Microvascular Disease

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30.1 Background

The link between myocardial ischemia and obstructive atherosclerosis of the epicardial coronary arteries is well established, and coronary angiography has proven the relationship between the severity and extent of coronary artery disease and patient survival. More recently, however, coronary microvascular abnormalities have been described in patients with normal coronary angiograms and different clinical conditions (Table 30.1). In some of these conditions, the abnormalities of the microvasculature represent important markers of risk and may even contribute to the pathogenesis of myocardial ischemia, thus becoming therapeutic targets [1]. Currently, no technique allows the direct visualization of the coronary microcirculation in vivo in humans. Several measurements that rely on the quantification of blood flow through the coronary circulation are commonly used to describe the function of the microvasculature in patients with normal coronary angiograms. These methods include positron emission tomography (PET), cardiovascular magnetic resonance (CMR), and echocardiography methods. The latter measure blood flow ultrasonographically, according to the Doppler principle, in an invasive, semi-invasive, or totally noninvasive way with intracoronary, transesophageal, or transthoracic Doppler echocardiography, respectively. In patients with coronary artery disease, the extent of the reduction in coronary/myocardial blood flow and flow reserve is directly, albeit only grossly, related to the severity of stenosis, whereas in subjects with angiographically normal arteries it is a marker of microvascular dysfunction. With last-generation ultrasound technology and advanced expertise, dual imaging (function and flow) stress echocardiography provides simultaneous insight into regional and global left ventricular function and coronary flow reserve, both necessary for the diagnostic and prognostic characterization of the heterogeneous population of patients with chest pain and angiographically normal coronary arteries [2].

Clinically, the term “chest pain with normal coronary angiogram” has been used to encompass a broad range of conditions. Patients often had coronary artery disease ranging from minimal disease to coronary stenosis up to 50% of luminal diameter and different comorbidities including diabetes and arterial hypertension [3]. A more homogeneous

E. Picano, *Stress Echocardiography*,

Table 30.1 The pathophysiological and clinical spectrum of microvascular disease (adapted from [1])

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

ACS acute coronary syndrome, *HCM* hypertrophic cardiomyopathy

set of patients would be defined if the following exclusion criteria are employed (Table 30.2): absence of even minimal irregularities on the arteriogram (since these patients have minor forms of coronary artery disease, and the prognosis of even a 20% stenosis is clearly worse than a normal coronary angiogram) [4]; absence of regional or global wall motion abnormalities on resting echocardiogram or of left bundle branch block either on the resting or exercise electrocardiogram (which identify patients who may develop dilated cardiomyopathy during follow-up) [5]; no evidence of diabetes mellitus, arterial hypertension, hyperlipidemia, valve disease (including mitral valve prolapse), and epicardial artery spasm. Clinical history electrocardiogram and resting transthoracic echocardiogram are therefore essential for identifying patients with true cardiac syndrome X that probably represent no more than 10% of all patients with chest pain and supposedly normal coronary arteries. The term “syndrome X” (originally the Group X in the 1973 paper by Arbogast and Bourassa) was coined to stress the uncertainty over the pathophysiology of chest pain [6]. This name is still appropriate, since from the pathophysiological point of view things are far from clear, and it remains unclear whether the chest pain in these patients is ischemic or nonischemic in nature.

Table 30.2 Chest pain with "normal" coronary arteries: more than syndrome X

Appropriate nosography	Nonsmooth coronary arteries)	Resting regional or global LV dysfunction, LBBB	Coronary vasospasm	LV hypertrophy, MVP, diabetes, hypertension	LVOT obstruction	Normal CFR	CFR ↓ (<2.0)	Metabolic or mechanical ischemia
Minor, initial CAD (30%)	√							
Early possible cardio myopathy		√						
Variant angina			√					
Secondary microvascular disease				√				
LVOTO (dynamic LV obstruction)					√			
Normal CFR (microvascular disease disproven)						√		
Microvascular disease (cardiac syndrome X)							√	
True ischemia with microvascular disease								√

LV left ventricle, *LBBB* left bundle branch block, *MVP* mitral valve prolapse, *LVOT* left ventricular outflow tract, *CFR* coronary flow reserve, *CAD* coronary artery disease, *LVOTO* left ventricular ourflow tract obstruction

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30.2 Pathophysiology of Microvascular Angina

Several conditions can be clustered together in the syndrome of microvascular disease, characterized by normal epicardial coronary arteries and reduction in coronary flow reserve, in the absence of epicardial coronary artery vasospasm [1]. Microvascular disease may also coexist with epicardial coronary artery stenosis, since a reduced vasodilator response in nonstenosed coronary arteries has been observed in patients with single-vessel disease [7] and in normal, non-infarct-related coronary arteries early after an acute myocardial infarction [8]. Therefore, abnormalities of small distal coronary vessels may contribute to determining an altered coronary flow reserve in patients with ischemic heart disease, independent of atherosclerotic coronary stenoses, and may at least partially account for the elusive link between the anatomical severity of coronary stenoses and clinical symptoms [1]. Reversible alterations in the coronary microcirculation have also been described soon after coronary angioplasty, where they may account for the relatively high rate of false-positive results on electrocardiography and perfusion imaging testing [9]. Microvascular disease can also be a codeterminant of the reduced coronary flow reserve found outside coronary artery disease, in dilated cardiomyopathy [10], hypertrophic cardiomyopathy [11], or in patients with secondary left ventricular hypertrophy, e.g., hypertension and aortic stenosis [12]. In all these conditions, coronary flow reserve impairment is often independent of the degree of left ventricular hypertrophy and the typical behavior of microvascular disease during stress testing is the frequent induction of chest pain, ST-segment depression, and perfusion abnormalities without regional or global wall motion changes (Fig. 30.1). The sequence of events is therefore strikingly different from the

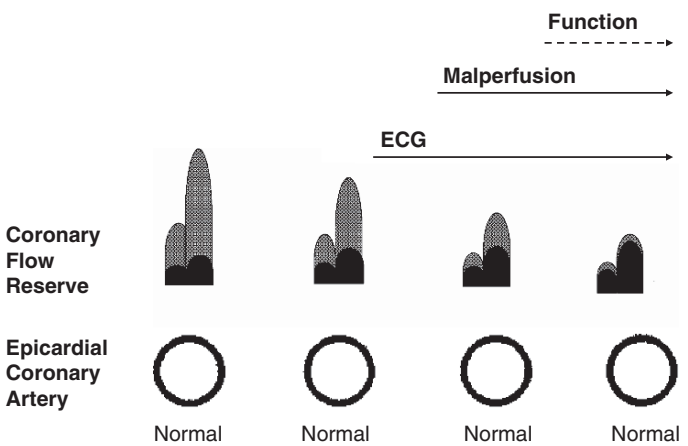


Fig. 30.1 The features of microvascular disease consist of normal epicardial coronary arteries (even when observed by intravascular ultrasound: *lower row*) and reduced coronary flow reserve (by Doppler tracing showing a spectrum of coronary hyperemic responses, from normal – *left* – to abolished – *far right*). Chest pain and ECG changes are frequent during stress, especially when flow reserve is reduced, whereas echocardiography changes (*dashed lines*) are only very rarely observed. (Modified from [2])

Table 30.3 Classic and alternative cascade during stress testing

	Classic	Alternative
Clinical models	Coronary stenosis	Microvascular disease
Epicardial coronary anatomy	Stenotic	Normal
Coronary flow reserve	Depressed	Depressed
Stress: chest pain	Present	Present
Stress: ST depression	Present	Present
Stress: dyssynergy	Present	Usually absent
Experimental model	Yes	No

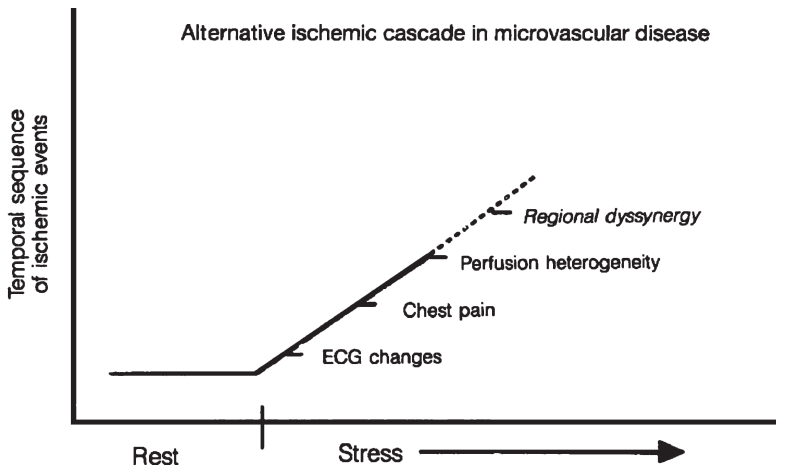


Fig. 30.2 In the model of microvascular disease (reduction in coronary flow reserve with normal epicardial arteries), such as that found in syndrome X or left ventricular hypertrophy, anginal pain and ST-segment changes usually appear in the absence of any detectable wall dysfunction. (Modified from [2])

classic ischemic cascade found during stress testing in the presence of a coronary stenosis (Table 30.3). The alternative ischemic cascade is illustrated in Fig. 30.2 and is derived from pragmatic clinical experience [2]. It integrates, in diagnostic practice, the classical monolithic concept of ischemic cascade. While the classic ischemic cascade was a clear laboratory phenomenon that waited 30 years for a clinical application, which became obvious in the era of cardiac imaging, the alternative ischemic cascade is a clear clinical finding disclosed by cardiac imaging techniques and still in search of a good laboratory model [2].

As Kemp wrote 30 years ago, many findings in syndrome X "like the clues in the first half of an Agatha Christie novel, may not be readily understandable, but we can be certain they are important" [13]. The very same ischemic nature of chest pain and ST-segment depression in cardiac syndrome X patients remains uncertain [14–17]. In theory, true ischemia

might develop in spite of normal coronary arteries. Maseri et al. have proposed that in these patients focal ischemia in small myocardial regions scattered throughout the myocardium and caused by prearteriolar dysfunction might explain the paradox of angina and ST-segment depression provoked by physical or pharmacological stress [18]. In keeping with this interpretation, Cannon and Epstein first hypothesized that the site of abnormally elevated resistances (in patients with reduced coronary flow reserve) is intramural, upstream from the endocardium–epicardium branching point, which is not visualized by coronary angiography [19] (Fig. 30.3). According to their hypothesis, the abnormal resistance to flow would result in maximal dilation of subendocardial arterioles in the rest conditions because of the concomitant higher metabolic demand of the subendocardium. The putative mechanism of the steal as a response to pharmacological or metabolic stimuli, such as dipyridamole or pacing or exercise, would be related to the inability of subendocardial arterioles to dilate further compared with a "normal" dilation of the subepicardial arterioles and the consequent decrease in pressure downstream from the site of increased resistance, with reduction of flow to the subendocardium. The concept of intramural steal cannot be considered proved to date, since we lack consistent and convincing evidence – on the basis of perfusion, metabolic, or mechanical markers – of the truly ischemic nature of ischemic-like stress-induced

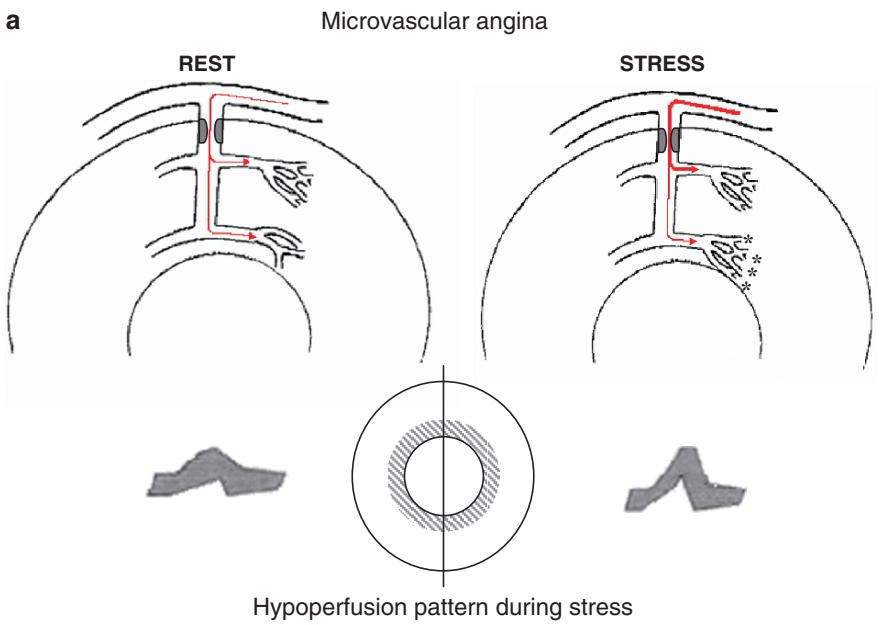


Fig. 30.3 Schematic representation of transmural coronary hemodynamics (*upper panels*), regional wall motion thickening (*lower panels*), and myocardial ischemia transmural distribution (*middle panels*) in syndrome X (**a**) and in epicardial stenosis (**b**). Induced myocardial hypoperfusion is more horizontally diffuse in syndrome X, and more transmurally extended in CAD: only in the latter case of critical mass of ischemic myocardium is reached. (Redrawn and modified from the original hypothesis of Epstein and Cannon [19])

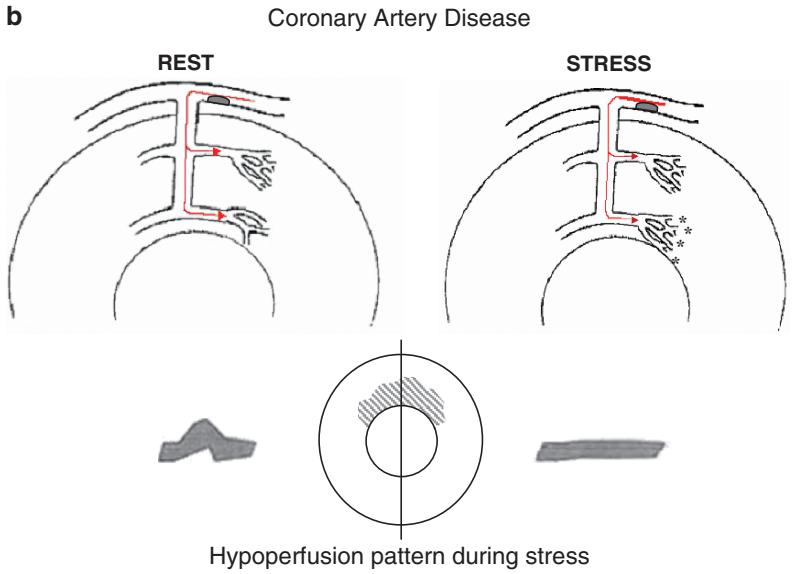


Fig. 30.3 (continued)

chest pain and ST-segment changes [3]. We must keep an open mind on this issue, waiting for more conclusive evidence. However, it is important to emphasize that normal left ventricular function consistently recorded during stress echocardiography is not incompatible with true myocardial ischemia, since the presence or absence of abnormal wall motion appears to be related to the amount of subendocardial tissue rendered ischemic, with minor degrees of transmural involvement (onion skin-like ischemia) or patchy myocardial ischemia (leopard skin-like ischemia), less likely to produce regional dysfunction [2]. In fact, for minimal flow reductions, abnormalities of regional systolic function are subtle and certainly below the threshold of detection by echocardiography. The appreciation of a regional dysfunction by two-dimensional (2D) echocardiography requires a critical ischemic mass of at least 20% of transmural wall thickness and about 5% of the total myocardial mass [20–22]. These experimental data have a clinical correlate. It is well known that even under ideal imaging conditions a subendocardial infarction – not ischemia, infarction – can be accompanied in 20% of cases by a perfectly normal/hyperkinetic regional and global wall thickening [23, 24]. In addition, we now know that regional thickening and motion – which are the cornerstone of clinical echocardiography – express radial function, which can be still normal when longitudinal and/or circumferential function are clearly impaired during less severe ischemia, as shown recently applying new echocardiography technologies (such as myocardial velocity imaging and speckle tracking) to experimental models of stress-induced ischemia [25–26]. In summary, sticking to the very definition of myocardial ischemia proposed by John Ross Jr. ("ischemia is a reduction in myocardial blood flow sufficient to cause a decrease in myocardial contraction" [27]), we can conclude that stress

echocardiographic findings in syndrome X are yet another clue in the first half of this novel: we can be certain they are important, but at present they are not sufficient to find the culprit, which was smart enough not to leave ischemia fingerprints on the stress echocardiography based on regional wall motion and thickening.

30.3 Stress Echocardiographic Findings in Cardiac Syndrome X

There are three main findings during stress echocardiography in syndrome X: (1) regional and global left ventricular hyperkinesia (but regional wall motion abnormalities are described in roughly 10% of patients); (2) reduced coronary flow reserve on mid-distal left anterior descending coronary arteries in about 20% of patients (but reserve is normal in the majority of patients) (3) stress-induced intraventricular pressure gradient (in appro-ximately 5–10% of patients). In cardiac syndrome X, the peculiar pattern during stress echocardiography is the regional and global left ventricular hyperkinesia with ST-segment depression and chest pain, consistently observed during dipyridamole [28], exercise [29], and dobutamine [30, 31]. The stress-induced hyperkinesis is coherent with the original report by Arbogast and Bourassa in 1973 with pacing left ventriculography [6, 13]. Coronary flow reserve can be measured during Doppler-transthoracic vasodilator stress echocardio-graphy on mid-distal left anterior descending coronary artery, semi-simultaneously with wall motion imaging, and shows a reduced (<2.0) coronary flow reserve in one out of five syndrome X patients, in the absence of wall motion abnormalities. The left ventricle is hyperdynamic during stress (too good to be ischemic) (Fig. 30.4), but perfusion changes are often found with perfusion scans [32, 33] and coronary flow reserve by transthoracic echocardiography can be normal (Fig. 30.5) or impaired (Fig. 30.6). CMR may show strictly subendocardial underperfusion during stress and metabolic abnormalities consistent with ischemia in at least 30% of cases but with some inconsistency of results across different laboratories [14–17].

Another stress echocardiographic finding has been observed with increasing frequency – when it is looked for – especially, but not only, in patients with left ventricular hypertrophy or young athletes [34–36]. In these subjects, symptoms such as chest pain or syncope typically occur during exercise. Resting echocardiography is within normal limits, as always in microvascular angina, coronary reserve can be normal, but exercise induces ST-segment depression and a significant (>50 mmHg) intraventricular gradient (Fig. 30.7). In these subjects, the abnormality detected during effort is not among the diagnoses that contraindicate participation in competitive sports according to the recommendations of the 36th Bethesda Conference [37] and the European Society of Cardiology [38]. It has been suggested that, in presence of a history of chest pain or syncope during exercise, the athletes should be advised to suspend sports activity [36]. In theory, this subgroup of patients might especially benefit from β-blocker therapy, which determines an inconstant benefit in the general population of patients with micro-vascular angina [14]. A similar left ventricular outflow tract obstruction has been described during dobutamine infusion in patients with chest pain that develop significantly higher intraventricular gradients [39–41]. Not surprisingly, treatment with the β-blockers bisoprolol resulted in a reduction of angina score, as well as normalization of intraventricular flow velocities [41].

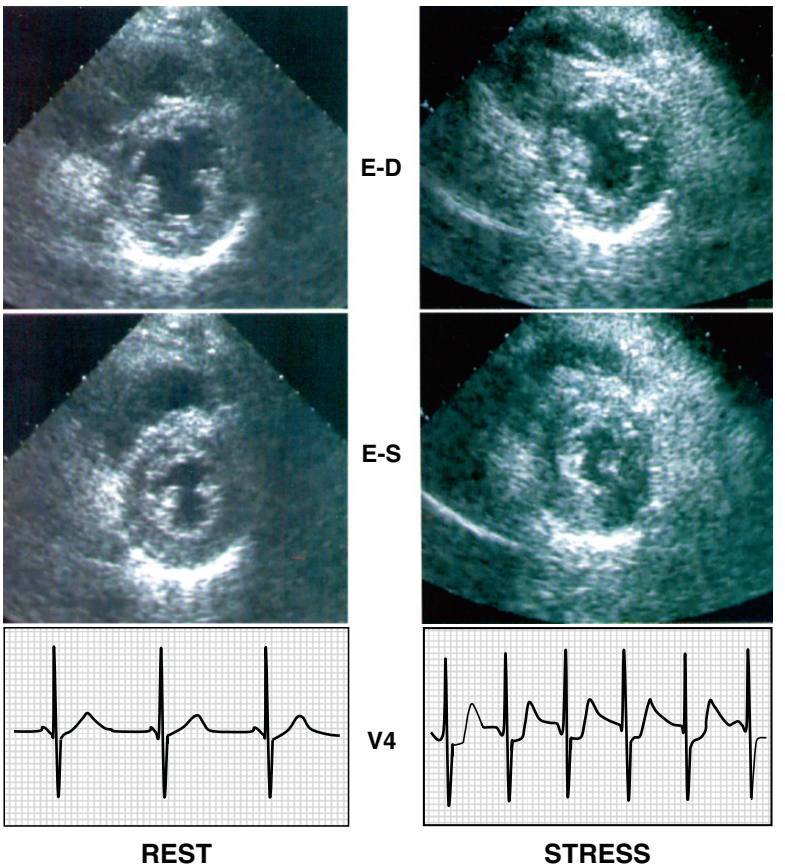


Fig. 30.4 Parasternal short-axis section of the left ventricle at the papillary muscle level under basal conditions (*left*) and after dipyridamole infusion (*right*). Despite ST-segment depression induced by dipyridamole, regional asynergy is not detectable. *E-D* end-diastole, *E-S* end-systole. This patient had a positive exercise electrocardiography test for both chest pain and ST-segment depression. Coronary angiography showed a normal coronary artery tree. (Modified from [28])

30.4 The Prognostic Heterogeneity of Chest Pain with Angiographically Normal Coronary Arteries

On a more pragmatic ground, it is generally considered that chest pain with the angiographic label of normal coronary arteries readily identifies a prognostically benign subset [42, 43], but with substantial heterogeneity. First, not all the patients with a history of chest pain, normal resting function, and normal coronary arteries have microvascular disease [1]. In fact, at least two other broad categories can contribute to the finding of normal coronary arteries: variant angina, which can certainly be overlooked if not considered,

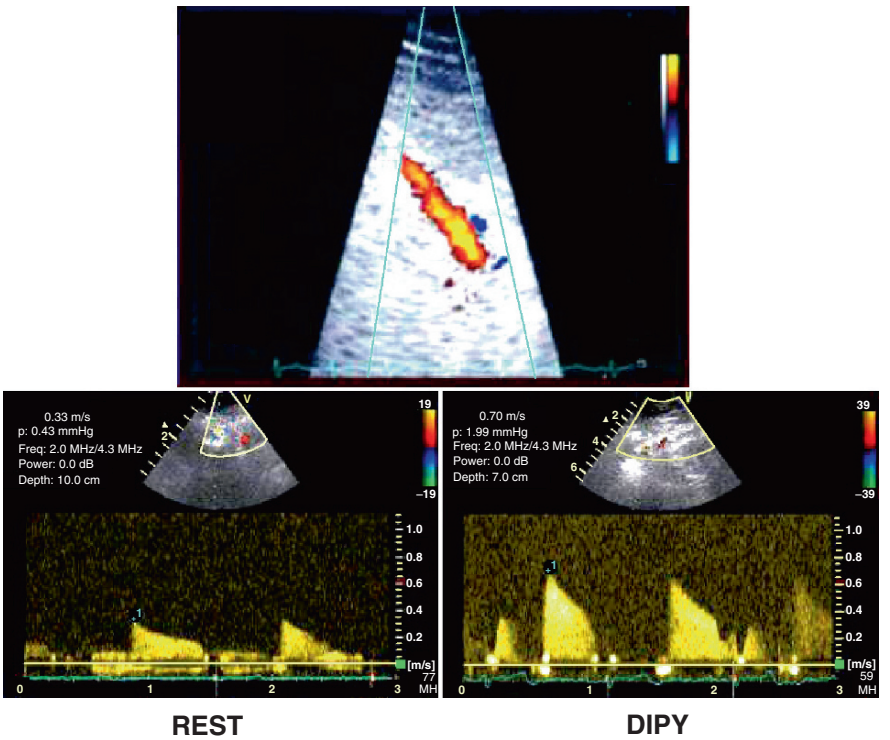


Fig. 30.5 Sample of coronary arteries assessment in patients with normal coronary arteries. Visualization of coronary flow in the mid-distal portion of left anterior descending artery using color Doppler flow mapping in the *upper panel*. Peak flow diastolic velocity was 33 cm s^{-1} under basal conditions (*lower left panel*) and 70 cm s^{-1} after dipyridamole infusion (*lower right panel*), with a normal coronary arteries value (2.1). (Courtesy of Dr. Fausto Rigo)

and a noncardiac origin of chest pain, as can be found in anxiety, psychotic disorders, and esophageal disease. Table 30.4 reports several clues that can aid in the often difficult recognition of these three noncardiac conditions. Second, even considering only patients with microvascular disease, as a group, it is true that these patients indeed have a good prognosis, but with some heterogeneity. Out of nine patients, six had no evidence of wall motion abnormalities and had a preserved coronary flow reserve (>2.0). The prognosis of these patients was found to be excellent (<0.5% hard event-rate per year). At the other end of the spectrum, 10% of patients showed stress-induced regional wall motion abnormalities. In these patients, the event-rate was threefold higher [44]. These patients are "wolves in sheep's clothing" (Fig. 30.8). Between the two extremes, we found about 20% of patients without wall motion abnormalities but with reduced coronary flow reserve (<2.0), with an intermediate hard-event rate (Fig. 30.9) [45]. The situation can be schematically represented as in Fig. 30.10: out of nine patients with identical clinical and angiographic presentation, and, as a group, supposedly good prognosis, six have excellent, two have good, and one has a poor prognosis. As always, stress echocardiography helps identify the pathophysiological heterogeneity hidden behind apparently similar clinical, stress electrocardiographic, and angiographic presentations.

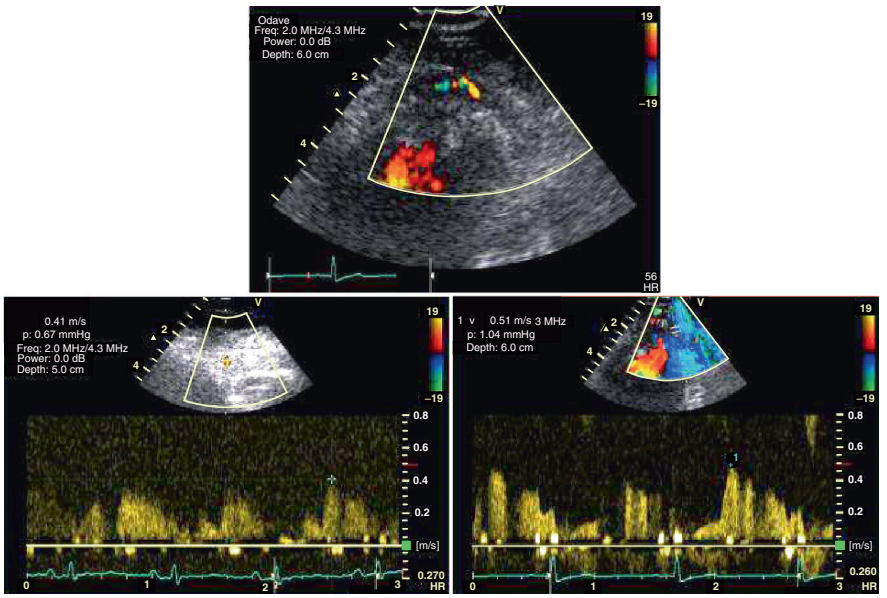


Fig. 30.6 Sample of coronary flow reserve assessment in patients with abnormal CFR. Visualization of coronary flow in the mid-distal portion of left anterior descending artery using color Doppler flow mapping in the *upper panel*. Peak flow diastolic velocity was 41 cm s^{-1} under basal conditions (*lower left panel*) and 51 cm s^{-1} after dipyridamole infusion (*lower right panel*), with an abnormal coronary flow reserve value (1.2). (Courtesy of Dr. Fausto Rigo)

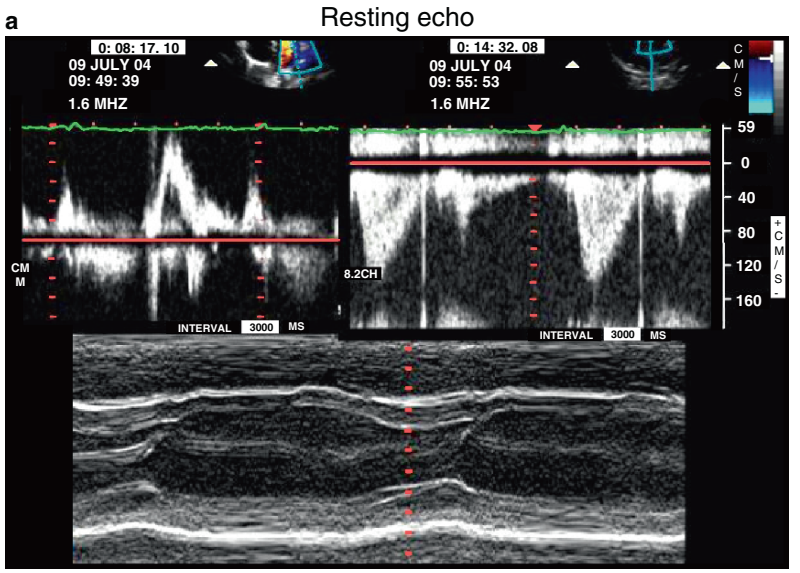
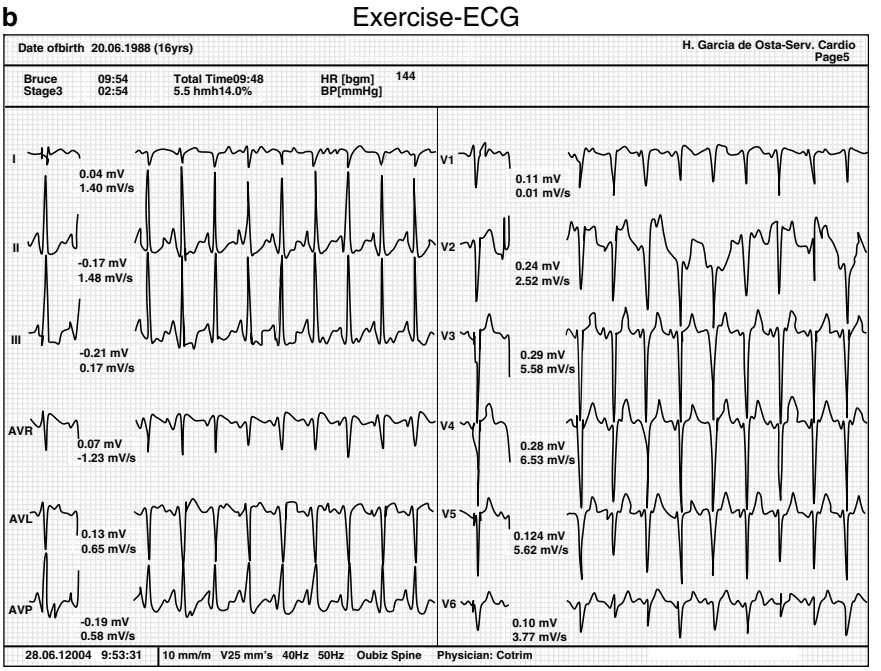


Fig. 30.7 **a** Normal echocardiogram without left ventricular hypertrophy. **b** Exercise test with alteration in ST segment in DII, DIII, and AF. **c** At peak exercise, systolic anterior movement of mitral valve and significant intraventricular gradient was detected. (Courtesy of Cotrim et al [36])

b



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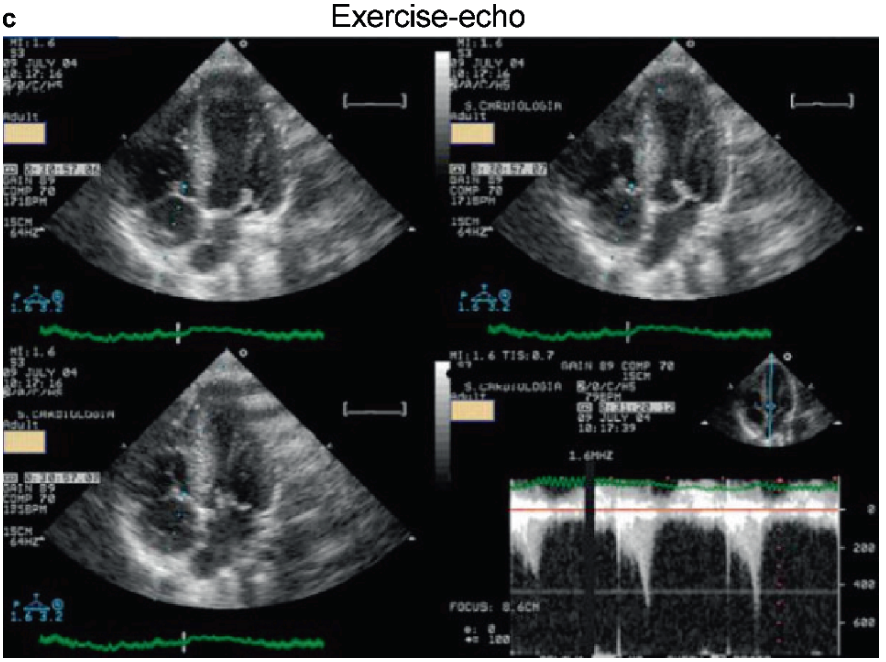

Fig. 30.7 (continued)

Table 30.4 Clues for the recognition of noncardiac conditions

	Microvascular disease	Variant angina	Noncardiac chest pain
Pathogenesis	Small-vessel alteration	Epicardial artery spasm	Anxiety, esophageal spasm, etc.
Chest pain pattern	On effort, emotion, at rest	At night, with palpitations and/or lipothymia	Nitrate sensitive or resistant, lasting second to hours
	Nitrate-resistant	Lasting up to 10 min, nitrate-sensitive	Localized or retrosternal
Resting LV function	Normal	Usually normal	Normal
Ergonovine test	Negative	Positive	Negative
Exercise stress test	Positive	Negative or positive	Negative
Stress test			
Chest pain	Yes	No	No or yes
ST segment	Yes	No	No
Perfusion changes	Frequent	No	Usually no
Echocardiographic changes	No	No	No
Coronary angiography	Normal	Normal (irregularities frequent)	Normal
ICUS	Frequently normal	Alterations on spasm site	Normal
Therapy	Trial and error	Nitrates and Ca^{2+} blockers	None

ICUS intracoronary ultrasound, *LV* left ventricle

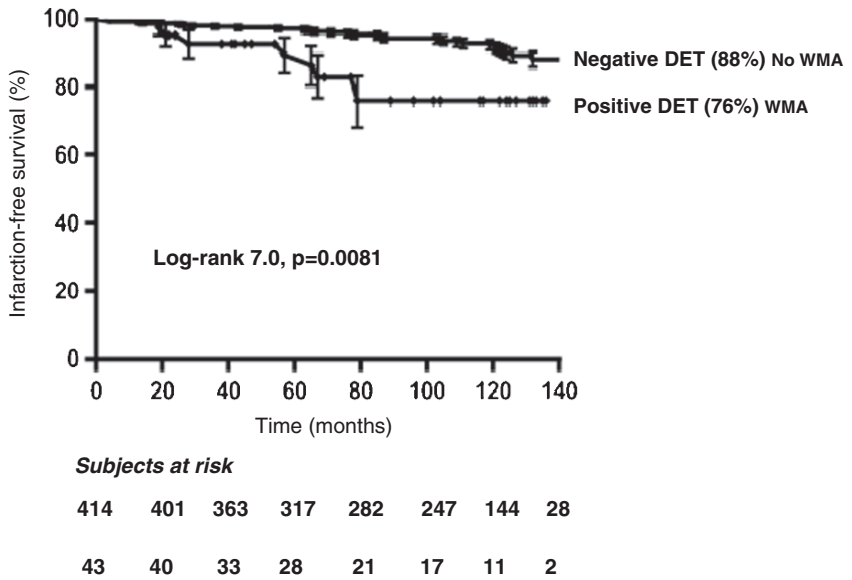

Fig. 30.8 Kaplan–Meier survival curves (considering hard events as an end point) in patients with presence (*DET+*) and absence *(DET−*) of wall motion abnormalities during dipyridamole stress and angiographically normal or near-normal coronary arteries. Survival is worse in patients with inducible ischemia. (Modified from [44])

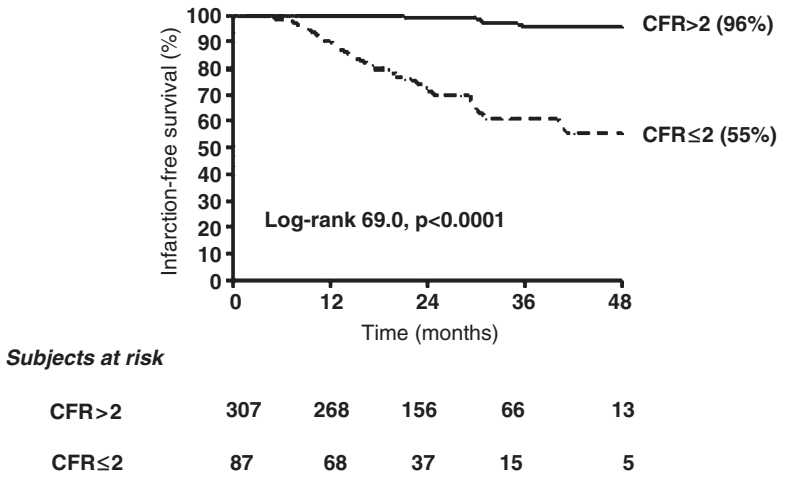

Fig. 30.9 Kaplan–Meier survival curves (considering hard cardiac events as an end point) in patients stratified according to normal (CFR>2) or abnormal (CFR<2) coronary flow reserve at Doppler echocardiography during DET. Survival rate in CFR>2 is significantly different from CFR<2 (p<0.0001). The best survival is observed in patients with normal coronary flow reserve; the worst survival is observed in patients with impaired coronary flow reserve. (Modified from [45])

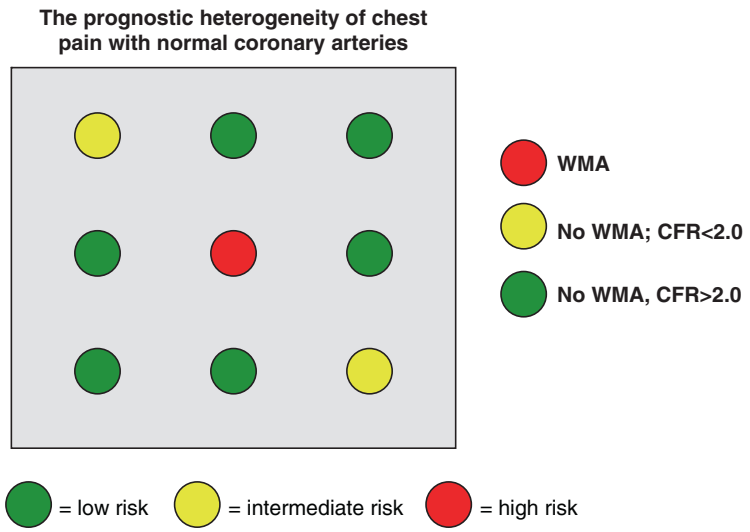

Fig. 30.10 The prognostic heterogeneity of patients with chest pain and angiographically normal coronary arteries. Although the prognosis as a group is good, there is considerable heterogeneity. Prognosis is less good in patients (one out of nine) with inducible wall motion abnormalities, and poor in patients with inducible regional wall motion abnormalities

These results are coherent with a recent meta-analysis [46] showing that patients with chest pain and angiographically nonsignificant coronary artery stenoses may have a prognosis that is not as benign as commonly thought. In fact, even in the absence of true ischemia associated with stress-induced wall motion abnormalities, coronary endothelial dysfunction, presence of left ventricular hypertrophy, and evidence of coronary microvascular dysfunction have been linked to adverse outcome [47].

30.5 The Diagnostic Flow Chart in Microvascular Angina

Stress echocardiography can play a key role in the diagnostic identification of the pathophysiological and prognostic heterogeneity underlying angina with normal coronary arteries. A stress for induction of coronary vasospasm (with ergometrine or hyperventilation) is required to exclude this condition as the cause of the symptoms [48], especially in patients with a clinical presentation suggestive of coronary vasospasm: angina also at rest and with highly variable exercise tolerance; marked seasonal and circadian variation, with worsening in springtime and early morning, worsening with β-blockers; association with palpitations and syncope; and ongoing therapy with methergin, 5-fluoromacil, or sumatriptan (Fig. 30.11). After ruling out coronary vasospasm in selected patients, stress echocardiography is again useful to stratify three risk groups: low risk (no wall motion abnormalities; normal

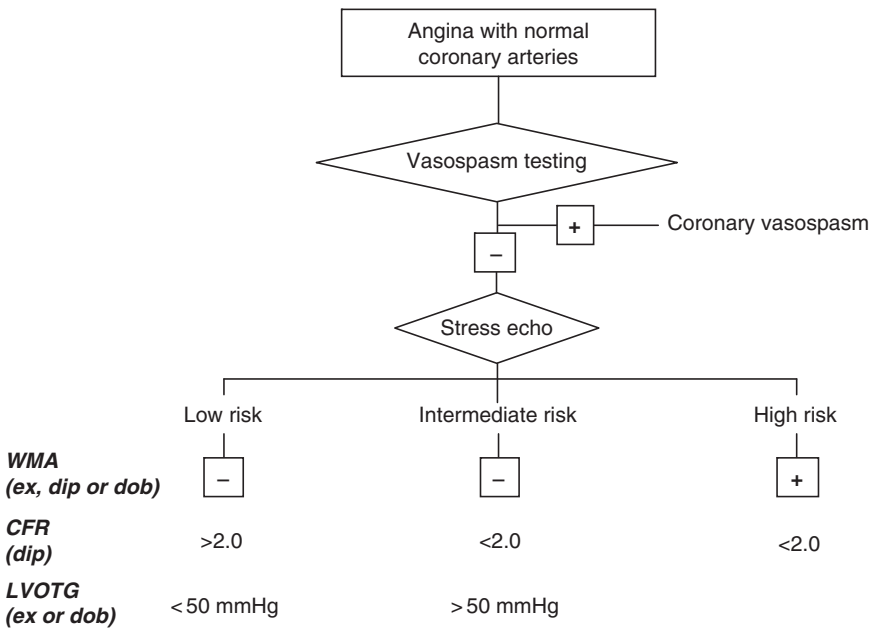

Fig. 30.11 The role of stress echocardiography in the diagnostic flow-chart of patients with chest pain and normal coronary arteries

coronary artery flow reserve); intermediate risk (no wall motion abnormalities, reduced coronary flow reserve); and high risk (inducible wall motion abnormalities). Wall motion can be easily assessed with all stresses (exercise, dobutamine, dipyridamole), whereas the evaluation of coronary flow is best performed with vasodilators (dipyridamole or adenosine). In patients at low risk, a special subset – to be systematically looked for in symptomatic athletes – at probably higher risk are those developing a significant intraventricular gradient during exercise or dobutamine. In them, sports activity can be theoretically at greater risk and β-blockers might be warranted, possibly with a more consistent therapeutic benefit that in the overall population, although certainly more data are needed at this point.

In conclusion, the patient with known or suspected cardiac syndrome X will benefit from the versatility of resting and stress echocardiography. In the screening phase, resting transthoracic echocardiography is helpful to rule out possible causes of angina with normal coronary arteries: left ventricular hypertrophy with or without valvular heart disease, mitral valve prolapse, regional or global left ventricular dysfunction, and left ventricular outflow tract obstruction. Following the initial screening, stress echocardiography can kill three birds with one stone: identification of wall motion, coronary flow reserve, and dynamic intraventricular obstruction with a single technique. A refined diagnostic and prognostic characterization of the different subsets will eventually allow targeting specific therapies on strictly selected patients, more likely to benefit from a tailored approach than with blind carpet bombing on the basis of nonspecific clinical and angiographic criteria.

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