Symptoms and Signs of Myocardial Ischemia

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A transient regional imbalance between oxygen supply and demand usually results in myocardial ischemia, the signs and symptoms of which can be used as a diagnostic tool [1]. Myocardial ischemia results in a typical "cascade" of events in which the various markers are hierarchically ranked in a well-defined time sequence [2]. Flow heterogeneity, especially between the subendocardial and subepicardial perfusion, is the forerunner of ischemia, followed by regional dyssynergy, and only at a later stage by electrocardiographic changes, global left ventricular dysfunction, and pain (Fig. 3.1). The ideal marker of ischemia should provide absolute values of sensitivity and specificity, as well as a diagnosis of the site and severity of ischemia. Unfortunately, such a marker does not exist; in contrast, we have a number if imperfect markers that it associated can provide a reasonably good noninvasive estimation of the presence, extent, and severity of myocardial ischemia. The pathophysiological concept of the ischemic cascade is translated into a gradient of sensitivity of different available clinical markers of ischemia, with chest pain being the least sensitive and regional malperfusion the most sensitive (Fig. 3.2).

3.1 Chest Pain

Chest pain is, in general, the reason the patient seeks medical care. However, many chest pain syndromes are not ischemic in origin and are due to extracardiac causes (such as anxiety or reflux esophagitis), and about 25% of deaths due to coronary artery disease are observed to occur in patients who had never complained of chest pain. Ischemia is "silent" when diagnostic electrocardiographic changes are not associated with symptoms; it is "supersilent" when mechanic and/or metabolic alterations are not associated with either chest pain or electrocardiographic signs (Fig. 3.3). More than 60% of ischemic episodes observed on Holter monitoring are silent, and about 20% of transient dyssynergies detected by echocardiography are supersilent. Thus, chest pain is an important clinical symptom, but it is also a simple diagnostic optional feature [3].

E. Picano, *Stress Echocardiography*,

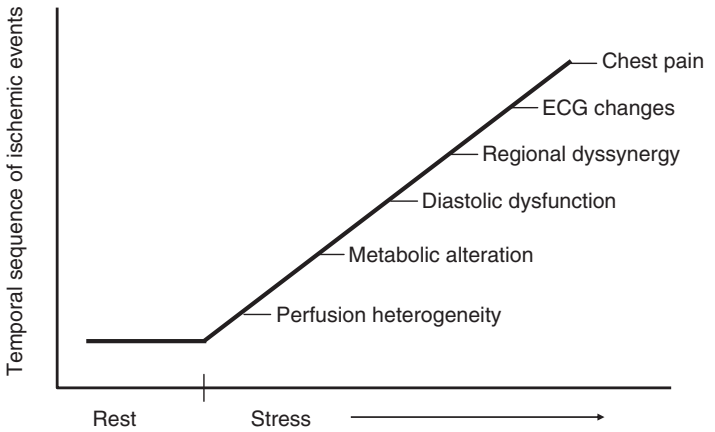

Fig. 3.1 The classical ischemic cascade, triggered by coronary vasospasm and/or epicardial stenosis. The various markers are usually ranked according to a well-defined time sequence

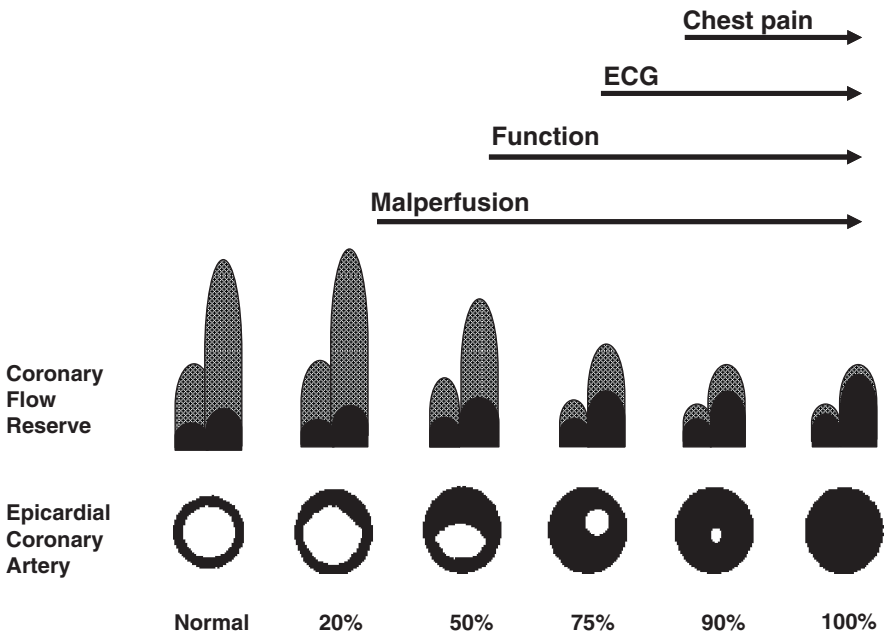

Fig. 3.2 The sensitivity of different diagnostic markers of ischemia ranked according to the underlying coronary anatomy and physiological impairment in coronary flow reserve. Electrocardiographic changes appear late during stress testing and provide only a modest sensitivity, barely superior to that of chest pain. The sensitivity of wall motion abnormalities is markedly superior to that of ECG changes. Malperfusion is more sensitive than wall motion abnormalities in detecting minor, but flow-limiting, levels of coronary artery stenosis

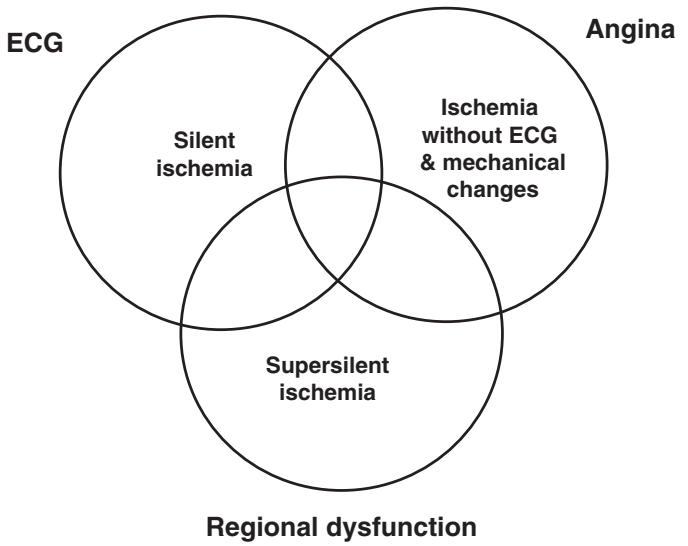

Fig. 3.3 Relative sensitivity of electrocardiography, pain, and echocardiography in diagnosing myocardial ischemia. In the domain of electrocardiography there is the entity of silent ischemia; in the domain of echocardiography there is the entity of so-called supersilent ischemia

3.2 Electrocardiographic Changes

Electrical alterations provoked by ischemia can easily be detected by the 12-lead electrocardiogram (ECG). The electrocardiographic signs of subendocardial ischemia are represented by ST-segment shift or T-wave changes; by contrast, transmural ischemia is generally associated with transient ST-segment elevation. The site of ST-segment elevation is correlated with the site of ischemia, while this agreement does not hold in the more frequently found ST-segment depression. However, ST-segment shifts and T-wave changes are often an equivocal marker of ischemia because the line dividing normal from abnormal is not sharp, and a series of factors (electrical, metabolic, pharmacological, neurohumoral, hemodynamic) can induce ischemia-like ST–T changes [4]. Therefore, the electrocardiographic marker – alone or associated with chest pain – is not always capable of detecting the presence of myocardial ischemia and usually cannot predict its site and extent. The ECG is no longer the definitive proof in the diagnostic process of myocardial ischemia, but only one of the clues.

3.3 Alterations in Left Ventricular Function

Myocardial ischemia causes left ventricular regional dyssynergy (an early, sensitive, and specific marker of ischemia) and global dysfunction (a late and nonsensitive sign). Various techniques have been proposed for the imaging of left ventricular function: echocardiography,

radioisotopic ventriculography (at first pass or equilibrium), fast computed tomography, and magnetic resonance imaging [5]. To date, echocardiography has been the technique of choice for the assessment of ventricular function, both in resting conditions and even more so during stress, in spite of the dependence of echocardiographic imaging on the patient's acoustic window and on the experience of the cardiologist interpreting the study. The advantages of feasibility, safety, reliability, and unsurpassed temporal and spatial resolution allow the documentation under optimal conditions of a regional dysfunction which can be extremely localized in space and transient in time.

3.4 Perfusion Abnormalities

An epicardial coronary artery stenosis reduces the maximal flow achievable in the related territory, although the blood flow in resting condition can be equal to that observed in regions supplied by normal coronary arteries. During hyperemia (either during exercise or after dipyridamole or adenosine) a perfusion heterogeneity will occur with lower blood flow increase in the regions supplied by the stenotic artery, even in the absence of regional ischemia [6]. The criterion of positivity is the presence of a regional flow heterogeneity or malperfusion between different zones of the left ventricle (Fig. 3.4). Perfusion imaging is routinely performed with gamma-camera scintigraphy, but it can be also obtained – with

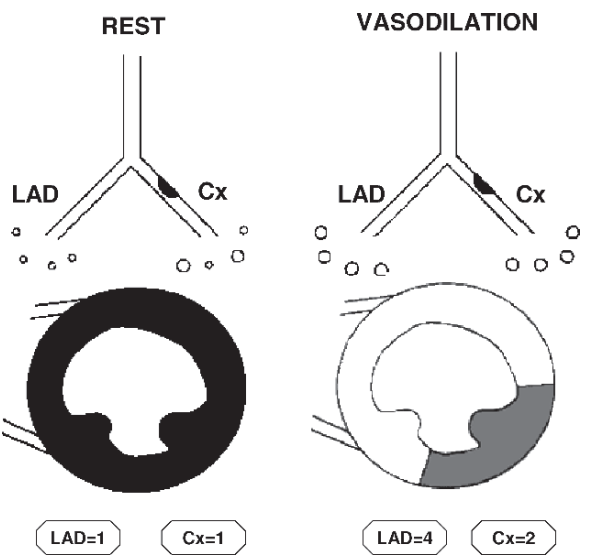

Fig. 3.4 Schematic illustration of the principle underlying myocardial perfusion imaging for the diagnosis of coronary artery disease. At rest, myocardial perfusion is homogeneous, with no differences between the territory of the normal coronary artery (*LAD*, left anterior descending artery) and that of the diseased coronary artery (*Cx*, left circumflex, with 80% stenosis). The resting flow image (obtained, for instance, with thallium-201 scintigraphy or with contrast echocardiography) does not

higher accuracy and at substantially greater cost – by means of positron emission tomography. Other techniques with potential for perfusion imaging are contrast echocardiography and magnetic resonance imaging with injection of specific contrast agents.

3.5 The Paradigm Challenged: The Alternative Ischemic Cascade

In diagnostic practice with stress imaging, not all patients follow the reassuring paradigm proposed by the "ischemic cascade." ECG changes may often occur with typical chest pain, in the absence of echocardiographic changes, and are often accompanied by real, not artifactual [6], reversible perfusion defects. In fact, the typical behavior of microvascular disease during stress testing is the frequent induction of chest pain, ST-segment depression, and also perfusion abnormalities without regional or global wall motion changes [7]. The sequence of events is therefore strikingly different from the classical ischemic cascade described in Fig. 3.1 and in the right panels of Fig. 3.5 as well as from that found during stress testing in the presence of a coronary stenosis. This alternative ischemic cascade is illustrated in the left panel of Fig. 3.5 and derives from real clinical experience [8]. The classical ischemic cascade was a clear laboratory phenomenon described as early as 1935 by Tennant and Wiggers [9], who demonstrated that the immediate result of a coronary occlusion was an instantaneous abnormality of wall motion. The alternative ischemic cascade was a clear clinical finding disclosed by cardiac imaging techniques and it still requires a good laboratory model. It was initially described in cardiac syndrome X by Kemp et al. in 1973 with pacing left ventriculography [10], and later observed with stress echocardiography [11–13]. The left ventricle is hyperdynamic during stress, in spite of the frequent occurrence of chest pain and ST-segment depression: it is "too good to be ischemic," [14] at least when the usual pattern of classic ischemia due to coronary artery stenosis is considered. The alternative cascade refers to a sequence of clinical events, during which the occurrence of ischemia usually cannot be proven [15], although in a subset of patients a reduction in coronary flow reserve [16, 17], and/or a metabolic evidence of inducible ischemia [18, 19], and/or a strictly subendocardial stress-induced hypoperfusion [20] have

Fig. 3.4 (continued) show any interregion variation. However, perfusion in the territory of the stenotic coronary artery is maintained at the price of a partial exhaustion of coronary reserve, with partial dilatation of the arteriolar bed – represented by *larger circles* located downstream from the epicardial coronary arteries. The normal arteriolar tone is represented by *smaller circles* (normally vasoconstricted arterioles). During vasodilation obtained with a metabolic stimulus, such as exercise, or with a pharmacological stimulus, such as dipyridamole, the arteriolar tone is lost determining an increase in flow that will be greater in the normal coronary artery (which, at rest, has a preserved tone in the entire arteriolar district) than in the stenotic coronary artery (with lower coronary reserve). Perfusion imaging will show the stenosis "mirrored" in the myocardium as a region with relative underconcentration of flow tracer when compared with the normal contralateral region. The septal and anterior wall appear "*brighter*" (due to greater echocontrast concentration) when compared with the "*darker*" inferoposterior wall (lower echocontrast concentration)

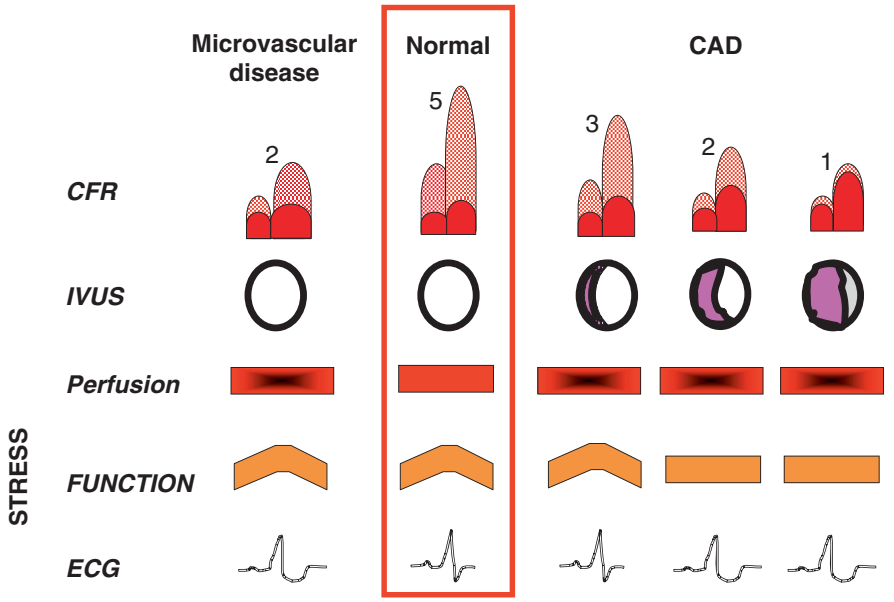

Fig. 3.5 A concise view of the different pathophysiological situations of the classic (*CAD*) and alternative (microvascular) ischemic cascade. In normal conditions (*framed, second column from left*) there is a normal coronary flow reserve (*CFR, first row, with intracoronary Doppler ultrasound*), normal coronary anatomy (*IVUS, second row, with intravascular ultrasound*), normal perfusion pattern with scintigraphy (*Perfusion, third row*), and normal contraction during stress (*Function, fourth row*). ECG is shown in the *last row*. Coronary flow reserve is pictorially expressed with a Doppler tracing before, during, and after a coronary occlusion. With the classic ischemic cascade, perfusion defects are present with mild (*third column from the right)*, moderate (*second column from the right*), and severe (*first column from the right*) coronary stenosis, mirroring reductions in coronary flow reserve and accompanied (for moderate-to-severe stenoses) by regional wall motion abnormalities, which are usually absent for mild degrees of stenosis, capable of limiting coronary flow reserve without inducing ischemia. In microvascular disease (*first column from the left*) the depressed coronary flow reserve is associated with a normal coronary anatomy, the frequent occurrence of stress-induced perfusion defects (often with ST-segment depression), and normal left ventricular function. (Modified from [8])

been described. Thus, while few would argue that induced myocardial dysfunction is an accurate marker of regional ischemia, the occurrence of ECG changes and demonstration of regional abnormal vasodilator reserve may or may not be associated with ischemia [8]. In this debate, one should consider that the absence of stress-induced dysfunction does not rule out the ischemic nature of the electrocardiographic abnormalities. It is well known that under ideal imaging conditions even a subendocardial infarction characterized by prolonged chest pain, a rise in serum enzymes, and ST-segment and T-wave changes can be accompanied in 20% of cases by a perfectly normal echocardiogram [21]. Several conditions can be clustered together with cardiac syndrome X in coronary microvascular disease, characterized by normal coronary arteries and reduced coronary flow reserve,

without epicardial coronary artery vasospasm [14]. In each of them, an echocardiographically silent ST-segment depression has been described as the typical pattern during stress testing. Among others, they include arterial hypertension (with normal coronary arteries, with or without left ventricular hypertrophy), hypertrophic cardiomyopathy [22], and diabetes [23]. It is entirely likely that our monolithic view of ischemia mirrored in the classical ischemic cascade should integrate awareness of the reverse or alternative ischemic cascade best describing microvascular disease, with ECG changes coming first, perfusion abnormalities second, and with echocardiographic changes usually absent during physical or pharmacological stress. Not all forms of myocardial ischemia are the same, and milder, patchy degrees of myocardial ischemia – like those possibly induced in microvascular angina – remain silent in its mechanical functional manifestations and may represent a physiological scotoma of stress echocardiography (Fig. 3.5). The typical stress imaging pattern of a hypertensive patient with epicardial coronary artery stenosis is displayed in Fig. 3.6: perfusion defect with wall motion abnormality. The typical stress imaging pattern of a patient with normal coronary arteries is displayed in Fig. 3.7: perfusion defect without wall motion abnormality. "Anatomic lies" on the ECG may well be turned into "physiologic truths," when coronary flow reserve or systemic endothelial function are considered, or even into correct prognostic predictions – possibly identifying troublemakers in the long run [22].

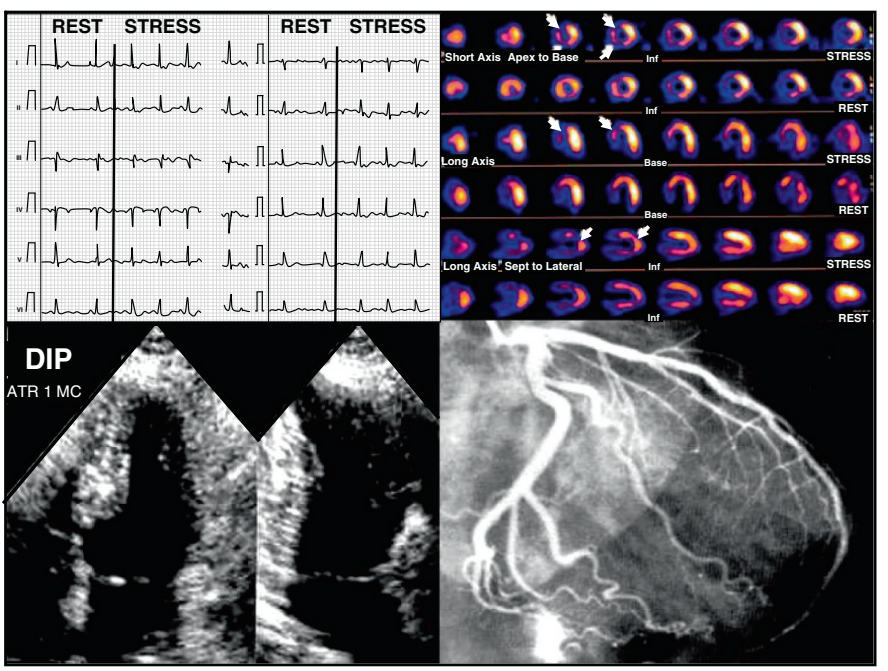

Fig. 3.6 Positive ECG response (*left upper panel*), positive thallium scan (*right upper panel*), apical 4- and 2-chamber view of end-systolic frames at peak stress with apical akinesis (*indicated by arrows, left lower panel*) of a patient with significant left anterior descending coronary artery stenosis (*right lower panel*). (From [13])

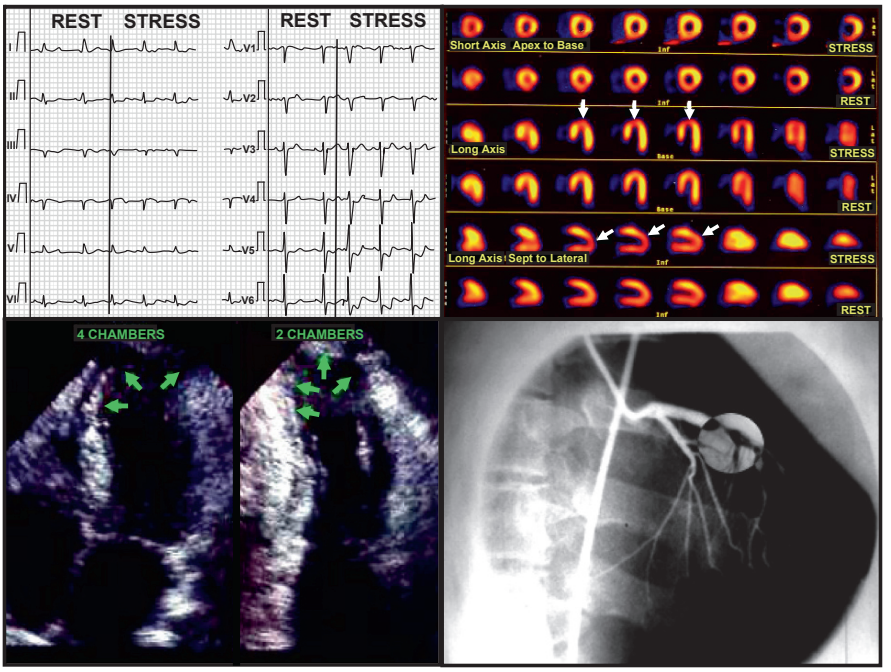

Fig. 3.7 Positive ECG response (*left upper panel*), positive thallium scan (*right upper panel*), apical 4- and 2-chamber view of end-systolic frames at peak stress with normal left ventricular motion of a patient without significant coronary artery disease (*right lower panel*). (From [13])

3.6 Equations in the Diagnosis of Ischemia

On the basis of the classical markers of ischemia, i.e., chest pain and ECG changes, diagnostic equations have been proposed, and are reported in Table 3.1. In view of the limitations of these traditional hallmarks of acute transient myocardial ischemia, "new practical objective criteria (other than ECG changes and pain) for the diagnosis of transient myocardial ischemia are needed" as pointed out by Maseri in 1980 [24]. The classic equations ignore the variable of mechanical changes. However, it is known that the three most commonly used markers of ischemia (chest pain, electrocardiographic changes, mechanical abnormalities) identify at least partially superimposed diagnostic fields (Fig. 3.3). In the absence of concomitant electrocardiographic changes, one is reluctant to affirm the ischemic nature of chest pain; however, ischemic processes resulting in angina pectoris may occur without significant alteration of the ECG [25], as shown by angiographic [26], hemodynamic [27], scintigraphic [28], and echocardiographic [29] studies. It is also well known that asymptomatic myocardial ischemia, as detected by ECG changes and wall motion abnormalities, is a frequent finding during daily activity and during stress testing [30]. The diagnostic accuracy of chest pain and ECG changes is markedly lower than that of

echocardiographic changes during all forms of stress [31]. In terms of prognostic impact, the stress-induced echocardiographically recognized dysfunction matters independently of the associated induced chest pain [32, 33]. Considering the low diagnostic and prognostic accuracy of the traditional hallmarks of acute transient ischemia, namely, pain and ST-segment depression, the standard diagnostic equations can be profoundly remodeled by introducing a new variable, such as transient mechanical changes detected by two-dimensional (2D) echocardiography, during spontaneously occurring chest pain or during stress (Table 3.2). Being highly specific for an ischemic event, the mechanical marker is the only "stand-alone" criterion (justifying even the equation "asynergy – ST change–pain = supersilent ischemia"). However, such a statement, although sound from the conceptual point of view, should be applied with caution to daily clinical practice when hypokinesis is involved, since at present we lack reliable quantitative criteria for the detection of hypokinesis with echocardiographic techniques. In clinical practice things are more complicated and the good old ECG can offer surprisingly important information in the imaging era. During stress testing, ECG changes can occur without scintigraphic abnormalities (which are more sensitive than echocardiographic changes) and are associated with poor long-term prognosis [34]. In patients with positive stress echocardiography results and underlying coronary artery disease, a concomitant ST-segment depression identifies a group at higher prognostic risk [35]. In patients with negative stress echocardiography results and normal coronary arteries, stress-induced ST-segment depression identifies patients with endothelial dysfunction [36]. Patients with positive stress echocardiography results may have no ST-segment changes, but have an increase in QT dispersion, which may be a marker of electrical instability and represents an electrocardiographic sign of ischemia different from the ST-segment shift [37, 38]. In conclusion, no diagnostic marker is perfect, but some are more imperfect than others.

3.7 A New Diagnostic Variable: Coronary Flow Reserve

The diagnostic equations based on ECG and wall motion abnormalities have been further remodeled in the last 5 years with the advent of coronary flow reserve evaluated by pulsed Doppler transthoracic echocardiography in the stress echocardiography laboratory [39]. It represents an ideal complement of regional wall motion in the stress echocardiography diagnostic one-stop shop [40]. The equations of ischemia become more robust with the integration of the two markers, one (regional wall motion) assessing mainly anatomic epicardial coronary artery disease, the other (reduced coronary flow reserve) also mirroring the functional condition of coronary microcirculation. The spectrum of responses will range anywhere from very abnormal (induced wall motion abnormalities and reduced coronary flow reserve, indicating epicardial stenosis and abnormal microcirculatory response) to completely normal (no inducible wall motion abnormalities and normal coronary flow reserve), indicating absence of hemodynamically significant macroepicardial upstream, and micro, distal, downstream arteriolar coronary alterations. The stress response can be stratified into a severity code, mirroring the experimental ischemic cascade: no evidence of abnormality (normal wall motion and normal coronary flow reserve) associated with

very low risk; isolated perfusion or coronary flow reserve abnormality (without inducible wall motion) associated with intermediate risk; and inducible wall motion abnormalities (usually with a perfusion or coronary flow reserve reduction) associated with the highest risk, in patients who will benefit most from ischemia-driven revascularization. When handling in clinical terms this exciting additional information, rich in novel diagnostic [41] and prognostic [42–44] dividends, we should be always aware that – as smart clinicians said already 25 years ago, at the very beginning of the cardiac imaging explosion – "*our surprise in finding out that a new approach gives information that the old methods do not give, in detecting myocardial ischemia, does not differ from the surprise that an intelligent primitive human would experience if he were suddenly confronted with the problem of understanding what makes a car run. After a short observation he would probably first conclude that if you smash your car probably it will not run any more. Then he will discover that even an intact car will not run if its engine is broken. With time he will come to the astonishing discovery that even intact cars with intact engines may not run if they run out of gasoline and, furthermore, that some will not run even when full of gasoline. This, they would probably classify as super-silent trouble.*" [45].

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