Anatomical and Functional Targets of Stress Testing

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The principle of stress under controlled conditions derives from the Industrial Revolution: metallic materials undergo endurance tests to identify the breaking load. This approach identifies structural defects, which – although occult in the resting or static state – might show up under real-life loading conditions, leading to a dysfunction of the industrial product. In the same way, a patient with normal findings at rest undergoes a stress test to identify any potential vulnerability of the myocardium to ischemia, if there is clinical suspicion of ischemic heart disease.

2.1 Pathways of Ischemia

Myocardial ischemia is the final common pathway of various morphological and functional substrates. In order to describe the pathways of ischemia, the normal heart can be conveniently schematized into its three fundamental anatomical components, each a potential target of pathological conditions leading to ischemia: epicardial coronary arteries, myocardium, and small coronary vessels (Fig. 2.1).

2.2 Epicardial Coronary Arteries

The alterations of epicardial coronary arteries can be either fixed or dynamic. Fixed epicardial artery stenosis is the target of functional stress testing, but we also know from pathology studies that the degree and number of coronary artery stenoses do not predict onset, course, complications, infarct size, or death in ischemic heart disease [1].

2.3 Fixed Stenosis

The human body incorporates a functional reserve that allows it to cope with the physiological emergencies and dangers of pathological states. By exploiting its functional reserve, each organ can – for a certain amount of time – play a role that

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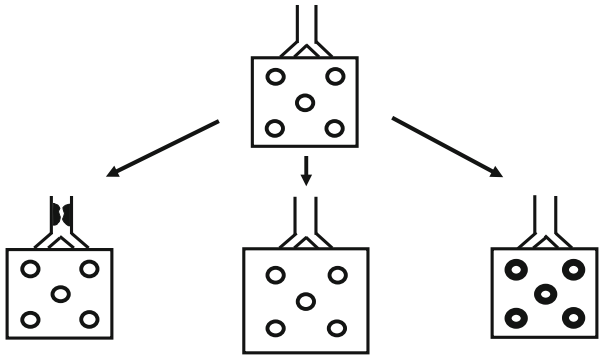

Fig. 2.1 The pathways of ischemia. *Upper panel*: The fundamental anatomical components of the normal heart are shown: epicardial coronary arteries (*parallel lines*), myocardium (*square box*), and small vessels (*circles*). *Lower panel*: The three main pathophysiological conditions that may provoke myocardial ischemia. *Left to right*: coronary stenosis (either fixed or dynamic), myocardial hypertrophy, and small vessel disease (Redrawn and modified from Marcus [2])

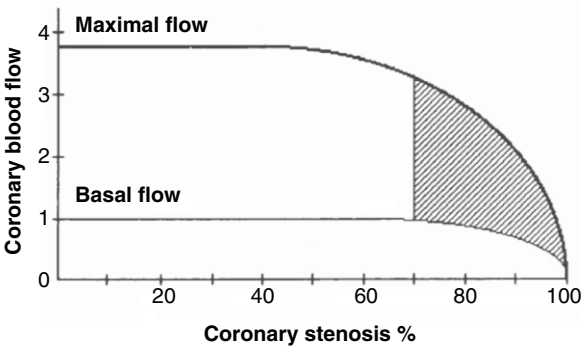

Fig. 2.2 Coronary blood flow curve (*on the ordinate*) for increasing levels of coronary stenosis (*on the abscissa*) experimentally obtained in resting conditions (*lower curve*) and at maximal post-ischemic vasodilation (*upper curve*). Coronary reserve – i.e., the capacity of the coronary circulation to dilate following increased myocardial metabolic demands – is expressed as the difference between hyperemic flow and the resting flow curve. The *dashed area* between the two curves identifies a critical value of coronary stenosis (70 %) beyond which the flow reduction is so severe as to make the myocardium vulnerable to ischemia in the presence of increased oxygen consumption (Modified from Gould and Lipscomb [3])

is much more demanding than the usual one, or when a pathological process develops, it can maintain normal function in resting conditions. Coronary circulation is no exception to this rule. Coronary reserve is the ability of the coronary arteriolar bed to dilate in response to increased cardiac metabolic demands [2]. It is fully exhausted when maximal vasodilation is reached, corresponding to about four times the resting coronary blood flow in the normal subject (Fig. 2.2). A fixed

atherosclerotic stenosis reduces the coronary reserve in a predictable way according to the curve described in Fig. 2.2 [3]. In this curve, four separate segments can be identified: (a) the hemodynamically silent zone, where stenoses ranging from 0 to 40 % do not affect the coronary flow reserve (CFR) to any detectable extent; (b) the clinically silent zone, where stenoses ranging from 40 to 70 % reduce the flow reserve without reaching the critical threshold required to provoke ischemia with the usual stresses; (c) the zone potentially capable of inducing ischemia, where stenoses exceeding the critical level of 70 % elicit myocardial ischemia when stress is applied, but not in resting conditions; and (d) the zone provoking ischemia at rest, where tight stenoses (>90 %) completely abolish the flow reserve and may critically reduce coronary blood flow even in resting conditions.

2.4 Dynamic Stenosis

From a theoretical point of view, dynamic stenoses may be the consequence of three different conditions: increased tone at the level of an eccentric coronary plaque, complete vasospasm caused by local hyperreactivity of the coronary smooth muscle cells, or intravascular thrombosis. The first mechanism can significantly modulate the anginal threshold in patients with chronic stable angina [4], while vasospasm is responsible for variant angina. All three mechanisms coexist in unstable angina [5]. The biochemical mechanisms of coronary vasoconstriction remain somewhat elusive; however, we know that coronary vasoconstriction can be superimposed on any degree of anatomical stenosis and that functional and organic (fixed and dynamic) stenoses can be associated to a variable extent over time, transiently lowering exercise tolerance in the individual patient (Fig. 2.3). Organic stenosis determines the fixed ceiling of flow reserve which cannot be exceeded without eliciting ischemia, whereas dynamic stenosis can modulate exercise capacity in a given patient in a transient, reversible, and unpredictable way [4].

2.5 Myocardium and Small Coronary Vessels

Even in the presence of normal epicardial arteries, myocardial hypertrophy can lower coronary reserve through several mechanisms: vascular growth that is inadequate with respect to myocardial growth, a reduction of the cross-sectional area of resistance of a vessel caused by vascular hypertrophy, and compression of intramural coronary vessels by increased extravascular resistance [2]. Furthermore, hypertrophy determines increased oxygen consumption in resting conditions; the resting flow curve shifts upward with a consequent reduction in coronary reserve (Fig. 2.2). Due to myocardial hypertrophy, as well as accompanying small vessel disease, coronary reserve may also be reduced in both dilated and hypertrophic cardiomyopathy. With normal epicardial coronary arteries and myocardial mass,

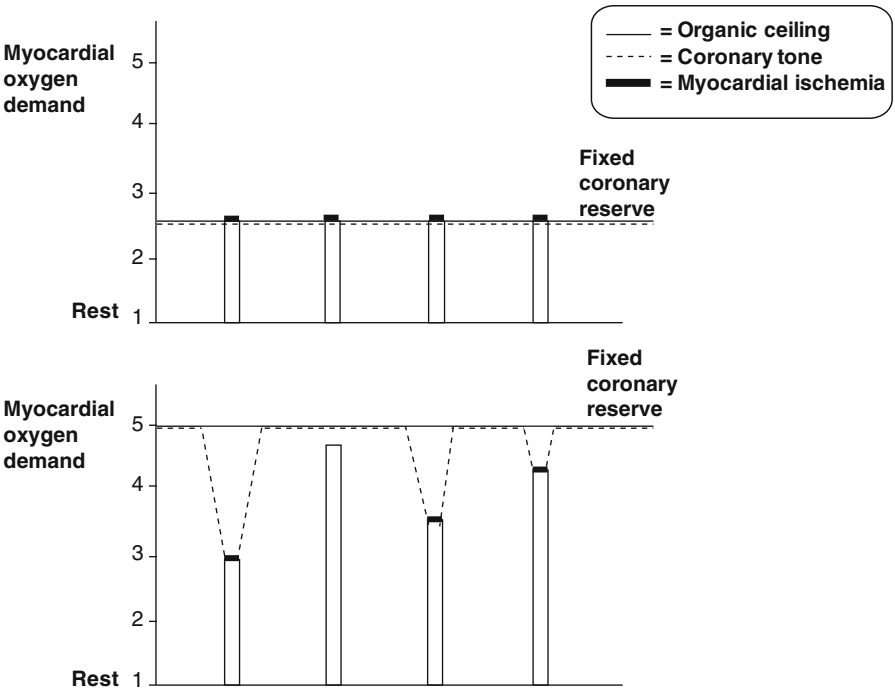

Fig. 2.3 In the presence of a fixed hemodynamically significant stenosis, there is a pathologically reduced "ceiling" of flow reserve (*continuous transverse line*) which induces ischemia when myocardial oxygen demand exceeds a definite threshold (*upper panel*). In the presence of a dynamic stenosis (*lower panel*), the effort tolerance is modulated – in an intermittent, unpredictable way – by fluctuations in coronary tone (*dashed line*), which may reduce the oxygen supply even in the presence of a normal organic ceiling of flow reserve (Modified from Maseri [4])

coronary reserve can still be reduced following increased resistance at the level of the small prearteriolar vessels, which are too small to be imaged by coronary angiography [6].

Small vessel disease can be either primary (as in syndrome X) or secondary (as in arterial hypertension [2]). The decreased flow reserve may be related to a functional and/or an organic factor of the coronary microcirculation. In the former situation, one must assume the inability of the microcirculation to vasodilate appropriately, due to errors in the decoding or transmission of the myocardial metabolic message. In the latter case, anatomical reduction of the microvascular cross-sectional area is likely to occur for medial hyperplasia, which determines an increased wall-to-lumen ratio (Fig. 2.1). This anatomical phenomenon may also determine hyperreactivity to functional stimuli for purely geometric reasons, since minimal caliber reductions cause a marked increase in resistance, with a consequently exaggerated response to normal vasoconstrictive stimuli.

2.6 The Target of Ischemia: The Subendocardial Layer

The many functional and anatomical pathways of ischemia share a common pathophysiological mechanism: the reduction of coronary reserve. This makes the myocardium vulnerable to ischemia during stress. Regardless of the stress employed and the morphological substrate, ischemia tends to propagate centrifugally with respect to the ventricular cavity [7, 8]: it involves the subendocardial layer, whereas the subepicardial layer is affected only at a later stage if the ischemia persists (Fig. 2.4).

In fact, extravascular pressure is higher in the subendocardial than in the subepicardial layer; this provokes a higher metabolic demand (wall tension being among the main determinants of myocardial oxygen consumption) and an increased

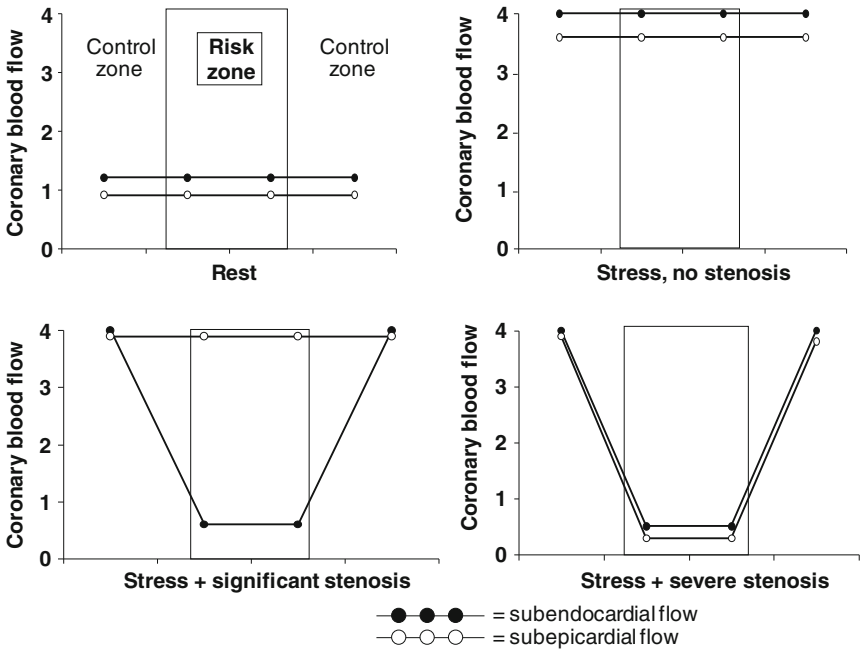

Fig. 2.4 Distribution of flow in the subendocardial and subepicardial layers under different hemodynamic conditions. *Upper left panel*: In resting conditions, the subendocardial and subepicardial flows overlap. *Upper right panel*: During stress, the flow increases homogeneously in both layers without affecting the transmural distribution. In the presence of a coronary stenosis, the resting flow is similar to that under normal conditions (*upper left panel*); however, during stress (*lower left panel*), flow remains elevated in the subepicardial layer but falls precipitously in the subendocardium, within the region supplied by the stenotic artery. In the presence of a severe stenosis (*lower right panel*), stress provokes a fall in the subendocardial as well as the subepicardial layer, therefore determining a transmural ischemia (Redrawn and modified from L'Abbate et al. [7])

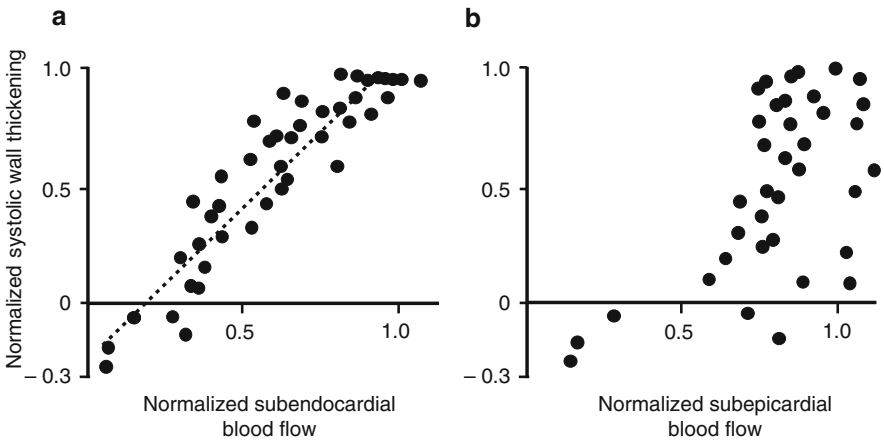

Fig. 2.5 The relationship between regional blood flow and systolic wall thickening in resting conscious dogs subjected to various degrees of circumflex coronary artery stenosis. Flow is expressed as a decimal fraction of that in a normal region of the ventricle, and percentage wall thickening (*%WTh*) is expressed as a fraction of the resting value prior to coronary stenosis. (**a**) Subendocardial blood flow vs. wall thickening, showing a nearly linear relationship (*solid line*). (**b**) Subepicardial blood flow vs. wall thickening, showing considerable scatter and no change in subepicardial flow until function is reduced by more than 50 % (Modified from Gallagher et al. [9])

resistance to flow. Selective stress-induced hypoperfusion is especially important for stress echocardiography applications, since regional systolic thickening is linearly and closely related to subendocardial perfusion and only loosely related to subepicardial perfusion [8, 9] (Fig. 2.5).

2.7 The Pitfalls of Coronary Anatomy Diagnostic "Gold Standard"

The results of noninvasive diagnostic tests (Table 2.1) are usually compared with a "gold standard," that is, angiographically assessed coronary artery disease. Although generally accepted, the gold standard has some limitations of both a theoretical and a practical nature [10].

Table 2.1 Standard terminologies in diagnostic testing

True positive = abnormal test result in individual with disease
False positive = abnormal test result in individual without disease
True negative = normal test result in individual without disease
False negative = normal test result in individual with disease
Sensitivity = true positives/true positives + false negatives
Specificity = true negatives/true negatives + false positives
Accuracy = true positives + true negatives/total number of tests performed
Positive predictive value = true positives/true positives + false positives
Negative predictive value = true negatives/true negatives + false negatives

First, coronary stenosis is estimated by angiography through the visually assessed percentage reduction of the vessel lumen. The percent of stenosis is a reliable index of severity only if the vascular segment immediately proximal and distal to the stenotic segment is normal and the lesion concentric and symmetrical. Both assumptions are valid in only a very limited number of cases: atherosclerotic involvement usually extends beyond the point of maximum lumen reduction, and the most frequent type of lesion is eccentric. Second, coronary angiography represents only the vessel lumen, an innocent bystander of atherosclerotic disease, rather than the vessel wall, which is the real victim. Minimal, "nonsignificant" lesions at angiography can harbor a diffuse severe atherosclerotic process [2]. The close correlation between coronary stenosis and CFR found in the experimental animal [3] is replaced in the clinical setting by an impressive scatter of data [11]. It is impossible to predict the physiological meaning of a stenosis solely on the basis of its angiographic appearance – unless selected patients with single vessel disease, no previous myocardial infarction, no collateral circulation, and no left ventricular hypertrophy are enrolled [12]. Coronary stenosis provokes ischemia as a result of hemodynamic consequences on the coronary reserve; however, the two parameters (anatomical and pathophysiological) can diverge, and the individual values of CFR vary substantially for stenoses of intermediate (40–80 %) angiographic severity. In these patients, positive stress test results are more frequently found in patients with depressed CFR (<2.0) than in patients with preserved CFR (>2.0). This is true for all forms of stress testing, including exercise electrocardiography [13–17], stress perfusion scintigraphy [18–21], and stress echocardiography [22–24]. Third, coronary angiography evaluates the anatomical component of myocardial ischemia, while stress tests can induce ischemia through mechanisms that are totally different from the organic stenosis (such as dynamic vasoconstriction) and cannot be assessed by means of a purely morphological, static evaluation of the coronary tree [25]. Extracoronary factors such as myocardial hypertrophy can also reduce CFR and therefore make the myocardium potentially vulnerable to ischemia during stress tests [26, 27]. Finally, the commonly employed visual and subjective assessment of stenosis is burdened by a marked intra- and interobserver variability, even among experienced angiographers, and arbitrary threshold criteria (such as the presence of a 50 % diameter stenosis in at least one major coronary vessel) are introduced to distinguish between "normal" and "sick" patients, when in fact the severity of the atherosclerotic disease ranges over a continuous spectrum. Anatomical coronary artery disease can be assessed much more accurately by intracoronary ultrasound (Fig. 2.6), which substantially improves the representation of atherosclerosis compared with coronary angiography [28]. However, intracoronary ultrasound knows nothing about perfusion territory, which is critical for functional evaluation of coronary stenosis. Functional significance of coronary stenosis cannot be predicted by any intracoronary imaging modality for anatomical assessment of coronary stenosis.

This improvement is comparable to that achieved in left ventricular imaging when moving from chest X-ray to transthoracic echocardiography. Chest X-ray outlines external profiles and provides a rough index of cardiac volumes, whereas transthoracic echocardiography describes tomographically the various heart

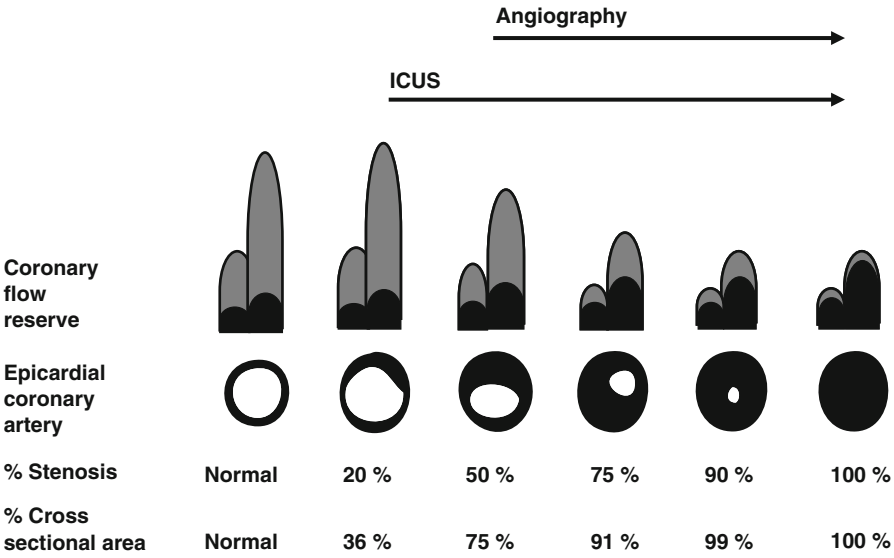

Fig. 2.6 Invasive diagnostic tests for the detection of coronary artery disease. Invasive tests include the luminogram of coronary angiography and the direct visualization of the coronary arterial wall by intracoronary ultrasound (*ICUS*). The percentage of a stenosis can be expressed in angiographic studies as a percentage reduction in diameter and as a percentage reduction in cross-sectional area. The percentage reduction is greater for area than for diameter because of the quadratic relationship between the diameter ($2r$) and area (πr^2) of a circle. The two estimates of stenosis correspond perfectly only for zero stenosis and for 100 % stenosis. For each level of stenosis severity, the CFR is expressed with a Doppler tracing before and after a coronary vasodilator (adenosine or dipyridamole). Stenoses of less than 50 % diameter reduction are not hyperemic flow limiting (Redrawn and modified from Erbel [29])

chambers and the thickness of the walls and identifies within each segment the different layers (endocardium, myocardium, and pericardium). In a similar fashion, coronary angiography offers only a luminogram of the vessel, whereas intracoronary ultrasound imaging provides an assessment of the lumen and of the vessel wall thickness [29]. In addition, at each site, the different layers (intima, media, and adventitia) can also be evaluated. Angiography and intracoronary ultrasound correlate closely in healthy vessels with a nearly circular lumen shape. However, as the lumen becomes progressively more irregular, the correlation between a silhouette imaging method (angiography) and a tomographic modality (ultrasound) diverges significantly. The most substantial disagreement is found in status after angioplasty in which angiography cannot accurately depict the true size of the complex and distorted luminal shape commonly encountered after interventions. Abnormal stress test results can be found in patients with nonsignificant coronary angiographic findings in whom intracoronary sonography may show angiographically unrecognized atherosclerotic changes [30], as typically happens in cardiac allograft vasculopathy [31]. Invasive angiographic gold standards are the obligatory reference for noninvasive stress testing procedures, but not all that glitters is gold [32]. In several

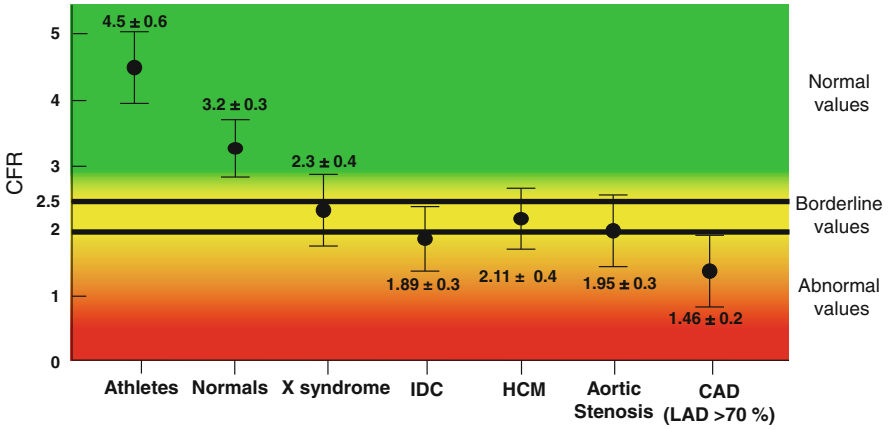

Fig. 2.7 The spectrum of clinical conditions with normal coronary arteries and reduced CFR on the left anterior descending artery by transthoracic vasodilatory stress echocardiography (Redrawn and modified from Rigo [33]). *CAD* coronary artery disease, *CFR* coronary flow reserve, *HCM* hypertrophic cardiomyopathy, *IDC* idiopathic dilated cardiomyopathy

conditions, coronary arteries are perfectly smooth, even with intracoronary ultrasound, and the CFR is impaired by transthoracic stress echocardiography, for instance, in aortic stenosis, syndrome X, or dilated cardiomyopathy [33] (Fig. 2.7).

A "false-positive" result by anatomic criteria (i.e., a reduced CFR with angiographically normal coronary arteries) can become a "true-positive" prognostic response in the long run, and patients with reduced CFR – assessed by complex techniques such as positron emission tomography or simple methods such as transthoracic vasodilatory stress echocardiography – are more likely to experience adverse events in a variety of clinical conditions such as chest pain with normal coronary arteries [34], dilated cardiomyopathy [35, 36], and hypertrophic cardiomyopathy [37, 38].

2.8 Assessment of Functional Severity of Coronary Lesions

Since coronary angiography is of limited value in defining the functional significance of stenosis, we need to integrate the anatomic information with a functional assessment, either by measuring CFR or intracoronary artery pressure with fractional flow reserve (FFR). CFR measurements depend on the status of the microcirculation, as well as on the severity of the lesion in the epicardial vessel. For practical and methodological reasons, measurement of CFR is not widely used in catheterization laboratories today and hence does not play any role in the patient management in the catheterization lab. The opposite is true in the stress echo lab, where FFR cannot be obtained and decision-making is founded on CFR assessment, obtained during vasodilator stress with Doppler imaging of left anterior descending coronary artery flow or – less frequently – with myocardial contrast echocardiography. FFR is considered nowadays to be the "gold standard" for invasive assessment of stenosis

physiologic significance and a helpful tool for decision-making in coronary revascularization. FFR is calculated as the ratio of distal coronary pressure to aortic pressure measured during maximal hyperemia. A normal value for FFR is 1.0, regardless of the status of the microcirculation, and stenoses with an FFR >0.80 are hardly ever associated with exercise-induced ischemia. It provides guidance for the clinician in situations when it is not clear whether a lesion of intermediate angiographic severity causes ischemia, and the use of FFR was upgraded to a Class IA classification in multivessel percutaneous coronary intervention in the European Society of Cardiology guidelines on coronary revascularization [39]. In general, the relation between FFR and angiographic assessment of coronary stenosis is mild to moderate with approximately 1/3 of coronary stenosis either over- or underestimated by angiography. On an individual level, this means that a patient with multivessel disease would have every third coronary stenosis misdiagnosed, with a possible wrong choice for revascularization procedure. It has been shown in the FAME trial [40, 41] that the rate of functional significant stenosis in two-vessel angiography stenosis is 43 % and in angiographically three-vessel coronary artery disease only 14 %. So, not only is there a significant mismatch in angiographic and functional assessment of coronary stenosis, but it seems that we are sometimes functionally blinded with the more severe angiographic appearance of diffuse coronary atherosclerosis.

The assessment of CFR with stress echo can be done upstream to the cath lab – which in practice is often a point of no return toward revascularization; it does not imply the additional cost (about 1000 dollars) [42] and the extra radiation exposure (about 5 milliSievert, corresponding to 250 chest X-rays, in addition to the 7 of a coronary angiography) of FFR performed in the cath lab [43] and provides insight into the functional status of coronary microcirculation, which is a major prognostic determinant independently of coronary stenosis [44]. The randomized trials such as FAME 1 [40] and FAME 2 [41] supporting the evidence-based use of FFR to guide revascularization are conspicuously lacking for CFR. Albeit conceptually different and performed in different operational theaters by different subspecialists (Table 2.2), both methods are useful for gaining insight into the key variable of

Table 2.2 Functional assessment of coronary stenosis severity

	Stress echo lab	Cath lab
Key variable	CFR	FFR
Additive to	Wall motion	Coronary stenosis
Vasodilator	Intravenous	Intracoronary
Normal values	>2.5	1.0
Borderline values	2.0–2.5	0.75–0.80
Abnormal values	<2.0	<0.8
Epicardial stenosis effect	Yes	Yes
Microcirculation effect	Yes	No
Randomized trial available	No	Yes (FAME 1 and 2)
Additional cost	Ø	$1000 US
Additional radiation	Ø	5 milliSievert

physiologic assessment of coronary stenosis in the clinical arena [45]. The other emerging point is that concordance between FFR and CFR is not ideal, i.e., in more than 25 % of patients, FFR and CFR do not point in the same diagnostic direction [45]. Where positive CFR and negative FFR are indicative for microvascular disease, positive FFR but negative CFR is both a pathophysiological and a prognostic challenge. Recently, it has been shown that negative CFR carries excellent prognosis even in the presence of positive FFR [46]. So, a combination of FFR and noninvasive or invasive CFR seems to be the mastermind algorithm in current diagnostic workup of the patient.

At present, FFR is recommended as definitely beneficial when noninvasive stress imaging is contraindicated, discordant, nondiagnostic, or unavailable in stable ischemic heart disease. In these conditions, FFR should be used to assess the functional significance of intermediate coronary stenosis (50–70 %) and more severe stenoses (<90 %) [47].

2.9 Beyond Ischemia and Stenosis: Cardiac Calcification and Plaque Vulnerability

The risk stratification strategies centered on functional stress testing and coronary angiography are practical and effective, yet they recognize a blind spot since clinical complications may depend on plaque composition, not only on plaque size. This blind spot can be at least in part enlightened with an integrated approach also considering cardiac calcification by transthoracic resting echocardiography and identification of the pre-intrusive atherosclerosis and pre-obstructive vulnerable plaque by vascular duplex scan of the carotid artery.

The main purpose of calcium screening is not to identify patients with obstructive coronary artery disease but to detect vessel wall atherosclerosis at a pre-obstructive stage. This information is usually obtained with the Agatston coronary calcification score with CCTA (see Chap. 39) but can also be obtained with a convenient proxy of coronary calcification such as cardiac calcification with baseline echocardiography (Fig. 2.8). A semiquantitative cardiac calcium score index can be derived from a simple assessment of calcification in mitral annulus, aortic root wall, and aortic leaflets and correlates nicely with coronary calcification evaluated with Agatston score and Framingham score, providing additive prognostic information compared to stress echo [48, 49].

A similar assessment of pre-obstructive atherosclerosis is obtained with carotid intima-media assessment, which if increased predicts subsequent events in asymptomatic subjects [50, 51]. Albeit conceptually different and performed in different operational theaters by different subspecialists (Table 2.3), both echo and CCTA are useful for gaining insight into the variable of assessment of inappropriate coronary and cardiovascular calcification and – with intima-media thickness – of prognostically meaningful pre-intrusive atherosclerosis in the clinical arena [52].

Identification of the vulnerable plaque is even more important. Vulnerable plaques are prone to rupture, and their rupture can trigger unfavorable pathology

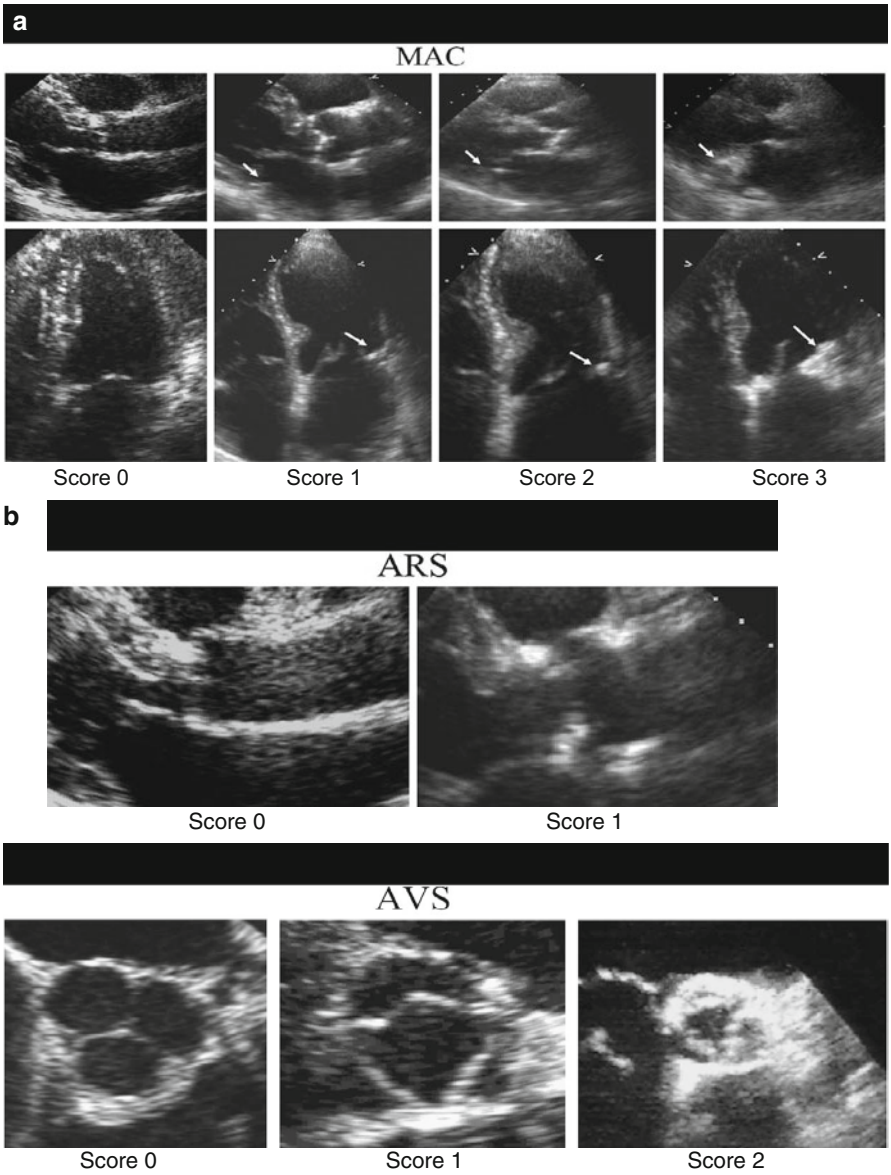

Fig. 2.8 A simple assessment of cardiac calcification through scoring of mitral annulus calcification (*upper panel* **a**, from 0 = no calcium, to 3 = extensive calcification), aortic root (*lower panel* **b**, from 0 = absent, to 1 =, present), and aortic valve leaflets (from 0 = no calcium, to 3 = calcification of all three leaflets) calcification (Modified from Corciu et al. [49]). *MAC* mitral annulus calcification, *ARS* aortic root sclerosis, *AVS* aortic valve sclerosis

events such as distal embolism, thrombosis, and plaque progression mirrored in clinical events such as (in coronary arteries) unstable angina, myocardial infarction and death, and (in carotid arteries) transient ischemic attacks and stroke [53].

Table 2.3 Assessment of inappropriate cardiovascular calcification and pre-obstructive atherosclerosis

	Echocardiography	CCTA
Key variable	Cardiac calcification	Coronary calcification
Prognostically additive to	Wall motion	Coronary stenosis
Measured parameter	Cardiac calcium score index	Coronary Agatston index
Normal values	0	0
Mildly abnormal values	1–3	1–100
Abnormal values	4–6	100–400
Severely abnormal values	>7 (up to 10)	>400
Prognostic value	Initial data	Established data
Additional radiation	Ø	2–3 milliSievert

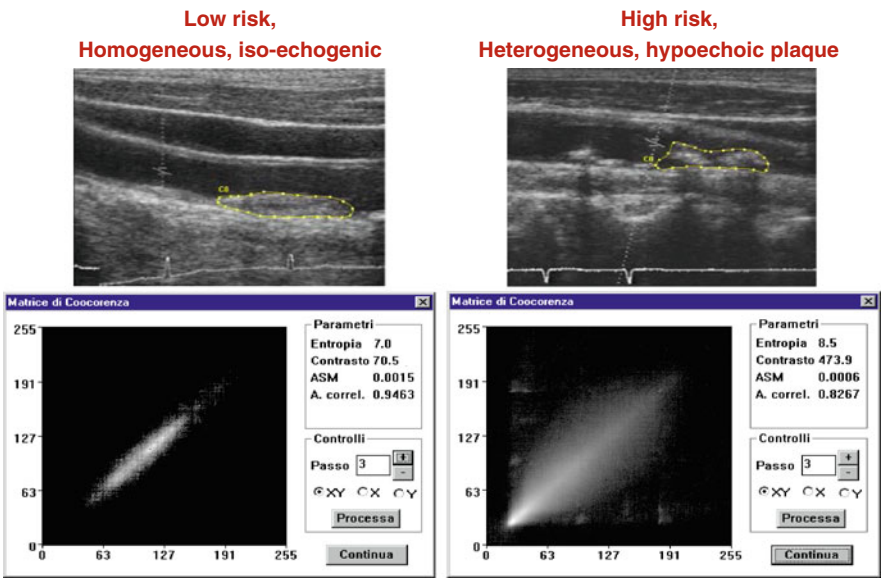

Fig. 2.9 A visual and videodensitometric assessment of carotid plaque morphology. Unstable, soft, lipid-rich plaques are less echogenic and more dishomogeneous than stable, fibrotic plaques. These texture features can also be more objectively described with simple textural analysis with quantitative descriptors of plaque echogenicity such as median gray level or plaque texture such as entropy (*lower panels*). Stable plaques show higher median gray levels and lower entropy values, related to the spatial disorder of the image (Modified from Mazzone et al. [63])

At histology, the vulnerable plaques are rich in lipids and hemorrhages and poor in fibrosis and with thin fibrotic cap and show only spotty calcification and possibly irregular plaque surface border and neovascularization [54]. These histologic features leave ultrasound fingerprints [55–60] and can be recognized by simple visual [61, 62], more objective videodensitometry [63–65] (Fig. 2.9), and quantitative backscatter analysis [66, 67], both noninvasively with duplex scan of the carotid and invasively with virtual histology and radiofrequency-based intracoronary

Table 2.4 Ultrasound texture and morphology as a predictor of plaque instability

	Low risk	High risk
Plaque border profile	Smooth	Irregular
Echo density	Iso-, hyperechoic	Hypo-, anechoic
Plaque luminal border[a]	Regular	Irregular
Plaque neovascularization[a]	Absent	Present
Spotty microcalcification	Rare	Frequent

[a]By contrast-enhanced ultrasound

ultrasound. Whatever the method and wherever the district, the ultrasound appearance of the vulnerable plaque can be distinguished from the low-risk stable plaque and identified as a group at higher risk of subsequent cardiovascular events [68–73].

The carotid unstable plaque is associated with a systemic (not only local) plaque instability, present in different districts (coronary and carotid) and on different sides (both ipsilateral and contralateral to symptomatic side), and is associated with unfavorable events in the follow-up [74, 75]. Hypoechoic or dishomogeneous plaques, with spotty microcalcification and large plaque burden, with plaque neovascularization and surface irregularities by contrast-enhanced ultrasound [76, 77], are more prone to clinical complications than hyperechoic, extensively calcified, homogeneous plaques with limited plaque burden, smooth surface, and absence of neovascularization (Table 2.4). Plaque ultrasound morphology is important, together with plaque geometry, in determining the atherosclerotic prognostic burden in the individual patient. A complex-type plaque coronary morphology at coronary angiography – for any given coronary stenosis – makes the myocardium more susceptible to induced ischemia during SE [78, 79]. With this integrated approach, SE, baseline resting echocardiography for cardiac calcification and carotid scan for intima-media thickness, and plaque geometry and plaque morphology assessment can team up with invasive studies for comprehensive risk stratification of most variables, including those in the blind spot of functional imaging and SE [80].

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