonpharmacological Treatments

Refractoriness to optimal medical therapy of chest pain episodes in some patients with MVA led to the assessment of some alternative, non pharmacological approaches, which had already been found effective in patients with refractory angina related to obstructive CAD.

8.2.4.1 Spinal Cord Stimulation

Spinal cord stimulation consists in the electrical stimulation of the dorsal horns of the spinal cord at C7-T1 level by a multipolar electrode wire, introduced in the epidural space through an intervertebral puncture and connected to a programmable generator, usually implanted in an abdominal pocket. Spinal cord stimulation seems to exert its anti-angina effects through modulation of cardiac pain transmission and processing and improvement of myocardial ischaemia, likely mainly through modulatory actions on sympathetic tone [81].

A few studies showed beneficial effects of spinal cord stimulation on exercise tolerance and on ischemic and anginal threshold in MVA [82, 83]. Furthermore, in a study of 19 patients with refractory MVA, spinal cord stimulation showed a significant long-term reduction of angina episodes and nitrate consumption, as well as improvement of quality of life, compared to a comparable control group of untreated patients [84] (Fig. 8.10).

8.2.4.2 Transcutaneous Electrical Nerve Stimulation

Transcutaneous electrical nerve stimulation consists in the electrical stimulation of cutaneous chest nerve terminations through multiple electrodes. Its effects are

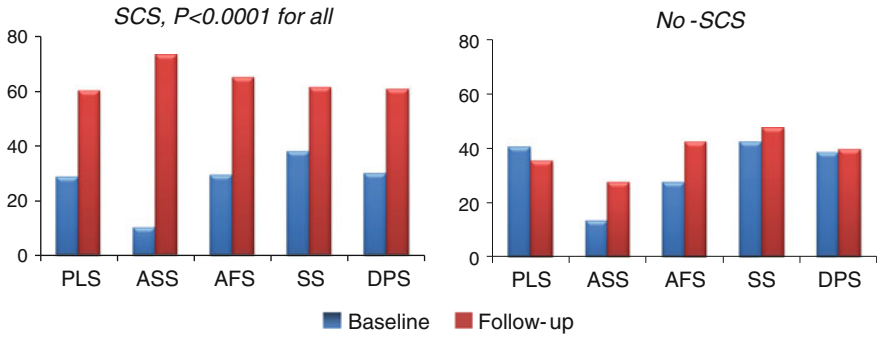

Fig. 8.10 Long-term effect of spinal cord stimulation (SCS) on Seattle Angina Questionnaire items in 19 patients with MVA and refractory angina episodes *(left)*. Long-term follow-up of nine patients with similar characteristics who refused SCS is shown as a comparison group *(right)*. Adapted from Sgueglia et al. [84]

believed to be similar to those of SCS [85]. Transcutaneous nerve stimulation [86] was found to increase resting CBF in MVA patients, suggesting coronary microvascular dilator effects. In another study [87], however, nerve stimulation paradoxically increased coronary resistance in such patients, likely due to a reduction of myocardial oxygen demand. Whether this therapy may improve symptoms in MVA patients, however, remains unknown.

8.2.4.3 Enhanced External Counterpulsation

Counterpulsation consists in the sequential beat-by-beat distal to proximal inflation (in diastole) and deflation (in systole) of three pneumatic cuffs applied to the patient's legs. The device increases diastolic coronary perfusion pressure, which seems also to improve coronary endothelial function [88].

Counterpulsation has recently been tested in a study including 30 patients with refractory MVA, showing improvement of angina status and of myocardial ischaemia on stress myocardial scintigraphy [89]. Further controlled studies are required, however, to define the role of counterpulsation in these patients with refractory MVA.

8.2.4.4 Cardiovascular Rehabilitation

Exercise rehabilitation programs have been shown to be helpful in reducing chest pain symptoms and improving pain tolerance in MVA patients [90], and should be therefore recommended in those with refractory symptoms.

8.2.4.5 Psychologic Interventions

Psychologic disorders, both minor and severe, have been described in patients with stable MVA and might, in fact, contribute to chronic chest pain and disability [91]. It is not clear, however, whether these disorders are actually increased in these patients and whether they constitute a causal factor for the syndrome or merely result from a severe clinical manifestation of the disease.

In these cases, however, psychological interventions can be helpful in the management of the disease. Various kinds of interventions have been assessed in small studies, including strategies for managing symptoms and for changing inappropriate beliefs and behavior, with improvement of psychologic morbidity and quality of life [92].

Accordingly, psychological treatment might be considered in patients with refractory MVA and evidence or suspect of psychologic disorders.

8.2.5 Approach to Treatment of MVA Patients

A schematic approach of treatment of patients with stable MVA is summarized in Fig. 8.11. The first line drug therapy is represented by ß-blockers or nondihydropiridine calcium antagonists, while a combination of a ß-blocker and a dihydropiridine (or also a nondihydropiridine) calcium antagonist should constitute the second step when single drugs fail to success. Ivabradine can be added when ß-blockers are scarcely tolerated, whereas ranolazine should now probably constitute the third pharmacological step.

Although long-acting nitrate can be added at any time, there is scarce evidence of their actual efficacy. Other drugs with potential anti-ischemic effects can further be selected, in addition or in substitution of previous drugs based on individual assessment of patients.

Analgesic drugs or nonpharmacological interventions may represent the last resource in patients with refractory MVA.

In the latter patients, rehabilitation exercise programs and/or psychological treatments, according to patient's characteristics, might be helpful. Importantly, reassurance and a sympathetic approach of cardiologists are also crucial measures to improve patient symptoms and compliance with the treatment, as well as to obtain a more positive attitude toward their symptoms.

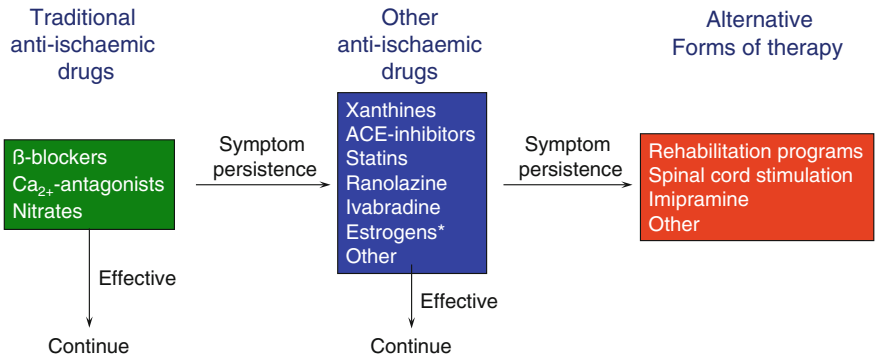

Fig. 8.11 Flow-chart for a rational approach to the management of patients with MVA. '*' In women. *ACE* angiotensin converting enzyme

8.3 Acute MVA/Takotsubo Cardiomyopathy

Because of the very few number of studies that have until now investigated the clinical characteristics and outcome of the syndrome of acute CMD, the optimal management of these patients remains unknown.

The recurrences of chest pain episode in the acute phase, as well as at follow-up, in these patients might be treated and prevented with the use of vasodilator drugs, mainly nitrates and calcium antagonists, but this recommendation is just based on the clinical judgment that these drugs might have effect of the coronary microvascular constriction responsible for angina symptoms in this condition.

In 10 patients with unstable rest angina and showing slow coronary flow at angiography, suggesting increased coronary microvascular constriction, the calcium T-channel blocker mibefradil improved CMD and angina symptoms in a study [93], thus supporting the hypothesis that calcium antagonists and other vasodilator drugs can be beneficial, and therefore the first-choice therapy, in these patients.

Interestingly, in a study, intracoronary nitroglycerin did not influence SCF [94], suggesting that nitrates may instead have limited effectiveness on coronary microvascular constriction in these patients, as already shown for stable MVA.

In patients with microvascular "variant angina" the rho-kinase inhibitor fasudil prevented acetylcholine-induced microvascular spasm, suggesting that enhanced cellular rho-kinase activity, which leads to enhanced cell calcium influx, may be involved as a pathogenetic mechanism [95]. Fasudil may therefore be used, if available, to treat this condition, with calcium antagonists being a possible alternative treatment.

Finally, no attempt to improve CMD in patients presenting with takotsubo syndrome has until now been tried, although adenosine, in a study, was found to reverse the dramatic impairment of MBF, which was paralleled by an improvement of left ventricular function 96.

Treatment of takotsubo syndrome is at present based on interventions able to sustain cardiac mechanical function and favor the spontaneous recovery of myocardial contractility and are mainly represented by inhibitors of the renin-angiotensin system and ß-blockers.

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Treatment of CMD in Myocardial Diseases

9

Treatment of cardiomyopathies is usually directed to improve ventricular function and systemic hemodynamics, as well as to prevent clinical complications. In rare cases only therapy is directed to specific causes of the myocardial disease.

Although CMD has been demonstrated and might play a clinical role in most myocardial diseases (see Chap. 5), studies specifically assessing the effect of therapy on CMD are largely lacking neither is known their effects on the outcome.

9.1 Hypertrophic Cardiomyopathy

While CMD in HCM has been found to be associated with an ominous prognosis, attempts to improve CMD in these patients have given controversial and, on the whole, disappointing results.

Favorable effects on CMD have been reported with alcohol septal ablation. In seven patients with HCM Jaber et al. [1] showed, indeed, that this form of treatment resulted in an immediate normalization of CFR, which seemed mainly related to an improvement of systolic CBF.

Soliman et al. assessed CBF response to adenosine by myocardial contrat echocardiography, before treatment and 6 months after alcohol septal ablation, in 14 patients with obstructive HCM [2] CFR significantly increased after the procedure and this was associated with an improvement of septal hyperemic endocardial-to-epicardial MBF ratio. Changes in LV end-diastolic pressure, LV mass index, and LV outflow tract peak systolic gradient correlated with improvement in CMD, thus suggesting that the latter depended on the relief of extravascular compression forces.

Finally, Timmer et al. [3] studied 15 patients who underwent alcohol septal ablation. MBF was assessed by PET, whereas LV mass and volumes were assessed by CMR. Both CFR and endocardial-to-epicardial MBF ratio significantly increased. The improvement of CMD correlated with the gradient reduction, thus

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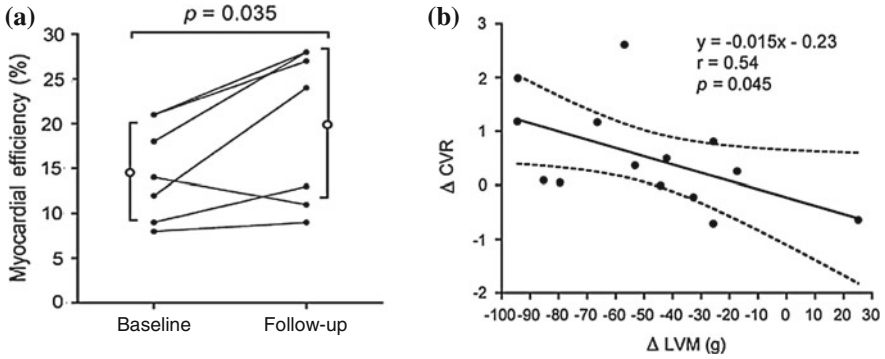

Fig. 9.1 *Panel a*. Myocardial efficiency at baseline and 6 months (follow-up) after alcohol septal ablation in patients with HCM. *Panel b*. Linear relationship between the changes (baseline vs. 6 months after alcool septal ablation) in coronary vasodilator reserve (CVR) and those in LV mass. Dotted lines represent the 95 % confidence interval of the regression line. Adapted from Timmer SA et al. [3]

suggesting a pronounced effect of LV loading conditions on coronary microvascular function (Fig. 9.1).

In contrast, verapamil administration, which has been reported to have beneficial hemodynamic and symptomatic effects in these patients, failed to show significant improvement of CMD. In one study [4] 15 patients with HCM underwent dipyridamole PET before and 4 weeks after treatment with high-dose verapamil. No significant effects were found on CFR, although an improvement of hyperemic septal endocardial-to-epicardial MBF ratio was observed in some patients. No significant effects by verapamil on both CFR and on hyperemic septal endocardial-to-epicardial MBF ratio were observed, however, in another study [5].

Finally, no effects on CMD were observed in HCM patients with disopyramide [6] or with ACE inhibitors [7].

In contrast, intravenous cibenzoline (1 mg/kg) [8], a class-Ia antiarrhythmic drug, was found to improve CBF response to adenosine triphosphate in 11 patients with obstructive and in 12 patients with nonobstructive HCM. Whether chronic oral therapy with this drug may safely improve CMD, however, remains unknown.

Overall, only alcohol septal ablation seems to be associated with a consistent improvement of CMD in HCM. The implications of these therapeutic results on clinical outcome, however, remain to be established.

9.2 Dilated Cardiomyopathy

Given its favorable effects on clinical outcome, two studies assessed whether carvedilol improves CMD in patients with idiopathic dilated cardiomyopathy.

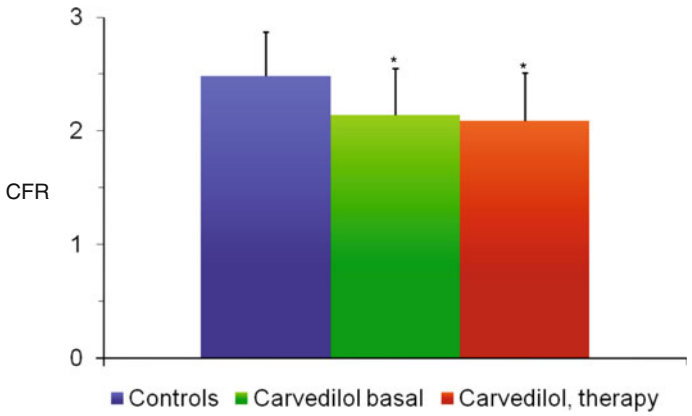

Fig. 9.2 Reduced CFR in patients with idiopathic dilated cardiomyopathy (carvedilol basal), compared to controls. Nonsignificant effect on CFR was observed with carvedilol treatment, despite improvement in clinical conditions (carvedilol therapy). *$p < 0.05$ vs. controls. Data from Calişkan M et al. [9]

Calişkan et al. [9] performed dipyridamole TTDE in 24 patients at baseline and after 19 weeks of therapy. Carvedilol reduced LV end-systolic volume and increased LV ejection fraction. No improvement in CFR, however, was observed.

In another study [10], instead, carvedilol was found to increase CFR in patients with idiopathic dilated cardiomyopathy after 6 months of therapy (Fig. 9.2). LV diastolic diameter, LVEF and the diastolic E/A ratio improved after treatment, suggesting a contributory role to improvement of CMD.

Nebivolol also was shown to significantly improve CMD in patients with idiopathic dilated cardiomyopathy [11]. CFR was measured in 21 patients at baseline and 1 month after treatment and was found to increase significantly. No changes in LV end-diastolic diameter and LV stroke volume were observed, although LV end-systolic diameter decreased significantly with treatment.

No significant effects of treatment with verapamil and/or enalapril on CFR, as assessed by dipyridamole PET, were observed in one study [12], despite combined treatment and enalapril alone prevented further deterioration of LV function.

Favorable effects on CMD have instead been reported with treatment with allopurinol [13]. In one study 24 patients with idiopathic dilated cardiomyopathy and high serum uric acid levels were given allopurinol for 3 months. CFR, assessed by TTDE, exhibited a significant improvement; it is believed that the beneficial effect of allopurinol on CMD might be mediated by its anti-oxidant action.

In summary, in patients with dilated cardiomyopathy, beta-blockade seems to have beneficial effects on CMD, likely as a result of improved hemodynamics. Whether allopurinol is a valid form of treatment to this scope in these patients deserves further investigation.

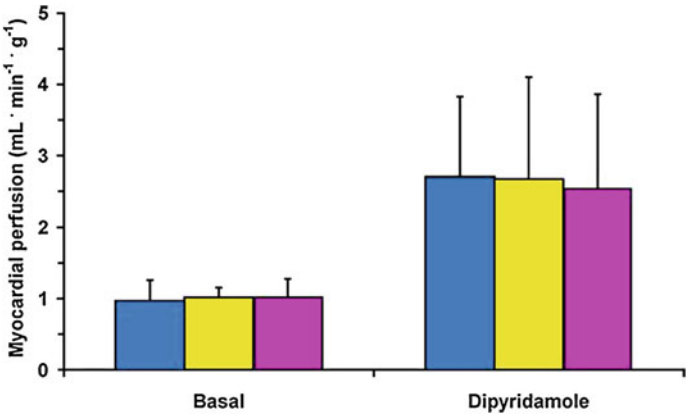

Fig. 9.3 Changes in baseline (basal) and hyperemic (dipyridamole) myocardial perfusion measured by PET before and after enzyme replacement therapy in patients with Anderson Fabry's disease. Blue bars = values before treatment; yellow bars = values after 6 months of treatment; pink bars = values after 12 months of treatment. Adapted from Kalliokoski RJ et al. [15]

9.3 Aortic Stenosis

As discussed in Chap. 6, the significant reduction of diastolic time of myocardial perfusion plays a significant role in causing the observed reduction of CFR and the appearance of angina in patients with aortic stenosis. Thus, drugs that increase diastolic time, like beta-blockers, might help in delaying the ominous onset of myocardial ischemia and angina in these patients. As an alternative, in case of contraindication or intolerance to beta-blockers, ivabradine, known to selectively reduce heart rate but not blood pressure, might be of help in these patients. These considerations, however, are purely speculative, as clinical studies about the effects of these drugs on coronary microvascular perfusion and on angina and clinical outcome are lacking and should therefore be investigated in prospective randomized trials.

9.4 Myocarditis

While CMD can be present and also play a role in the clinical presentation of acute myocarditis (see Chap. 6), no study has hitherto assessed the effects of any form of intervention on CMD in these patients.

Thus consequences of treatment and their clinical implications remain undefined.

9.5 Infiltrative Heart Diseases

a. *Anderson-Fabry's Disease*

Enzyme replacement therapy with alpha-galactosidase A has significantly reduced LV mass and improved cardiac function and clinical outcome of patients with Anderson-Fabry's disease.

A few small studies have investigated whether the beneficial effects of enzyme replacement therapy with alpha-galactosidase A on symptoms are associated with improvement of CMD. Results, however, have been disappointing. In one study, Elliott et al. [14] assessed MBF by PET at rest and during hyperemia with adenosine in five male patients at baseline and 10 months after enzyme replacement therapy. They found no effect of enzyme replacement thrapy on resting or hyperemic MBF, and therefore on CFR.

Similar results were reported by Kalliokoski et al. [15]. They studied 10 patients with Anderson-Fabry's disease. Myocardial perfusion was measured at rest and during dipyridamole-induced hyperemia by PET, both at baseline and 6 and 12 months after enzyme replacement therapy (Fig. 9.3). Despite improvement of chest pain, myocardial perfusion or CFR did not show any significant improvement. It remains to establish whether a longer period of replacement therapy may lead to improvement of CMD in Anderson-Fabry's disease.

b. *Amylodosis*

Treatment of amyloidosis depends on the type of the disease. Thus, treatment of primary amyloidosis includes oral chemotherapy (melphalan and prednisone) or high-dose chemotherapy with autologous stem cell transplantation. The benefit of oral chemotherapy is limited, however, and the greatest survival benefits are limited to patients without cardiac involvement [16, 17]. Treatment of secondary amyloidosis, on the other hand, is directed to the underlying disease, whereas liver transplantation, which removes the source of mutant transthyretin, is, at present, the only effective treatment of hereditary amyloidosis [18].

To the best of our knowledge, however, no study has yet assessed the effects of specific or nonspecific forms of therapy on CMD in amyloidosis.

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Treatment of CMD in Obstructive CAD 10

As discussed in Chap. 7, although CMD is present in a large proportion of patients with obstructive CAD, it is difficult to investigate its role in individual patients, as its influence on myocardial perfusion is largely confounded by the concomitant presence of obstructive atherosclerosis in large epicardial arteries. For the same reason, the effect of treatment on CMD in patients with obstructive CAD has not been assessed, and therefore remains unknown.

There are two important clinical aspects, however, that concern patients with obstructive CAD, which specifically involve the microcirculation and have been the object of a large number of studies aimed at assessing the effects of various forms of treatment: (1) angiogenic treatment in patients with refractory angina, and (2) treatment of MVO in the setting of STEMI.

10.1 Angiogenic Treatment in Patients with Refractory Angina

Formation of collateral coronary vessels is a complex process regulated by a myriad of signals (see Chap. 1). The growth of coronary collaterals might allow adequate MBF and oxygen supply to severely hypoperfused myocardial regions. Accordingly, therapeutic interventions able to promote collateral growth may have an impact on outcome as well as on symptoms in patients with refractory angina, i.e., those with frequent angina attacks in spite of optimal medical therapy, who are also judged not to be candidates for revascularization procedures.

Several forms of therapy have been proposed to promote angiogenesis and collateral circulation in ischemic areas in this clinical setting (Fig. 10.1) [1], but their exact role still waits to be definitely clarified.

Gene therapy initially appeared as the most applicable and potentially valid form of therapy to stimulate and enhance microcirculation and collateral growth in refractory angina patients. Intracoronary delivery of virus vectors transporting modified genes encoding for angiogenic factors, as vascular endothelial growth factor or basic fibroblast growth factor, has been tested in placebo-controlled trials.

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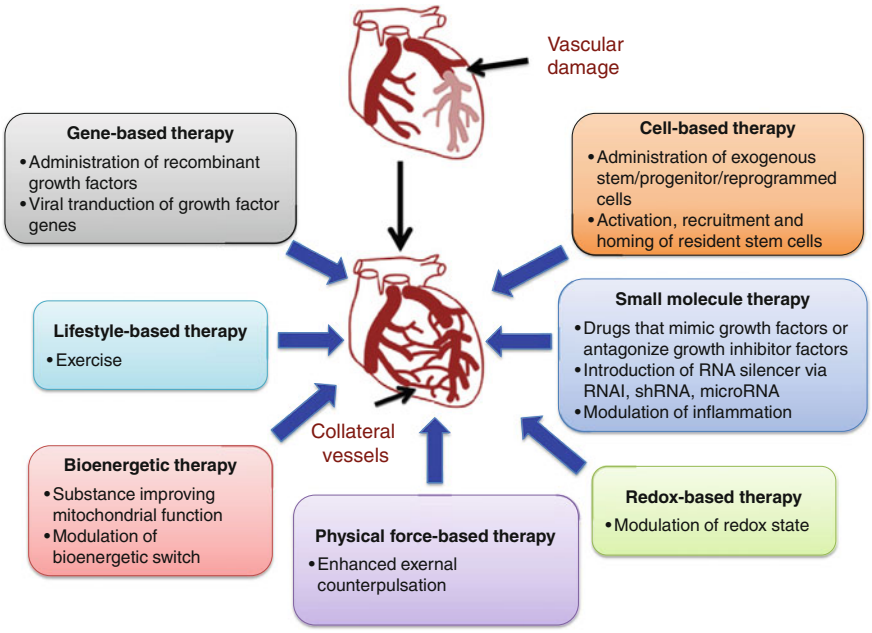

Fig. 10.1 Therapeutic interventions potentially able to promote collateral vessel growth. Adapted from Chillian et al. [1]

In contrast with findings observed in animal models [1], and after some initial promising data in uncontrolled studies, the results in controlled randomized studies have on the whole been disappointing, as they failed to show a detectable increase of collateral growth in patients, together with no or negligible benefit on symptoms and myocardial ischemia, as compared with control groups (Fig. 10.2) [2–4]. It has been suggested that an increase of oxidative stress might deny the favorable effects of gene therapy. Accordingly, therapy associated with drugs able to restore redox balance is under investigation to establish whether a combined approach has the potential to improve myocardial perfusion. Similar disappointing results have been shown in controlled clinical trials for the direct intracoronary or intramyocardial injection of recombinant angiogenic factors, as vascular endothelial growth factor or basic fibroblast growth factor [5].

Attempts to promote collateral circulation in patients with refractory angina have been based also on the intramyocardial administration of *progenitor vascular cells* (Fig. 10.3) [6–9]. In this case, again, the early clinical results do not allow to establish firm conclusions about the efficacy of this form of therapy, which needs to be addressed in larger studies. Furthermore, in one of these trials some concern derived from the observation of troponin rise during cell mobilization and collection [9].

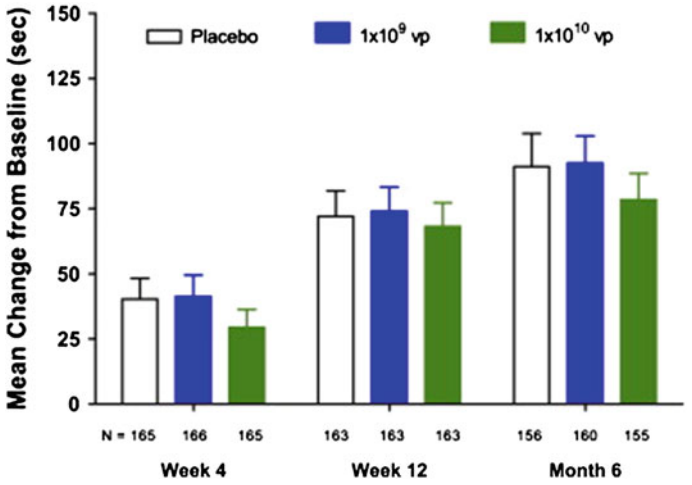

Fig. 10.2 Change in duration of exercise stress test at 4, 12 weeks, and 6 months in patients enrolled in the AGENT-3 and AGENT-4 trials. Data are mean and standard error. *vp* = viral particles. Adapted from Henry et al. [3]

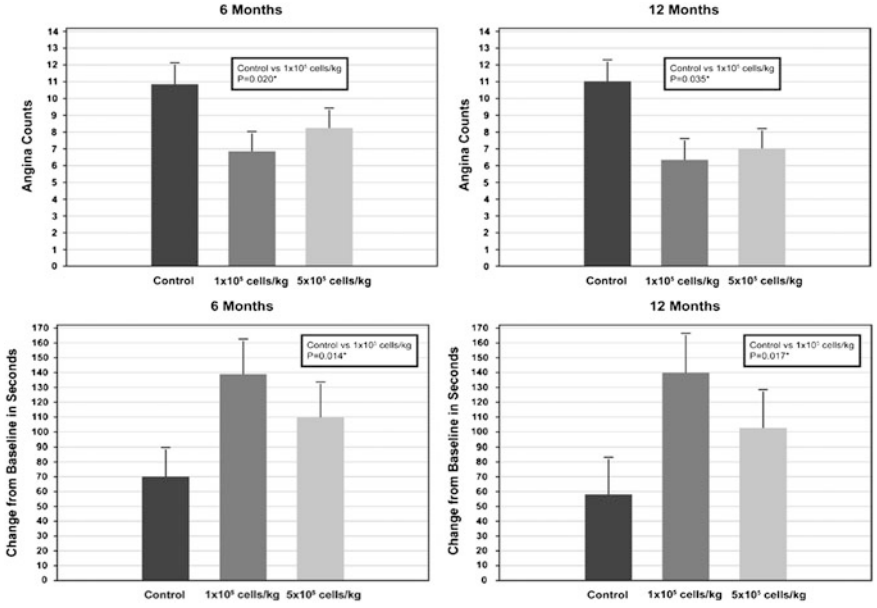

Fig. 10.3 *Top panel*: Number of anginal episodes per week at 6 and 12 months in patients randomized to intramyocardial injection of placebo or two increasing doses of mobilized autologous CD 34+ cells; both active treatments resulted in a reduction of angina frequency which, however, was statistically significant for the lower dose only. *Bottom panel*: Change in exercise time at 6 and 12 months after randomization; results are consistent with those for angina frequency. Adapted from Losordo et al. [9]

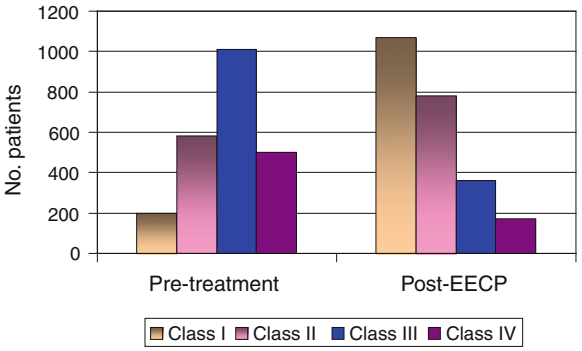

Fig. 10.4 Effect of enhanced external counterpulsation (EECP) on Canadian Cardiovascular Society class in patients with stable angina. Adapted from Wu et al. [16]

Exercise is a possible physiologic stimulator of collateral growth, as repetitive increase of myocardial oxygen requirements might activate stimuli for collateral growth; the few studies carried out to this scope, however, have produced controversial results [10–14].

Bioenergetics therapy, e.g., the administration of substances able to improve defective mitochondrial function, such as mitochondrial directed free radical scavengers, have been able to improve collateral circulation in animal models with metabolic syndrome [1], but data in humans are lacking.

Enhanced external counterpulsation has been suggested to stimulate angiogenesis, although the mechanism remains speculative [15]. Clinical observational studies have consistently reported beneficial effects of this form of treatment in patients with refractory angina (Fig. 10.4) [16] and some benefits have been shown in a small randomized sham controlled study [17]. The role of collateral growth stimulation in mediating these beneficial effects, however, remains to be clarified.

Finally, *small molecule therapies* to target key pathways for stimulation and inhibition are also on the horizon, but are still under investigation [18].

10.2 Treatment of MVO in STEMI

MVO denies the benefits of successful epicardial coronary revascularization in about one-third of STEMI patients, as it is associated with increased morbidity and mortality (see Chap. 6). Several forms of interventions have been proposed in the attempt to prevent or treat MVO, and therefore improve clinical outcome of STEMI patients.

10.2.1 Prevention

Among cardiovascular risk factors, hypercholesterolemia and hyperglycemia, have been shown to be significantly associated with MVO during STEMI [19, 20]; thus,

optimal control of these risk factors might provide the advantage, in addition to the other well-known beneficial effects, of preventing MVO in case of STEMI.

Avoidance of substances which contrast preconditioning, like sulfonylureas [21] and high doses of alcohol [22] can be another way to prevent MVO during STEMI. Of note in several studies, sulfonylureas have been found to be associated with a higher rate of death and major cardiovascular events as compared to metformin [23]; although several interpretations can be given for this finding, inhibition of ischemic conditioning by sulfonylureas likely significantly contributes to their detrimental effects.

10.2.2 Mechanical Therapy

Distal embolization of thrombus and debris material during primary PCI has been suggested to play a major role in MVO. This has suggested that the use of devices able to avoid distal embolization might reduce MVO and AMI extension, and improve clinical outcome.

Minimization of balloon inflations with direct stent deployment and no predilatation was first suggested to limit coronary embolization and MVO [24], but results have been inconclusive.

Distal protection devices prevent embolization either by the occlusion of the coronary artery distally to thrombosis with a balloon catheter and the subsequent aspiration of the thrombotic material, or by trapping the embolizing material during PCI in a distal umbrella-like device. A proximal balloon occlusion has also been used with aspiration of debris before balloon deflation (Fig. 10.5) [25].

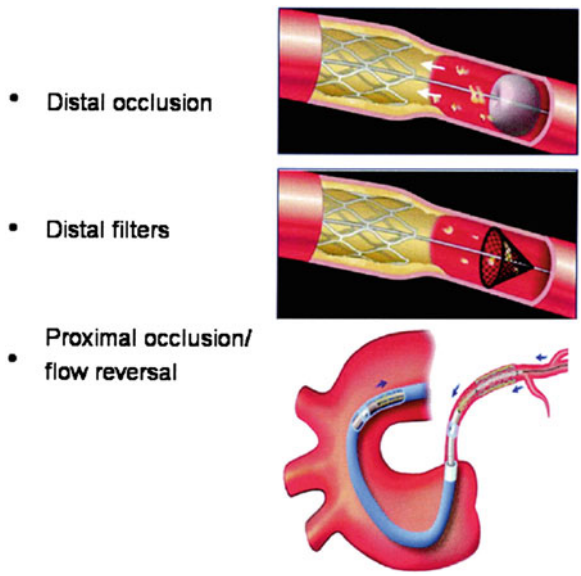

Fig. 10.5 Mechanism of action of devices utilized to prevent distal embolization in STEMI. Adapted from Mauri et al. [25]

Embolic protection devices were initially found effective in the setting of STEMI, showing, in small studies, earlier ST-segment resolution, better TIMI flow and MBG, lower peak enzyme, and improved LV function [26]. Yet, the initial data were not confirmed in larger studies, which failed to show benefit on infarct size and clinical outcome [27]. Meta-analyses [28, 29] have confirmed these disappointing clinical results, in spite of an overall significant improvement of TIMI flow and myocardial blush grade [30].

The lack of success of these devices in acute STEMI may be related to several factors, including prolongation of time to reperfusion, lack of microvascular protection from vasoconstrictor substances, inadequate protection of side branches, embolisation of thrombus material despite the device while crossing the culprit lesion [31].

Direct thrombus aspiration with a dedicated catheter has shown more favorable results. Indeed, two small randomized studies [32, 33] found a beneficial effect of thrombus aspiration on surrogate end-points of myocardial reperfusion. Then, in the TAPAS trial, which randomized 1,071 STEMI patients undergoing primary PCI to thrombus aspiration or control, thrombus aspiration was associated with a significant reduction of major cardiac events (death/re-infarction) at 12 months [34, 35]. This study, however, was characterized by an unusually high rate of deaths in the control group (Fig. 10.6); thus, questioning the applicability of the results. Furthermore, in a recent study, thrombus aspiration failed to reduce infarct size [36].

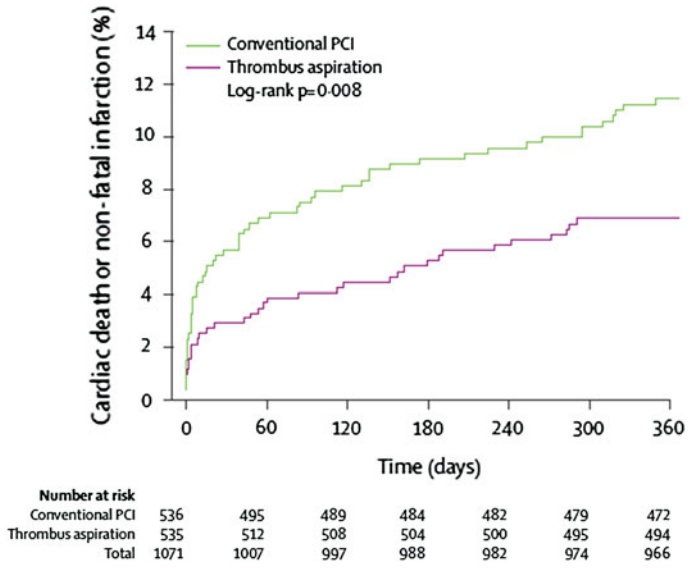

Fig. 10.6 Death rate in the TAPAS trial in patients with STEMI randomized to conventional primary PCI or PCI preceded by manual thrombus aspiration. Death rate was significantly lower in patients randomized to thrombus aspiration. Adapted from Vlaar et al. [34]

Thus, thrombus aspiration seems promising and it is widely applied and recommended by international guidelines [37], but more studies are warranted to definitely prove its real efficacy.

10.2.3 Pharmacological Therapy

10.2.3.1 Antiplatelet Drugs

The use of antiplatelet drugs is based on the central role that platelet activation plays in MVO. The administration of glycoprotein-IIb/IIIa inhibitors, and in particular abciximab, given prior to recanalization, has been shown to improve myocardial perfusion and reduce infarct size in both animal [38] and human studies [39–41], probably through an improvement of MVO. A meta-analysis confirmed that abciximab in patients with STEMI undergoing primary PCI was associated with a lower rate of death and reinfarction up to 3 years follow-up [42], which is consistent with the beneficial effect on clinical outcome shown by abciximab in patients with non-ST segment elevation myocardial infarction [43, 44].

Initial studies suggested that intracoronary administration of abciximab might be more beneficial than intravenous administration [45]. More recent controlled randomized trials, however, have produced conflicting results [46, 47]. Overall, the evidence suggests that platelet glycoprotein-IIb/IIIa antagonists can be helpful in acute STEMI treated by PCI when the intervention is performed on high-risk coronary lesions [48]. Accordingly, current guidelines recommend the use of IIb/IIIa antagonists in patients undergoing primary PCI at high risk due to with a large thrombotic burden [37].

10.2.3.2 Adenosine

Adenosine has been proposed for the prevention of MVO for its multiple potential pharmacological effects, including myocardial conditioning, arteriolar dilatation, inhibition of neutrophil adhesion and migration, platelet activation, and oxygen free radical generation [49].

The AMISTAD trial showed that intravenous adenosine administration, started prior to thrombolysis, was associated with a reduction of infarct size [50], although the benefit was limited to anterior STEMI. Thus, the AMISTAD-II study randomized 2,118 patients with anterior STEMI to intravenous adenosine infusion (50 or 70 μg/kg/min) or placebo prior to thrombolysis or primary PCI [51]. The trial failed to show a benefit of adenosine on clinical outcome, despite a reduction of infarct size with the higher dose (Fig. 10.7). Post-hoc analysis of the AMISTAD-II trial, however, showed that early (<3 h) adenosine administration was associated with a reduction of mortality and major cardiac events at follow-up. Other studies confirmed that adenosine might be beneficial on MVO only when started early (within 4 h) after STEMI onset [52].

Further studies suggested that high doses of intracoronary (rather than intravenous) adenosine can be associated with a lower occurrence of MVO and a more

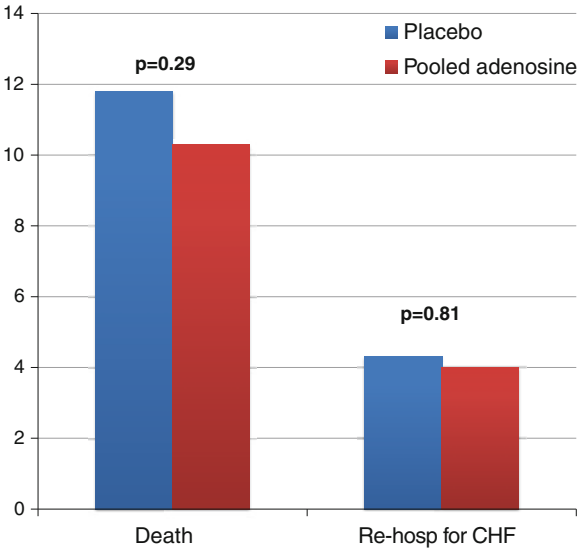

Fig. 10.7 Clinical end-points in STEMI patients treated with adenosine or placebo in the AMISTAD-II trial. Adapted from Ross et al. [51]

favorable clinical outcome in STEMI [49]. Accordingly, a recent medium-sized controlled randomized trial found that a high dose of intracoronary adenosine, but not nitroprusside, given immediately after thrombus aspiration in patients treated with abciximab, resulted in a lower rate of MVO as compared to placebo; the trial was not powered enough, however, to assess the effects on clinical end-points [53].

In summary, adenosine has shown promising results, in particular with early high-dose intracoronary administration, in the prevention and treatment of MVO; however, further studies are needed to confirm these promising data and to assess whether these favorable effects translate into improvement of clinical outcome.

10.2.3.3 Sodium Nitroprusside

Several studies have assessed the effects of sodium nitroprusside on MVO. This drug is a direct donor of NO, with powerful arteriolar dilatator activity. Excess NO, however, might be detrimental, because of enhanced generation of reactive oxygen species.

Compared to adenosine, in small observational studies intracoronary sodium nitroprusside was associated with a rapid improvement of TIMI flow [54–57].

In another observational study, sodium nitroprusside failed to reduce in-hospital death [57]. Furthermore, in a small randomized, double blind placebo-controlled study [58] intracoronary nitroprusside did not improve TIMI frame count or ST-segment resolution, although its use was associated with a reduction of the composite secondary end-point of target lesion revascularization, re-AMI or death. Finally, in a recent study, adenosine but not nitropruside improved MVO [53].

Thus, intracoronary sodium nitroprusside has the potential to improve myocardial perfusion in patients exhibiting MVO, but the results of clinical studies are rather conflicting.

10.2.3.4 Calcium Channel Blockers

Calcium channel blockers may improve CBF by direct relaxation of SMCs, and by endothelium-mediated vasodilatation; they also may reduce myocardial oxygen consumption by negative inotropic and chronotropic effects, and may reduce oxygen free radical damage during reperfusion [59].

Calcium channel blockers have extensively been investigated in both the prevention and treatment of MVO. In a rat heart model of ischemia-reperfusion, pretreatment with diltiazem, verapamil, or nifedipine improved both endothelium-dependent and endothelium-independent coronary microvascular functions [60]. Furthermore, gallopamil [61] was found to reduce MVO in rabbit hearts.

In STEMI, verapamil was shown to improve TIMI flow when administered before but not after PCI [62]. In other studies, however, intracoronary verapamil improved TIMI flow in patients with established MVO [63, 64].

Thus, nonrandomized/observational studies suggest benefit from intracoronary administration of verapamil also in patients with established MVO. These studies, however, require validation in larger, controlled randomized trials.

10.2.3.5 Nicorandil

Nicorandil is an ATP-sensitive potassium channel opener and NO donor. Studies in animals have demonstrated that nicorandil favors myocardial recovery, reduces infarct size, and possibly decreases neutrophil activation [65].

In several small trials, nicorandil demonstrated benefits in the setting of STEMI [66] with improvement of CBF, regional wall motion and infarct size. In one study [67], nicorandil decreased urinary excretion of the marker of oxidative stress 8-epi-prostaglandin-$F_{2\alpha}$, with a nonsignificant trend toward a reduction of MVO.

It is possible, therefore, that nicorandil might reduce MVO by reduction of oxygen free radical generation. Again, larger clinical trials are required to validate these promising initial clinical findings.

10.2.3.6 Intracoronary Thrombolysis

Intravenous thrombolysis significantly improved survival in STEMI patients, particularly when administered within 3 h from symptom onset [68, 69]. Intracoronary thrombolysis was hypothesized to prevent MVO in STEMI patients treated by PCI, due to the presumed pathogenetic role of microembolization. However, trials of intracoronary thrombolytics in this setting suggested little or no benefit [70]. A recent randomized study showed, in fact, that intracoronary streptokinase improved CFR [71], but these acute effects were not associated with improved LV function at 6 months, thus questioning the actual role of thrombolysis in this setting.

10.2.4 Ischemic Conditioning

Ischemic preconditioning consists in an increased resistance of myocardial cells to ischemic injury conferred by the exposure to previous short ischemic episodes [72].

More recently, it has been demonstrated that the induction of short episodes of myocardial ischemia during myocardial reperfusion achieved by PCI in the infarct-related occluded artery also portends protection on myocardium, likely reducing reperfusion injury, a phenomenon defined "ischemic post-conditioning" [73, 74]. Similar complex signal pathways seem involved in these two phenomena, including cell-surface receptors, reperfusion injury salvage kinases, free radicals, ATP-dependent potassium channels, and mitochondrial permeability-transition pores [75, 76]. Also nonmyocardial mechanisms might be involved in vivo, including vascular/collateral modulation and platelet reactivity [77].

The role of preconditioning has been confirmed in several clinical studies, in particular during serial balloon inflations during PCI, with reduction of clinical, ECG, hemodynamic, and metabolic evidence of myocardial ischemia [78]. Ischemic preconditioning is likely involved in the reduction of AMI size and improved in-hospital outcome in patients who had preinfarction angina [79].

In the setting of STEMI with PCI, postconditioning by repeated brief episodes of balloon inflation after stenting in the infarct-related artery limited enzyme release with improvement in myocardial blush grade [80], as well as infarct size as assessed by PET and LVEF at echocardiography [81].

The "preconditioning pathway" can be activated also by remote preconditioning. In a recent pilot study [82], remote ischemic preconditioning in patients with evolving STEMI (intermittent arm ischemia through four cycles of 5-min inflations and 5-min deflations of a blood-pressure cuff) significantly improved myocardial salvage as measured by myocardial perfusion imaging (Fig. 10.8). However, these findings need to be confirmed in larger clinical studies.

As noted above, preconditioning and postconditioning as well as remote conditioning appear to involve signal-transduction pathways that act on mitochondrial permeability-transition pores [83]. The immunosuppressant cyclosporine also inhibits mitochondrial permeability-transition pore opening. In a small pilot study [84], cyclosporine has recently been shown to reduce infarct size (as measured by CK release and CMR imaging) when given intravenously immediately before primary PCI, with a trend to an improvement of LV end-systolic volume at 6 months [85].

Atrial natriuretic peptide also appears to activate preconditioning; in the J-WIND study patients with STEMI undergoing reperfusion therapy randomized to intravenous administration of atrial natriuretic peptide exhibited lower infarct size, fewer reperfusion injuries, and better outcomes than controls [86].

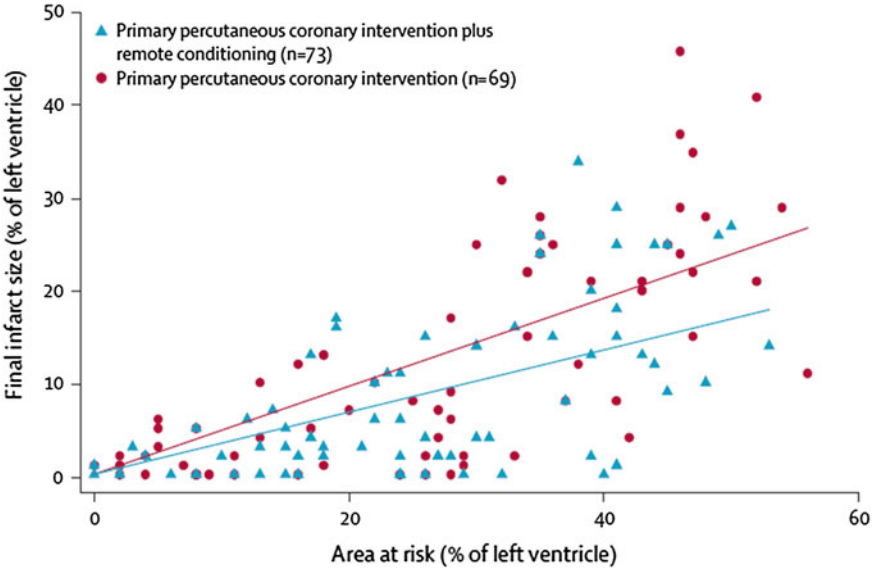

Fig. 10.8 Relation between final infarct size and area at risk for patients receiving primary PCI with or without remote conditioning (per-protocol analysis). The improvement given by remote preconditioning was proportional to the extent of the area at risk. Adapted from Botker et al. [82]

10.2.5 New Potential Approaches

Other potential approaches have been suggested for the prevention of MVO, including: (1) endothelin-1 receptor antagonists, which induce vasodilatation and also reduce microvascular permeability and the consequent myocardial edema [87]; (2) prostacyclin analogs, which are potent vasodilators and inhibitors of platelet aggregation [88]; and (3) thromboxane A_2 receptor antagonists which may mitigate the potent vasoconstrictor and platelet aggregatory properties of thromboxane-A2 [89].

All these drugs have not yet been tested in man, however, and therefore need to be assessed in adequately designed controlled studies.

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Prevention of Iatrogenic CMD

11

11.1 Prevention of PCI-Related CMD

Rise of cardiac necrosis enzymes following PCI is associated with increased mortality and major cardiac events at follow-up (see Chap. 7). Accordingly, it would be highly desirable to prevent periprocedural myocardial infarction. Several forms of therapy have been proposed to this scope.

11.1.1 Mechanical Prevention

11.1.1.1 Direct Stenting

Direct stenting of the coronary lesion, without pre-dilatation, was found to reduce post-procedural increase of TnI levels in a randomized controlled trial [1]. Accordingly, a recent study [2] showed that direct stenting, in stable angina patients, reduced CMD after PCI, compared with conventional PCI.

The clinical implications of these findings, however, need further investigation. A meta-analysis indeed failed to find a benefit with direct stenting compared to conventional stenting on clinical end points [3].

11.1.1.2 Distal and Proximal Protection Filters

Distal protection with filters has been demonstrated to be of benefit during PCI for obstructed saphenous vein grafts. In the SAFER trial [4], an embolic protection device in saphenous vein graft interventions significantly reduced the occurrence of periprocedural myocardial infarction with a 42 % relative risk reduction of major cardiac events at 30 days of follow-up (Fig. 11.1).

Proximal protection devices are an alternative to distal filters when the latter cannot be used. In the PROXIMAL trial these protection devices were non-inferior to distal devices in reducing the occurrence of peri-procedural AMI during PCI for obstructed saphenous vein grafts, also showing similar occurrence of major cardiac

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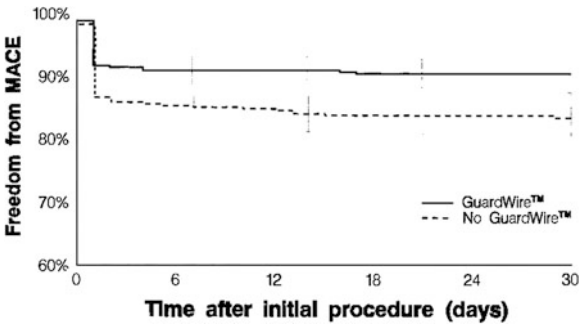

Fig. 11.1 The Kaplan-Meier curves show the main results of a randomized trial testing the use of a distal embolic protection device during PCI of saphenous vein aorto-coronary bypass grafts A 6.9 % absolute (42 % relative) reduction in the 30 days primary end point (a composite of death, myocardial infarction, emergency bypass, or target lesion revascularization) ($p = 0.004$) was observed in patients randomized to the distal embolic protection device GuardWire. Adapted from Baim et al. [4]

events [5]. In contrast, there is no evidence, at present, that the use of these device is efficacious during PCI of native coronary arteries [6].

11.1.2 Ischaemic Preconditioning

In one study ischemic preconditioning, obtained by two 90 s coronary balloon inflations, separated by 5 min reperfusion, prior to PCI was associated with a significant reduction of CK elevation [7] (Fig. 11.2). A similar beneficial effect was observed with remote ischemic preconditioning [8].

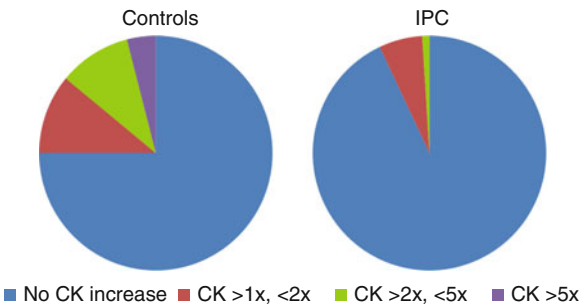

Fig. 11.2 Frequency of any CK elevation in patients undergoing PCI and randomized to ischemic preconditiong (IPC) or conventional PCI. CK elevation was seen in 7.1 % of patients undergoing PCI plus IPC and in 25 % of patients undergoing PCI without IPC (controls) ($p < 0.005$). Adapted from Laskey [7]

11.1.3 Pharmacological Prevention

11.1.3.1 Antiplatelet Drugs

As platelet activation is believed to play a relevant role in the pathophysiology of PCI-related myocardial infarction, antiplatelet and antithrombotic drugs have been proposed to prevent this complication or minimize myocardial damage.

Several studies have suggested that aspirin prevents peri-procedural Q-wave acute myocardial infarction [9, 10]. The dose suggested is 75−325 mg before PCI in patients who are already taking low-dose aspirin and 300−325 mg in patients not taking the drug [11].

Thienopyridines (clopidogrel, ticlopidine, prasugrel) are adenosine antagonists for P_{2y12} receptor [12]. In the ARMYDA-2 trial, a loading oral dose of clopidogrel, 600 mg, was associated with an approximately 50 % reduction of peri-procedural myocardial infarction as compared to a loading dose of 300 mg [13].

GPIIb/IIIa inhibitors also have been shown to reduce peri-procedural infarction in several clinical trials, a finding confirmed in a meta-analysis [14]. However, in the era of double platelet antiaggregation, GPIIb/IIIa inhibitors are recommended only in high risk patients with intracoronary thrombus [15].

11.1.3.2 Adenosine

Several pharmacological effects of adenosine might fight the occurrence of peri-procedural infarction during elective PCI (see also Chap. 10). Adenosine has been shown to decrease peri-procedural cardiac enzyme release in a small randomized study [16]. A more recent randomized placebo-controlled trial in non urgent PCI also showed reduction in peri-procedural AMI in patients randomized to receive intracoronary adenosine (50 mg) compared with placebo [17]. Larger studies are required, however, to establish the real clinical benefits of this approach.

11.1.3.3 Statins

Administration of atorvastatin was shown to reduce peri-procedural AMI during elective PCI compared to controls in the ARMYDA and in the NAPLES II trials [18, 19]. Also in patients with NSTE-ACS undergoing urgent PCI, both atorvastatin and rosuvastatin were shown to reduce peri-procedural AMI compared with controls [20, 21].

A meta-analysis [22] showed that statin administration prior to PCI almost halves the rate of peri-procedural myocardial infarction (Fig. 11.3).

Of note, an atorvastatin load (120 mg) before PCI was shown to reduce post-procedural CK-MB and TnI elevation in patients with with NSTE-ACS who were on previous statin therapy in the ARMYDA-RECAPTURE trial [23], while this effect was not observed in patients with stable angina.

It is well accepted that the benefits deriving from statins during long-term follow-up are related to their lipid-lowering effect, whereas the potential clinical benefits related to their pleiotropic effects, including improvement of endothelial function and reduction of oxidative stress and of platelet adhesion have long been

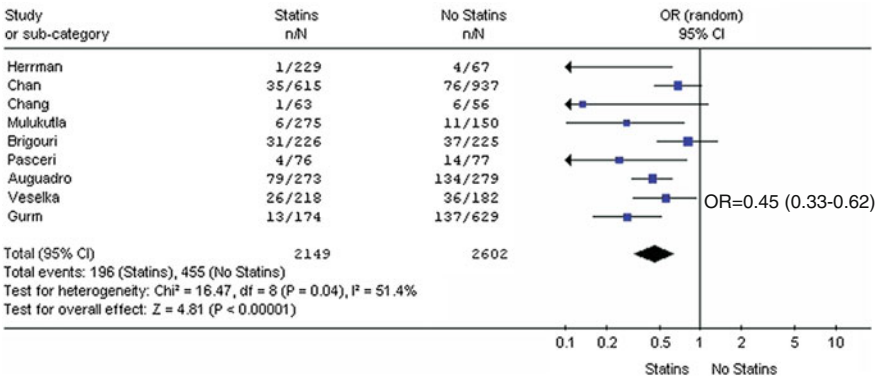

Fig. 11.3 The results of this meta-analysis show that statin administration prior to PCI almost halves the rate of peri-procedural myocardial infarction (OR 0.45, 95 %, CI 0.33–0.62, $p < 0.01$). Adapted from Merla et al. [22]

questioned [24]. However, the early benefits observed with statins within few hours of their administration in the setting of PCI are probably the most compelling evidence that pleiotropic effects likely play a relevant role in the clinical effects of these drugs.

11.1.3.4 Beta-Blockers

Intracoronary propranolol (15 μg/kg) before PCI was shown to reduce peri-procedural AMI during PCI, compared with controls [25], in particular when a GPIIb/IIIa inhibitor (eptifibatide) was added [26]. It has been suggested that the reduction in myocardial oxygen consumption might account for the beneficial effects of propranolol, although an increase in the endocardial/epicardial ratio of tissue perfusion in the ischemic area might also play a role [27].

11.1.3.5 Trimetazidine

Trimetazidine, a piperazine derivative, might prevent peri-procedural myocardial damage during PCI because of its cardioprotective properties [28].

A randomized, placebo-controlled trial showed that trimetazidine (loading dose 60 mg 30 min before recanalization) was associated with a significant reduction in post-procedural TnI levels [29]. The possible role of the drug in this context, however, needs further assessment in larger studies.

11.2 Prevention of CABG-Related CMD

Several pharmacological and non pharmacological approaches have been proposed to preserve coronary microcirculation and myocardial integrity in patients undergoing CABG.

11.2.1 Ischemic Conditioning

Ischemic preconditioning in the setting of CABG was the first 'conditioning' strategy applied in man [30]. In this study, patients undergoing CABG were randomized to preconditioning or the standard procedure. Preconditioning was induced by clamping and unclamping the aorta every 2 min, in order to cause brief episodes of global myocardial ischemia and reperfusion, before the sustained global myocardial ischemia induced by aortic cross-clamping during CABG surgery. Patients randomized to preconditioning had preserved ATP levels in ventricular biopsies and less peri-operative myocardial injury as evidenced by lower serum TnT concentrations.

A recent meta-analysis of 22 studies has been published, showing that preconditioning in this setting is associated with fewer ventricular arrhythmias and need for inotropic support (Fig. 11.4) [31]. However, due to the risk of arterial thrombo-embolism during clamping and unclamping of the aorta, it can be difficult to justify a large prospective study to definitely prove that preconditioning can improve clinical outcome.

Besides before the sustained aortic cross-clamping, the 'conditioning' stimulus during CABG surgery can be applied at the end of the index global ischemic event, at the time of reperfusion (ischemic post-conditioning), when the patient comes off cardiac bypass and the heart is subjected to a period of global reperfusion. Beneficial effects have been reported with this strategy in one study [32]. However, whether post-conditioning can impact on clinical outcomes in patients undergoing CABG surgery remains to be determined.

Remote preconditioning also has been attempted [33]. In one study, patients undergoing elective CABG and valve surgery were randomized to remote preconditioning (three 5-min inflations/deflations of a blood pressure cuff placed on the upper arm) or control prior to surgery. Peri-operative myocardial injury (as measured by the 72 h area-under-the-curve of serum TnT concentrations) was reduced by 43 % in treated patients compared with controls. Subsequent studies, however, gave discordant results [34, 35], likely due to differences in remote preconditioning protocols, concomitant medications, patient selection and type of

Outcome	IPC group	Control	OR (95% IC)	p
Death	0/374	5/402	0.33 (0.07-1.64)	0.17
Myocardial infarction	5/301	4/301	1.10 (0.27-4.54)	0.89
Cerebrovascular accident	2/194	4/193	0.69 (0.16-2.93)	0.62
Ventricular arrhythmias	28/153	65/182	0.11 (0.04-0.29)	0.001
Inotrope use	84/289	157/318	0.34 (0.17-0.68)	0.002

Fig. 11.4 The results of this meta-analysis show that ischemic preconditioning during cardiac surgery is associated with fewer ventricular arrhythmias and need for inotropic support. Adapted from Walsh et al. [31]

surgery. Thus a large randomized controlled clinical trial is warranted to investigate whether this intervention may offer cardioprotective effects in patients undergoing cardiac surgery.

11.2.2 Pharmacological Prevention

Several pharmacological cardioprotective strategies have been tested to protect the heart from the acute global ischemia–reperfusion injury during CABG. Drugs can be administered prior to aortic cross-clamping, added to the cardioplegic solution, or given at the time of aortic cross-clamp removal, or variably combining these different approaches.

11.2.2.1 Pharmacological Conditioning

Drugs believed to reproduce ischemic conditioning through their pharmacological effects have been tried in the setting of CABG.

Adenosine has been shown in several clinical studies to reduce peri-operative myocardial injury and improve cardiac indices when administered either as an intravenous therapy or when added to the cardioplegic solution [36–38]. However, the results of these studies are rather conflicting [39, 40].

Acadesine, which increases local availability of adenosine in ischemic tissues, showed initial benefits, but discordant effects were shown in subsequent trials [41–43].

Bradykinin has also been investigated in the setting of CABG surgery, but it only demonstrated a weak anti-inflammatory cardioprotective effect at the expense of significant hemodynamic instability [44, 45].

Diazoxide, a mitochondrial ATP-dependent potassium channel opener, administered during cardioplegia, improved functional recovery following CABG, but it did not reduce peri-operative myocardial injury as measured by CK-MB release [46, 47].

Volatile anesthetic agents have also been shown to induce conditioning in animal studies [48]. In patients undergoing CABG these drugs have been assessed in several studies [49, 50]. A meta-analysis including 2979 patients in 27 clinical trials showed that, compared with patients receiving intravenous anaesthesia, those who received volatile anesthetic agents had better cardiac function, less requirement for inotropic response, less peri-operative myocardial injury, as assessed by serum TnI levels, and a shorter duration of mechanical ventilation and hospital stay. However, no differences were observed in the incidence of infarction, intensive care unit stay and in-hospital mortality [49]. Other meta-analyses confirmed these data [50, 51].

Outcome	Sample size (*N*)	Treatment group % (*N*)	Incidence % (*N*)	Absolute RR%	χ^2 test (*P*-value)
Mortality	28 517	Statin: 53.6% (15 296) Control: 46.4% (13 221)	2.2% (340) 3.7% (490)	1.5%	<0.0001
Myocardial infarction	14 330	Statin: 62.9% (9012) Control: 37.1% (5318)	4.2% (380) 3.9% (208)	−0.3%	0.373
Atrial fibrillation	7643	Statin: 52.7% (4027) Control: 47.3% (3616)	24.9% (1004) 29.2% (1056)	4.3%	<0.0001
Stroke	16 390	Statin: 61.0% (10 003) Control: 39.0% (6387)	2.1% (212) 2.9% (187)	0.8%	0.001
Renal failure	6408	Statin: 66.1% (4236) Control: 33.9% (2172)	3.9% (165) 4.5% (97)	0.6%	0.275

Fig. 11.5 The results of this meta-analysis show that pre-operative statins or early post-operative statins following CABG reduce the rate of all-cause mortality, atrial fibrillation, and stroke in the absence of any beneficial effect on post-operative infarction or renal failure. Data from Liakopoulos et al. [55]

11.2.2.2 Anti-inflammatory Agents

In the PRIMO-CABG I trial, treatment with pexelizumab, an anti-C5 complement antibody, compared to placebo was associated with a borderline reduction of the rate of death and non-fatal acute myocardial infarction at 30 days follow up in patients undergoing CABG [52]. In the larger PRIMO-CABG II trial, however, pexelizumab had no effect on the same combined end-point, thus questioning the utility of this form of treatment.

11.2.2.3 Statins

As animal studies have shown that statins can limit infarct size when administered prior to ischemia or at the onset of myocardial reperfusion [24], the effects of these drugs in the setting of CABG have been assessed in a few clinical studies [53, 54]. According to a recent meta-analysis pre-operative statins or early post-operative statins in CABG surgery reduce the rate of all-cause mortality, atrial fibrillation, and stroke in the absence of any beneficial effect on post-operative infarction or renal failure [55] (Fig. 11.5).

11.2.2.4 Sodium–Hydrogen Exchange Inhibitors

During myocardial ischemia, intracellular acidosis drives the sodium-hydrogen (Na^+-H^+) ion exchanger to extrude protons from the cell in exchange for sodium, thus resulting in an elevation in intracellular sodium and a rise in intracellular calcium, the effect of which is detrimental for cardiomyocyte survival. The Na+/H+ ion exchange inhibitor cariporide prevents these effects and, in experimental studies, has been reported to reduce infarct size if administered prior to the index ischemic insult [56].

The GUARDIAN trial showed, in high-risk patients undergoing CABG, that pre-treatment with cariporide was associated with less peri-operative CK-MB release and a 25 % reduction in risk of death and non-fatal AMI, when compared with placebo, at 6 months [57].

The larger EXPEDITION trial confirmed these findings; yet, while cariporide reduced infarction rate, it was associated with a higher rate of death and of cerebrovascular events, the reason why this approach has been abandoned [58].

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