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 subendocardial and subepicardial perfusion, is the forerunner of ischemia, followed by metabolic alterations, diastolic dysfunction, induced systolic dysfunction, and only at a later stage 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, an accurate prediction of the patient's outcome and reliable guidance in the decision-making process. Unfortunately, such a marker does not exist; in contrast, we have a number of imperfect markers that if 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. As in any other field of medicine, a correct and comprehensive clinical history is the most important step to achieving a correct diagnosis and making the most appropriate decisions. However, many chest pain syndromes are not ischemic in origin and are due to extra-cardiac causes (such as anxiety or reflux esophagitis), and about 25 % of deaths due to coronary artery disease (CAD) are observed to occur in patients who had never complained of chest pain. Typical or definite angina pectoris can be defined as (1) substernal chest pain or discomfort that is (2) provoked by exertion or emotional stress and (3) relieved by rest and/or nitroglycerin. Atypical or probable

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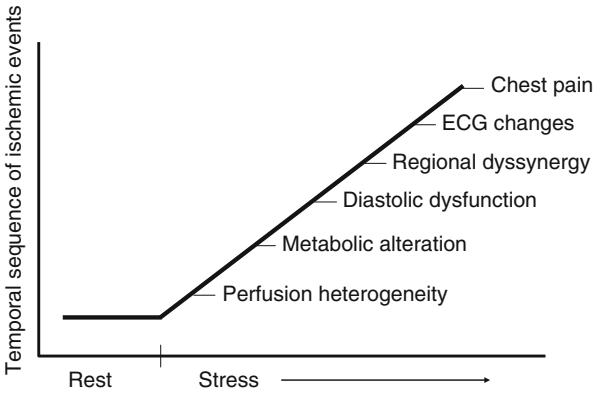

Fig. 3.1 The classic ischemic cascade, triggered by coronary vasospasm and/or epicardial stenosis. The various markers are usually ranked according to a well-defined time sequence

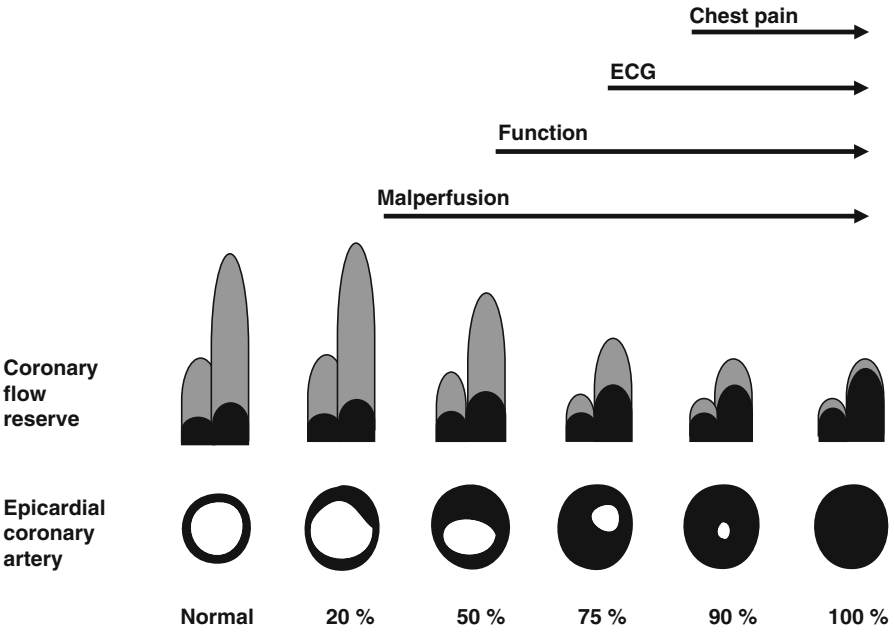

Fig. 3.2 The sensitivity of different diagnostic markers of ischemia ranked according to the underlying coronary anatomy and physiological impairment in coronary flow reserve. Electrocardiographic changes appear late during stress testing and provide only a modest sensitivity, barely superior to that 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

angina can be defined as chest pain or discomfort that lacks one of the three characteristics of definite or typical angina pectoris [3].

Ischemia is "silent" when evidence of myocardial perfusion deficit is not associated with symptoms; it is "supersilent" when mechanical and/or metabolic alterations are not associated with either chest pain or electrocardiographic signs

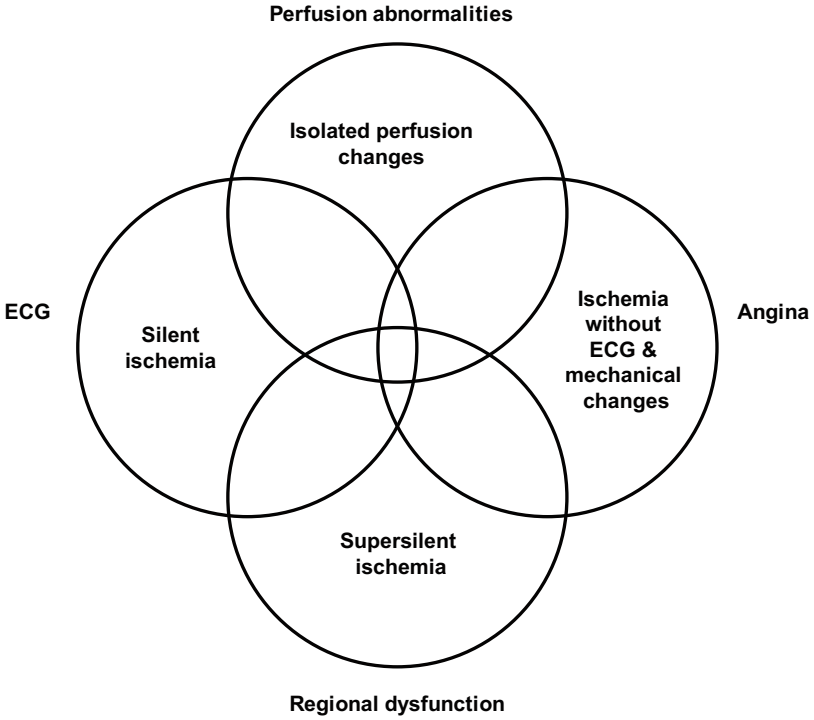

Fig. 3.3 Relative sensitivity of electrocardiography, pain, perfusion, and wall motion changes in diagnosing myocardial ischemia. In the domain of electrocardiography, there is the entity of silent ischemia; in the domain of echocardiography, there is the entity of the so-called supersilent ischemia

(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.

Other symptoms such as dyspnea or pain in other locations different from the chest, i.e., the elbows, neck, stomach, or jaw, may be the only clinical manifestations of myocardial ischemia. In the case of these atypical presentations, the rhythm of symptoms (that are normally triggered by effort or stress and vanish at rest) should prompt the clinical suspicion of myocardial ischemia.

Beyond diagnosis, the characteristics of chest pain can also provide some clues for risk stratification when other routine prognostic markers (namely, ECG and necrosis markers) are normal. Effort-related chest pain and the presence of more than two episodes in the previous 24 h have been shown to double the probability of clinical events in the following 30 days [4] (Fig. 3.4).

It is obvious that symptoms do matter, but we should probably find better ways to select patients referred for cardiac stress imaging, whose positivity rate has fallen from 30 % in the early 1990s to 5 % in recent years with a reduction in overall diagnostic yield [5].

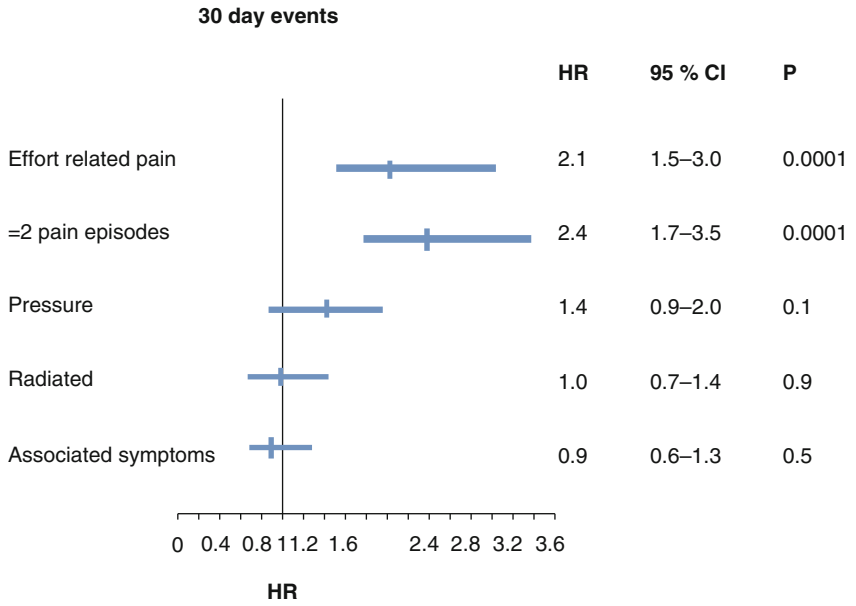

Fig. 3.4 Predictive value of chest pain characteristics for prediction of cardiac events (death, readmission for acute coronary syndrome, or unplanned revascularization) at 30 days in a population of 789 patients with acute chest pain without ECG changes and normal troponin (Modified from Sanchis et al. [4])

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 [6]. 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. Moreover, in clinical practice, out of the context of acute coronary syndromes, it is unusual for patients to complain of chest pain during clinical evaluation. Thus, in stable CAD, baseline ECG seldom contributes definitive proof regarding the presence and location of myocardial ischemia.

Exercise ECG has been proven to be effective in the diagnosis and risk stratification of patients. This test is based on the provocation of typical symptoms and

ECG changes during physical exercise. In absence of any contraindications (such as inability to exercise or baseline ECG abnormalities), it is used in many outpatient clinics and chest pain units for the diagnosis of stable or acute chest pain of uncertain origin. Accomplishment of conclusive and normal maximal exercise predicts an excellent prognosis in the near future [7, 8]. Unfortunately, in more than 50 % of cases, exercise testing is inconclusive or cannot be carried out. This, along with its relatively low diagnostic accuracy (in the range of 70 %), makes it necessary to use additional tools (mainly an imaging stress test) in a significant number of patients.

3.3 Alterations in Left Ventricular Function

Diastolic dysfunction constitutes the first abnormality induced by ischemia on global left ventricular function. Using dobutamine stress echo, an induced abnormal relaxation left ventricular filling pattern has been described before the occurrence of systolic dysfunction [9]. However, beyond its pathophysiological interest in the confirmation of the hierarchy of steps in the ischemic cascade, this sign has rarely been applied in the routine examination of patients, due to many technical difficulties, vulnerability to artifacts, and conceptual limitations, making the reliable, dynamic assessment of diastolic function still a challenging task in the cardiac stress imaging lab (see Chap. 25).

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 stress cardiac magnetic resonance (stress CMR) [3]. 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 that can be extremely localized in space and transient in time. Stress CMR, attending to its extraordinary spatial resolution and its capability to simultaneously evaluate a variety of relevant parameters in CAD, is an excellent alternative to stress echo.

Induced systolic dysfunction represents an advanced step in the ischemic cascade, and its provocation during cardiac imaging stress tests (especially with vasodilators) strongly correlates with a higher probability of cardiac events. Unsurprisingly, taking into account the widely validated prognostic value of baseline systolic function, the magnitude of systolic dysfunction at peak stress (which embraces both baseline and stress-induced systolic abnormalities) has been reported both in stress-echo [10] and in stress-CMR studies [11] as a powerful index for predicting patient outcome.

3.4 Metabolic Abnormalities

In the classic ischemic cascade, metabolic alteration follows perfusion heterogeneity and thus represents an early step in the succession of processes triggered by coronary flow restriction. In order to optimize the lack of available oxygen, cell metabolism shifts from a predominant free fatty acid uptake to glucose consumption. The latter permits generation of adenosine triphosphate with a lesser use of oxygen. However, in the case of severe or prolonged myocardial ischemia, these compensatory mechanisms soon fail. As a consequence of the loss of the energetic fuel, the ischemic cascade moves toward the next steps, namely, diastolic and systolic dysfunction. Myocardial ischemia-related metabolic abnormalities have been well-characterized and they are a promising source of novel biomarkers for the early detection of myocardial ischemia [12]. This knowledge has also been applied in cardiac imaging in the field of positron emission tomography.

3.5 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), perfusion heterogeneity will occur with lower blood flow increase in the regions supplied by the stenotic artery [13]. The criterion of positivity is the presence of a regional flow heterogeneity or malperfusion between different zones of the left ventricle (Fig. 3.5). Perfusion imaging is routinely performed with gamma-camera scintigraphy, but it can be also obtained – with 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. Echocardiography and magnetic resonance imaging do not use radiation; this is a significant advantage taking into account the expected exponential growth in the use of radiation throughout the lifespan of patients as well as its well-known deleterious effects [14].

Induced abnormalities in perfusion occur early in the ischemic cascade, and consequently it is a highly sensitive marker of myocardial ischemia that can be easily provoked by a variety of stressors. Currently stress-induced perfusion deficit, mainly by vasodilators or exercise, has become a cornerstone of the diagnosis of myocardial ischemia.

Beyond diagnosis, in patients with known or suspected ischemic heart disease, there is a great need for reliable tools for risk stratification and decision-making. The ischemic cascade is a reasonable platform for these endeavors. In general, vasodilators are well-tolerated by patients, and their use in cardiac imaging techniques, especially stress echocardiography and stress cardiac magnetic resonance, contribute valuable information to detecting two relevant steps of the ischemic cascade, namely, perfusion abnormalities and induced systolic dysfunction. The first is an

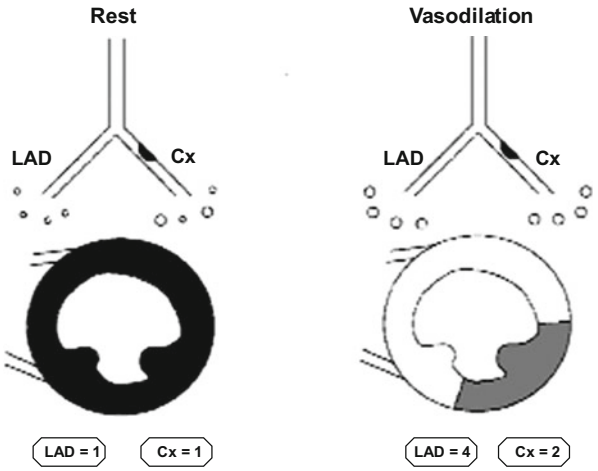

Fig. 3.5 Schematic illustration of the principle underlying myocardial perfusion imaging for the diagnosis of coronary artery disease. At rest, myocardial perfusion is homogeneous, with no differences between the territory of the normal coronary artery (*LAD*, left anterior descending artery) and that 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 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)

early and universal event in the pathophysiology of myocardial ischemia and thus constitutes a robust diagnostic marker. The latter takes place in the case of an important imbalance between coronary flow and myocardial demand, and as a consequence its detection is highly specific for severe myocardial ischemia, denoting a worse prognosis and permitting the identification of those patients who can benefit most from revascularization [15, 16] (Figs. 3.6 and 3.7).

3.6 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

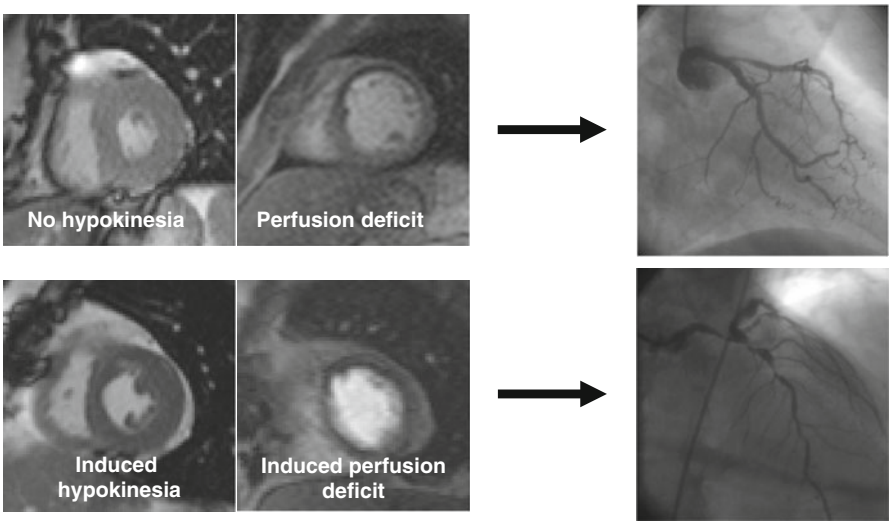

Fig. 3.6 Vasodilator stress imaging: "Two birds with one stone." In stress imaging using vasodilators (such as dipyridamole or adenosine, which are maximal hyperemic stresses with potential to induce true ischemia), induction of isolated perfusion abnormalities (an early step in the ischemic cascade) is highly sensitive for myocardial ischemia and in general is associated with non-critical coronary lesions. Induction of simultaneous perfusion abnormalities and systolic dysfunction (an advanced step of the ischemic cascade) is highly specific and identifies patients with a severe coronary atherosclerotic burden – thus those with a higher risk of events and who potentially will benefit most from revascularization. The *top panels* correspond to a patient with a non-critical lesion in the proximal left anterior descending artery in whom dipyridamole stress-CMR-induced perfusion abnormalities without induced systolic dysfunction. The *bottom panels* correspond to a patient with severe lesions in the proximal and mid-left anterior descending artery and in the left main stem; in dipyridamole stress CMR, both perfusion abnormalities and systolic dysfunction were induced

accompanied by real, not artifactual [17], 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 perfusion abnormalities without regional or global wall motion changes [18]. The sequence of events is therefore strikingly different from the classic ischemic cascade described in Fig. 3.1 and in the right-hand panels of Fig. 3.8 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-hand panel of Fig. 3.8 and derives from real clinical experience [18]. The classic ischemic cascade was a clear laboratory phenomenon described as early as 1935 by Tennant and Wiggers [19], 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 [20] and later observed with stress echocardiography [21–23]. The left ventricle is

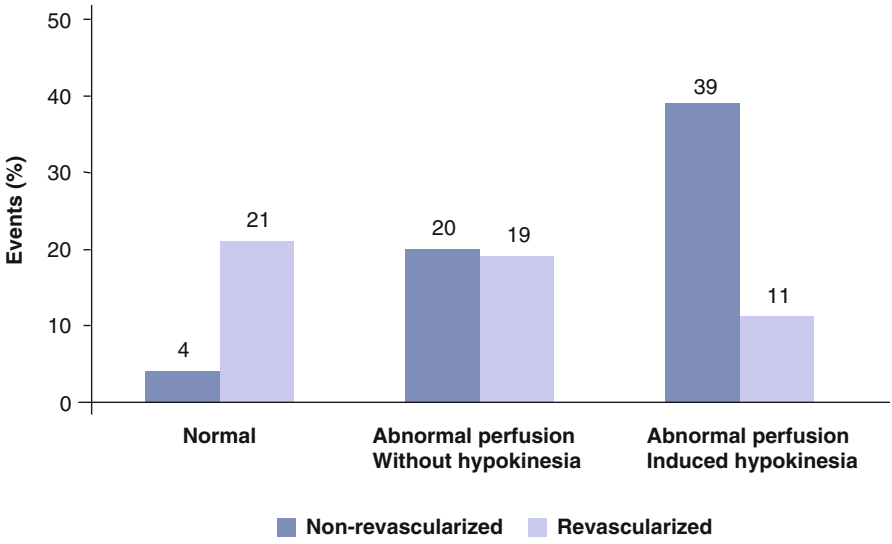

Fig. 3.7 Implications of stress imaging in the decision-making process. In a series of 601 patients with known or suspected ischemic heart disease studied with dipyridamole stress CMR and follow-up for a median of almost 3 years, patients without evidence of ischemia (normal study) who underwent revascularization displayed a worse prognosis, with more adverse events including cardiac death, nonfatal infarction, and hospital readmission for unstable angina. The effect of revascularization on patients' outcome was neutral in the case of non-severe ischemia (induced perfusion deficit without induced systolic dysfunction). The only group of patients that benefited from revascularization was that of cases with severe ischemia (induced perfusion deficit and systolic dysfunction) (Modified from Bodi et al. [15])

hyperdynamic during stress, in spite of the frequent occurrence of chest pain and ST-segment depression: it is "too good to be ischemic," [24] 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 [18], although in a subset of patients a reduction in coronary flow reserve [24, 25, 26, 27], and/or metabolic evidence of inducible ischemia [28, 29], and/or a strictly subendocardial stress-induced hypoperfusion [30] has 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 [13]. 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 [31]. Several conditions can be clustered together with cardiac syndrome X in coronary microvascular disease, characterized by normal coronary arteries and reduced coronary flow reserve,

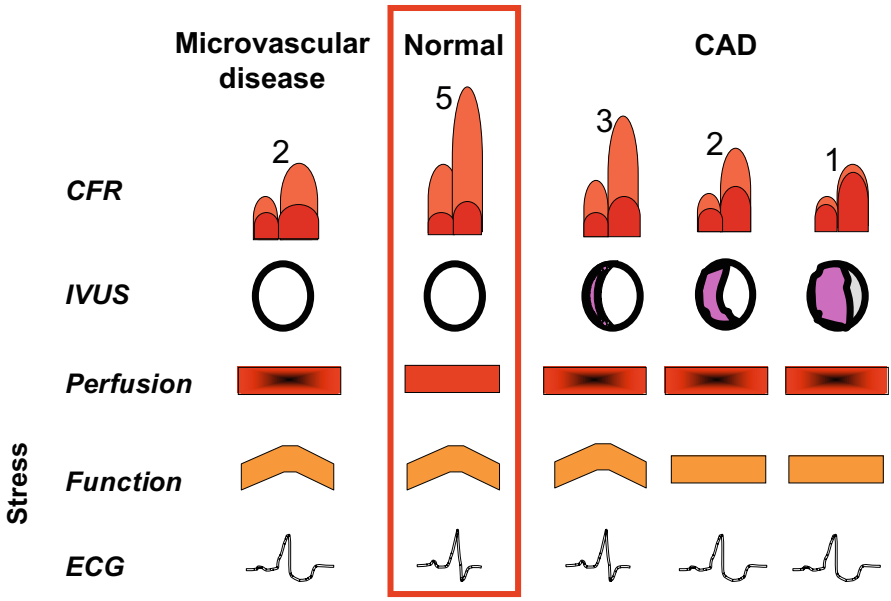

Fig. 3.8 A concise view of the different pathophysiological situations of the classic (*CAD*) and alternative (microvascular) ischemic cascade. In normal conditions (*framed*, *second column from left*), there are a normal coronary flow reserve (*CFR*, *first row*, *with intracoronary Doppler ultrasound*), 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 Picano et al. [18])

without epicardial coronary artery vasospasm [17]. 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, and diabetes [18, 32]. It is entirely likely that our monolithic view of ischemia mirrored in the classic ischemic cascade should integrate awareness of the reverse or alternative ischemic cascade best describing microvascular disease, with ECG changes coming first and 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. 3.8). "Anatomic lies" on the ECG may well be turned into "physiological truths," when coronary flow reserve or systemic endothelial function is considered, or even into correct prognostic predictions – possibly identifying troublemakers in the long run [24].

3.7 Equations in the Diagnosis of Ischemia

On the basis of the classic 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 [33]. The classic equations ignore the variable of wall motion and perfusion changes, both available today in the stress-echo and stress-CMR labs. It is known that the four most commonly used markers of ischemia (chest pain, electrocardiographic changes, wall motion abnormalities, and perfusion changes) identify at least partially superimposed diagnostic fields (Fig. 3.3). 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 new variables, such as transient wall motion abnormalities and/or perfusion changes detected during stress (Table 3.2). Regional wall motion has been present in the echo lab from the very beginning, but coronary flow reserve is a relative newcomer, brought into the lab with the advent of coronary flow reserve evaluated by pulsed Doppler transthoracic echocardiography in the stress echocardiography laboratory [34]. It is an ideal complement of regional wall motion in the stress echocardiography diagnostic one-stop shop [35]. 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 and the other (reduced coronary flow reserve) also mirroring

Table 3.1 Classic markers of ischemia during stress

Chest pain	ECG changes	Diagnosis
No	No	Excluded
Yes	No	Possible
No	Yes	Probable
Yes	Yes	Certain

Table 3.2 The imaging markers of ischemia during stress

WMA	Perfusion changes	Diagnosis	Prognosis
No	No	Unlikely	Excellent
No	Yes	Possible	Fair
Yes	No	Probable	Unfair
Yes	Yes	Certain	Poor

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.

In theory, the presence of wall motion abnormalities without perfusion changes is a pathophysiological paradox, since regional under-perfusion is a prerequisite of ischemia and occurs earlier in the ischemic cascade. In practice, this can be observed and has several potential reasons. First, the relation between true increments in blood flow and the flow signal strength obtained with the current imaging methods is not linear, but reaches a plateau in the high flow range. Therefore, a difference in perfusion can result undetectable by MCE or Doppler CFR evaluation or perfusion CMR. Second, the wall motion change is linked to a reduction in subendocardial flow, which can occur with subepicardial overperfusion and net unchanged transmural flow. Third, flow and function measurements are vulnerable to artifacts and interpretation mistakes, and this gives rise in the real world to an unavoidable percentage of "false" or artifactual positives [36]. As a result, both stress echo and stress CMR can detect patients with CAD and isolated wall motion abnormalities – albeit less frequently than patients with abnormal perfusion without wall motion abnormalities. Patients with perfusion/contraction mismatches have an intermediate prognosis when compared with those with unanimous negative response and good outcome and those with unanimous positivity and worse outcome. These conclusions are supported by data obtained with exercise, vasodilator, and dobutamine stress coupled with dual-imaging stress echo or stress CMR [15, 16, 37–42].

Conclusions

Signs and symptoms of myocardial ischemia are a first and mandatory step in the evaluation of suspected CAD. For accurate management of patients, an individualized assignment into the main steps of the classical or alternative ischemic cascade is required. Stress echo or stress CMR can be a fruitful way to circumvent the limitations of the currently recognized cardiovascular paradigm based on identification and treatment of coronary artery stenosis. Stress echo and stress CMR may evidence genuine ischemia (through regional wall motion abnormalities) and less severe physiological alterations (with isolated reduction in CFR without associated wall motion abnormalities), with its gradient in cardiovascular risk, higher for wall motion, and lower for "lone" perfusion changes. Coronary angiography then assesses the anatomic severity as a basis for treatment.

Unfortunately, the anatomy-based paradigm is unable to identify patients who will receive prognostic benefit from revascularization. Stress-echo and stress-CMR response can provide not only a clinical physiology guide, mapping the coronary flow velocity reserve and myocardial function in different territories, but also provide a guide to stress-driven prognostically beneficial myocardial revascularization. The time to challenge this testable hypothesis with randomized prospective trials has come.

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