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, and death in ischemic heart disease [1].

E. Picano, *Stress Echocardiography*,

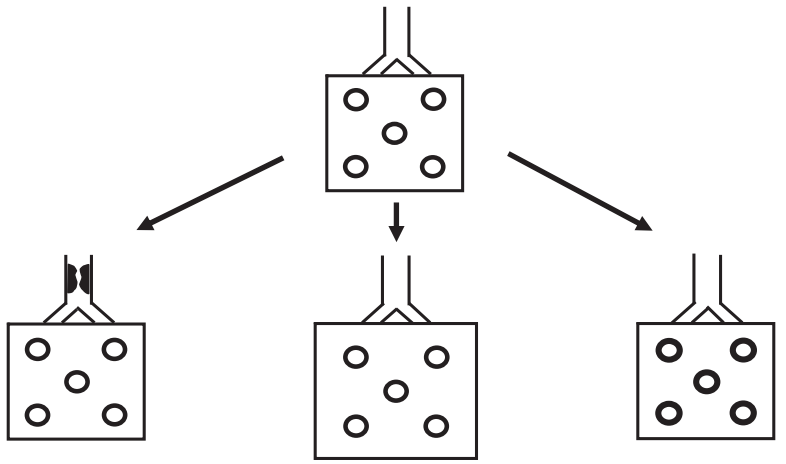

Fig. 2.1 The pathways of ischemia. *Upper panel*: The fundamental anatomical components of the normal heart are shown: epicardial coronary arteries (*parallel lines*), myocardium (*square box*), small vessels (*circles*). *Lower panel*: The three main pathophysiological conditions that may provoke myocardial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

2.3 Fixed Stenosis

The human body incorporates a functional reserve, which 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 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 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.

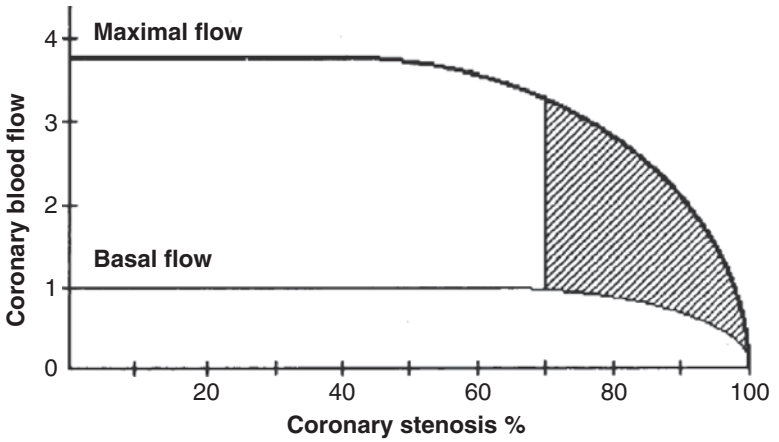

Fig. 2.2 Coronary blood flow curve (*on the ordinate*) for increasing levels of coronary stenosis (*on the abscissa*) experimentally obtained in resting conditions (*lower curve*) and at maximal postischemic vasodilation (*upper curve*). Coronary reserve – i.e., the capacity of the coronary circulation 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 [3])

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

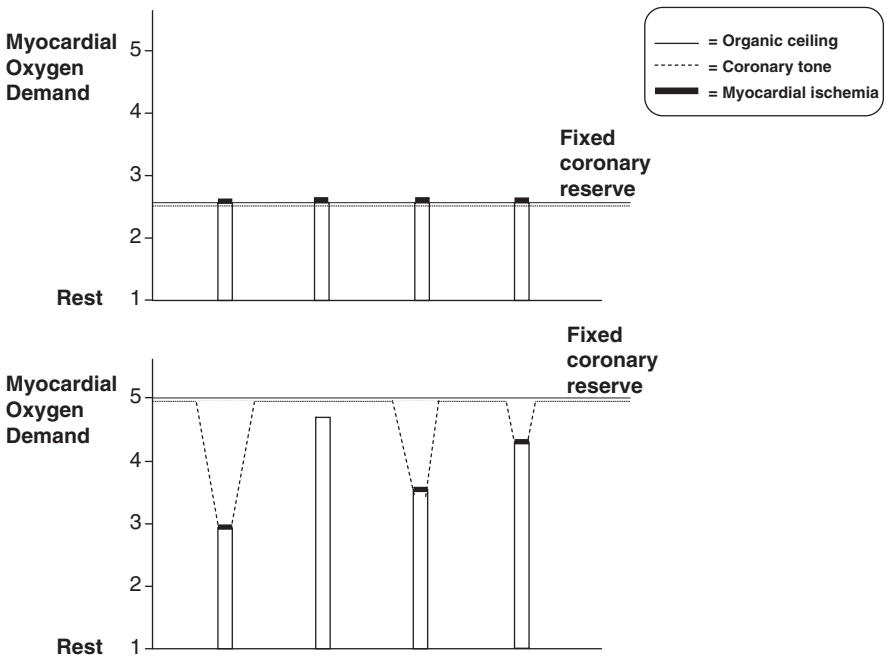

Fig. 2.3 In the presence of a fixed hemodynamically significant stenosis, there is a pathologically reduced "ceiling" of flow reserve (*continuous transverse line*) which induces ischemia when myocardial oxygen demand exceeds a definite threshold (*upper panel*). In the presence of a dynamic stenosis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

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, 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 resistances, 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 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 Diagnostic "Gold Standard": Pure Gold?

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 2.2).

First, coronary stenosis is assessed 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 coronary flow reserve 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

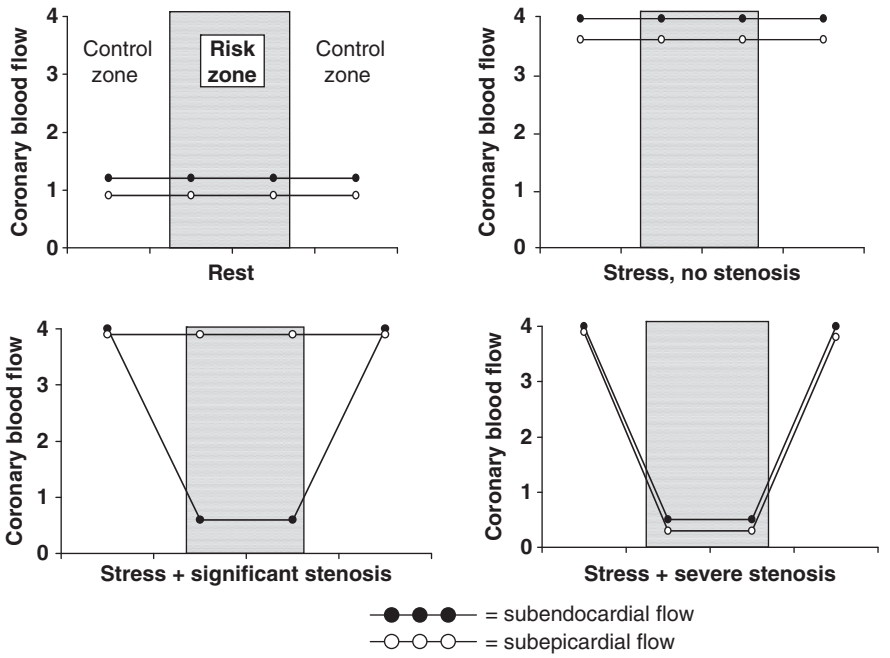

Fig. 2.4 Distribution of flow in the subendocardial and subepicardial layers under different hemodynamic conditions. *Upper left panel*: In resting conditions the subendocardial and subepicardial flows overlap. *Upper right panel*: During stress, the flow increases homogeneously in both layers without 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 [7])

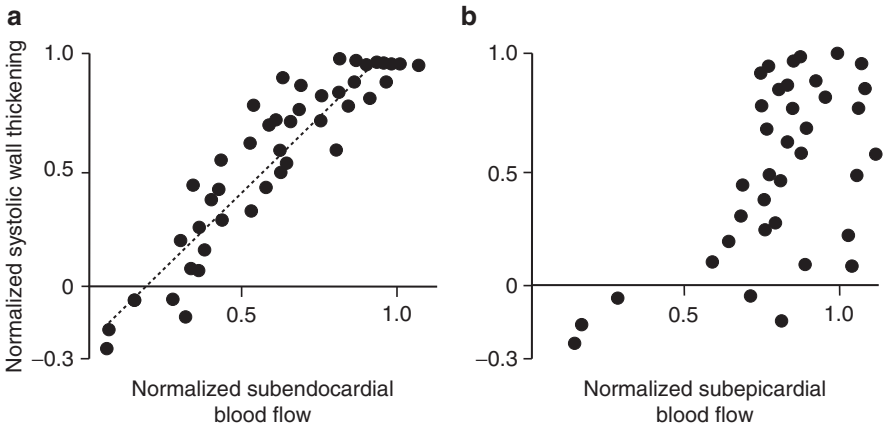

Table 2.1 Standard terminology in diagnostic testing

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

Table 2.2 Limitations of the coronary angiographic gold standard

	Practical	Theoretical
Limited reproducibility % stenosis	++	
% stenosis unrelated to CFR		+++
Underestimation of diffuse disease	++	
Infarct-producing plaques often noncritical		++
Static luminogram	++	
Thrombus, spasm, inflammation, rupture, and embolization unrelated to plaque size		+++

CFR coronary flow reserve

hemodynamic consequences on the coronary reserve; however, the two parameters (anatomical and pathophysiological) can diverge, and the individual values of coronary flow reserve 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 coronary flow reserve (<2.0) than in patients with preserved flow reserve (>2.0). This is true for all forms of stress testing, including exercise electrocardiography [13–17] and, to a greater extent, 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

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 [9])

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 coronary flow reserve 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, 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]. 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 chambers and

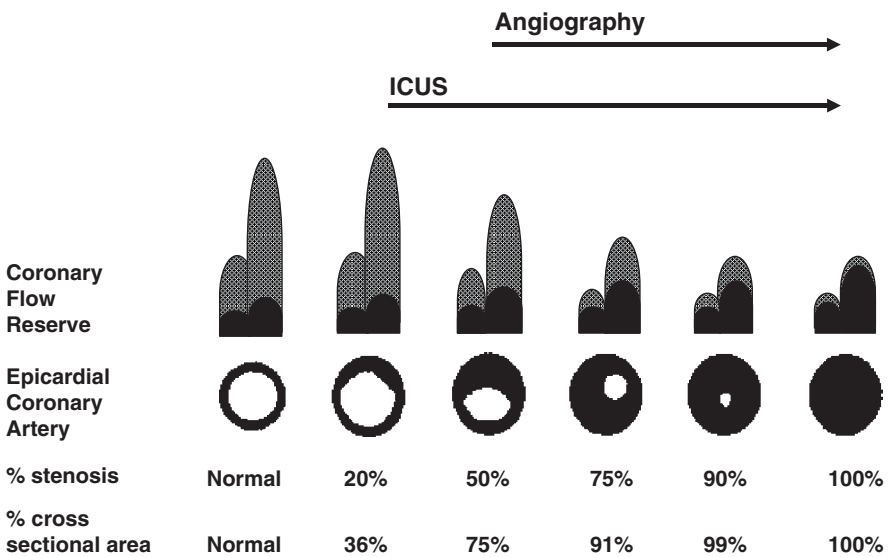

Fig. 2.6 Invasive diagnostic tests for the detection of coronary artery disease. Invasive tests include the luminogram of coronary angiography and the direct visualization of the coronary arterial wall by intracoronary ultrasound (*ICUS*). The percentage of a stenosis can be expressed in angiographic 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 coronary flow reserve 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 [29])

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 conditions, coronary arteries are perfectly smooth, even with intracoronary ultrasound, and the coronary flow reserve 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 coronary flow reserve with angiographically normal coronary arteries) can became a "true-positive" prognostic response in the long run, and patients with reduced coronary flow reserve – 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].

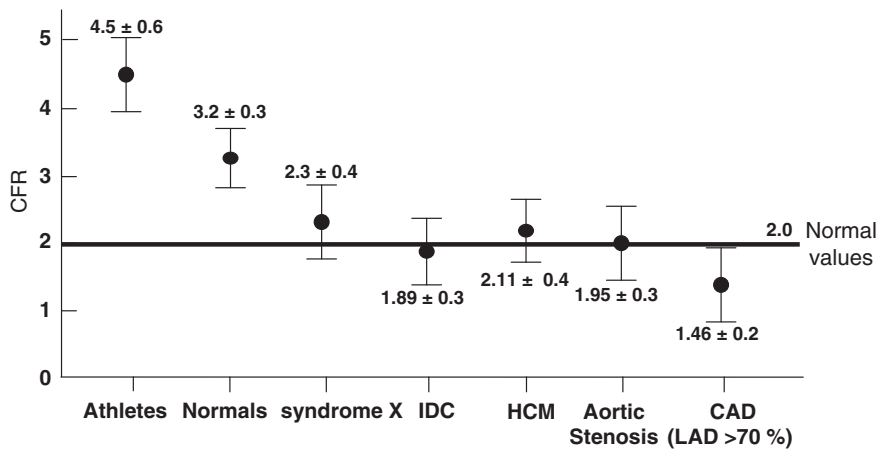

Fig. 2.7 The spectrum of clinical conditions with normal coronary arteries and reduced coronary flow reserve on the left anterior descending artery by transthoracic vasodilatory stress echocardiography. (Redrawn and modified from [33])

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