Rational Basis of Stress Echocardiography

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Stress echocardiography stems from three lines of evidence on three different levels: biochemical, pathophysiological, and clinical. The pathophysiological hallmark of stress echocardiography positivity is myocardial ischemia: when the stress echocardiography study shows abnormalities, myocardial ischemia is present. The presence of regional dysfunction requires ischemia, and – in the words of John Ross Jr. – the very definition of ischemia requires an alteration of myocardial function: "Ischemia is a reduction in myocardial blood flow sufficient to cause a decrease in myocardial contraction" [1]. However, "decrease in myocardial contraction" is not synonymous with "reduction in visually assessed regional systolic thickening," which expresses only one dimension (radial strain) of the complex three-dimensional event of myocardial contraction. This latter also includes circumferential and longitudinal strain, all contributing to changes in ejection fraction and to the pump function. In addition, systolic thickening is evaluated in a subjective and qualitative, not objective and quantitative, way and reflects the average transmural function, without discriminating between the subendocardium (highly vulnerable to ischemia) and subepicardium (more resistant to ischemia) [2]. The clinical world is not the experimental laboratory, stress echocardiography is not equivalent to implanted sonomicrometry, and therefore the fundamental parameter of regional systolic thickening by two-dimensional (2D) echocardiography should be integrated with information derived from clinical presentation, patient specificity, and information provided by other markers of ischemia.

4.1 Biochemical Basis

At rest, about 60 % of the high-energy phosphates produced by cell metabolism are used for development of contractile force, about 15 % for relaxation, 3–5 % for maintenance of electrical activity, and the remaining 20 % for "wear and repair" [3]. The cell's top priority is to repair itself. Therefore, during ischemia the cell minimizes its expenditure of energy on cardiac work and utilizes whatever is left for maintenance of cell integrity. In the normal heart at rest, intracellular calcium is

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sequestered mostly in the sarcoplasmic reticulum, where it cannot be used for myocardial contraction (mediated by the actin–myosin system). Cell membrane excitation and depolarization are followed by a rapid "downhill" (i.e., along the concentration gradient) influx of extracellular calcium, triggering the release of intracellular calcium from sarcoplasmic reticulum; this activates the contraction following the calcium–troponin interaction, which exposes myosin to the binding site of actin. For relaxation to occur, intracellular calcium must be sequestered back "uphill" (i.e., with energy expenditure against a concentration gradient) to the sarcoplasmic reticulum; in this phase, a calcium efflux through the plasma membrane also takes place. When ischemia occurs, the process of contraction and relaxation is slowed by two main intracellular biochemical events: the reduction of high-energy phosphates, due to the blockade of mitochondrial aerobic metabolism, which requires oxygen, and the increased concentration of hydrogen ions, due to the activation of anaerobic glycolysis. Hydrogen ions compete with calcium ions for the troponin activation sites – thereby slowing the actin–myosin interaction. The reduction of intracellular high-energy phosphates in turn reduces the rate of the energy-dependent active reuptake of calcium into the sarcoplasmic reticulum, thus determining an impairment in relaxation [2].

4.2 Physiological Heterogeneity of Myocardial Function

The contraction of the heart is a complex phenomenon involving a deformation (strain) along three coordinates: radial thickening, longitudinal contraction, and circumferential contraction. The fourth coordinate is time. Although myocardial contraction is mostly circumferential, a contraction wave along the axial direction is important because it influences left ventricular efficiency. The mechanical events parallel the apex-to-base direction of electrical activation. By spreading from base to apex during ejection, the peristaltic contraction wave propels the blood toward the left ventricular outflow tracts, at the same time preventing a drift of blood toward the apex. The emptying systolic time increases in a smooth progression from the apical to the basal regions. In addition to this temporal heterogeneity with apex first and base last to contract in healthy conditions [3], the normal adult left ventricle is characterized both morphologically and functionally by a high degree of regional functional nonuniformity [4] (Fig. 4.1).

Myocardial strain is defined as the difference between any end-systolic and end-diastolic dimension divided by the reference end-diastolic dimension and as such is dimensionless and presented as percent values. Positive radial strains represent wall thickening, whereas negative strains represent segment shortening (e.g., circumferential shortening). In the clinical assessment of myocardial function, all three types of strain can be measured, at least in principle: systolic thickening with *M*-mode and 2D echocardiography (by far the most frequently used and the only one adequately validated for clinical applications), longitudinal contraction, and circumferential shortening with 2D speckle tracking (Table 4.1). In addition, regional ejection fraction can now also be measured with real-time 3D echocardiography. The inward motion and deformation (circumferentially and longitudinally) of the endocardium

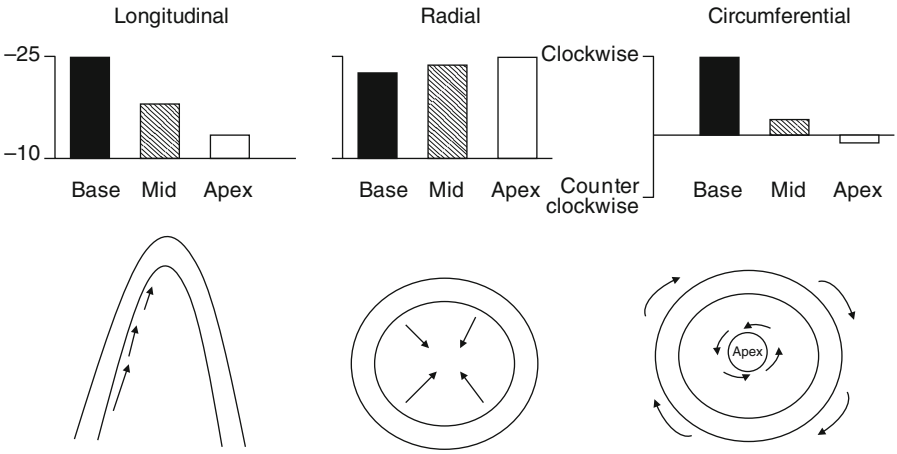

Fig. 4.1 Base-to-apex heterogeneity in radial (*middle panel*), longitudinal (*left panel*), and circumferential (*right panel*) function

Table 4.1 Physiological heterogeneity of myocardial functions

	Transmural gradient	Base to apex	Horizontal gradient	Echocardiography method	Alternative method
% Systolic thickening (radial strain)	+++	++	±	*M*-mode, 2D	MRI
Longitudinal strain	++	+++	±	Speckle tracking	MRI tagging
Circumferential strain	+	+++	±	Speckle tracking	MRI tagging
Regional ejection fraction	+	++	±	Real time (RT3D)	MRI tagging

RT real time

determine changes in intracavitary volume, and endocardial regional ejection fraction can thus be viewed as a composite measure of the local contribution to ejection. The regional ejection fraction increases significantly from base to apex, and remarkably the regions with the highest ejection fraction show the least wall thickening (Fig. 4.2).

There is some degree of horizontal (intersegment) variation of myocardial function, but it is less marked than in the vertical (base-to-apex) and transmural (subendocardium-to-subepicardium) direction. In healthy subjects, radial strain is larger in the free wall compared to the interventricular septum, whereas circumferential strain is larger in the interventricular septum compared to the free wall. Intersegment variability becomes more obvious in pathological conditions, when a global diffuse hypokinesis at visual assessment exhibits a pronounced heterogeneity of regional contraction and synchronicity even in resting conditions (Fig. 4.3).

This gradient is magnified by stress also in healthy normal subjects, suggesting that a "relative" hyperkinesia during stress is a normal variant which should imply

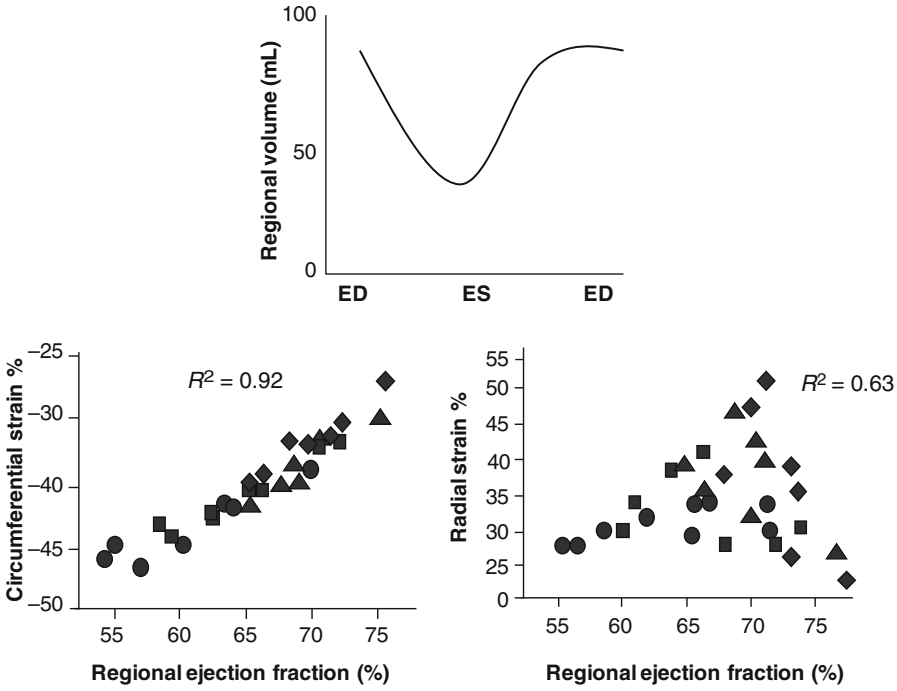

Fig. 4.2 Regional ejection fraction can be obtained with real-time 3D imaging in the echocardiography laboratory (*upper panel*). It is correlated only weakly with % systolic thickening (*lower right panel*) and tightly with circumferential strain (*lower left panel*) (Redrawn and adapted from original MRI tagging data from Bogaert and Rademakers [4])

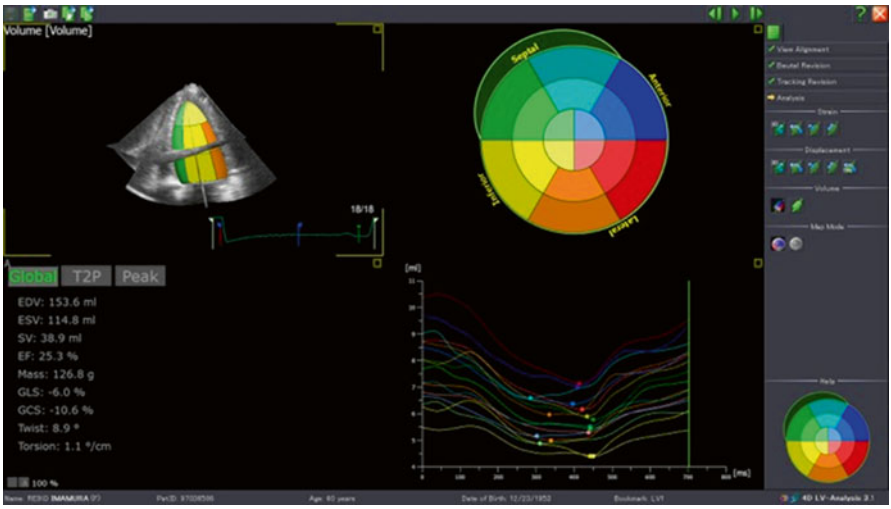

Fig. 4.3 Regional heterogeneity in left ventricular function mirrored by different peak values of regional ejection fraction by real-time 3D echocardiography in a patient with diffuse, global left ventricular dysfunction (ejection fraction = 25 %). Also the timing of contraction shows considerable dyssynchrony in different segments, some with peak in mid-systole and others in late systole

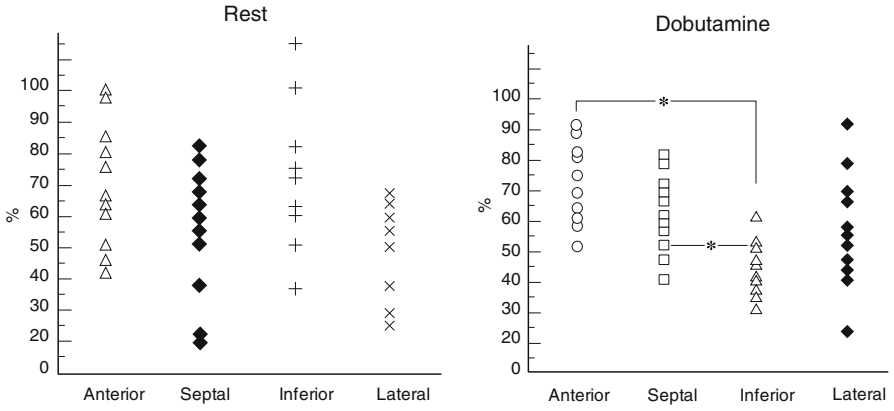

Fig. 4.4 Circumferential heterogeneity in radial strain (% systolic thickening) magnified during stress (*right panel*) in healthy subjects (From Borges et al. [5])

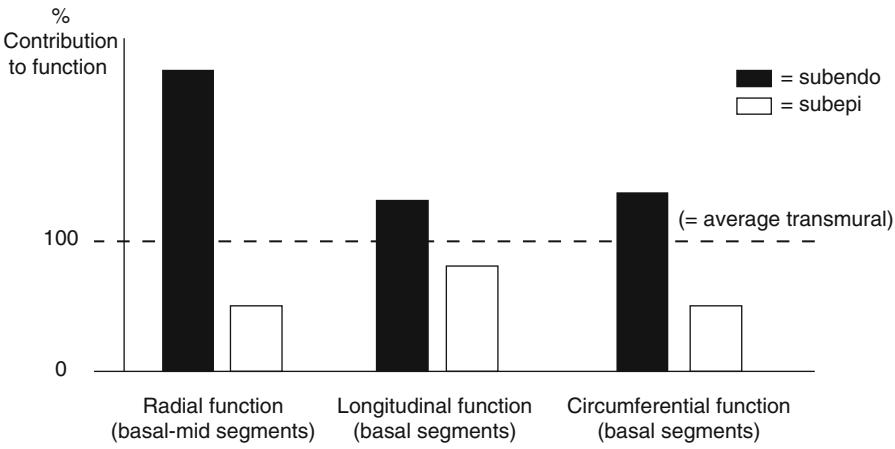

Fig. 4.5 Physiological, transmural heterogeneity determined as % systolic thickening (radial strain, *left panel*), longitudinal strain (*middle panel*), and circumferential strain (*right panel*) (Adapted from [7, 8])

a conservative reading of stress echocardiograms, to avoid an exorbitant number of false-positive responses [5] (Fig. 4.4).

Normal myocardial function is rather heterogeneous at different levels (base to apex) since the relative contribution to ejection increases toward the apex and, within the same segment, at different layers (subendocardium–subepicardium) of the left ventricular walls (Fig. 4.5).

Measurements of intramyocardial thickening show that normally 67 % of thickening occurs in the inner half of the wall [7]. Thus, normally there is only a small contribution of the subepicardium to the overall thickening (Fig. 4.6).

A "functional" gradient, although less significant, also exists at the various levels of the left ventricle, with greater systolic thickening in the apical than in the basal segments [6–9]. This heterogeneity of function is mirrored by perfusion, since

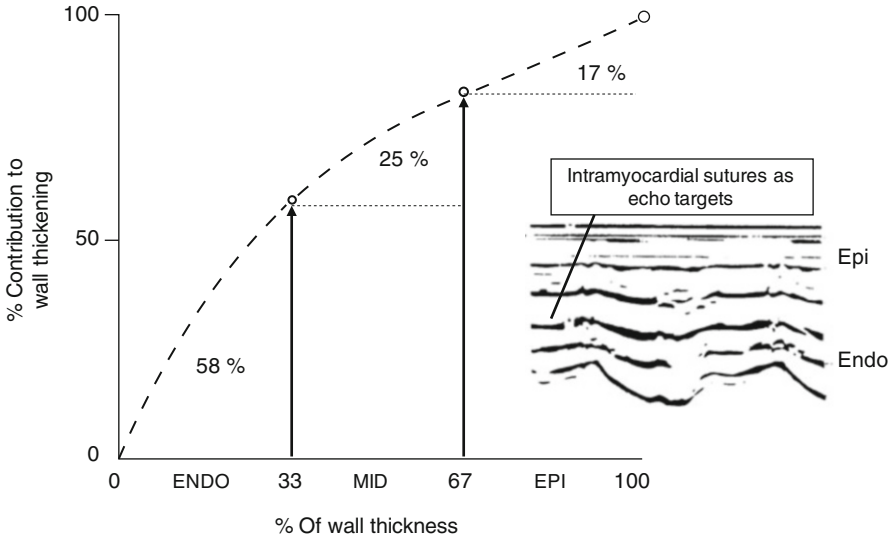

Fig. 4.6 A gradient of thickening (radial function) exists across the myocardial wall, with the inner, middle, and outer thirds of the myocardial wall contributing to 50, 25, and 17 % of total wall thickening, respectively. In the *right part* of the graph, the echocardiographic tracing obtained with an epicardial *M*-mode echocardiographic transducer and a suture inserted in the wall of an open-chest dog and used as an intramural echocardiography target (Adapted from original data from Myers et al. [7])

contractility is a major determinant of myocardial oxygen consumption and there is a close beat-by-beat coupling between myocardial oxygen consumption and coronary blood flow [9]. Thus, coronary flow is greater in the subendocardium than in the subepicardium and greater at the apex than at the base, whereas no significant interregional variations can be observed. Flow and function tend to show a physiological variability not only in space but also over time with minimal, continuous variations in contractility and perfusion. The relationship between regional flow and function holds true not only in physiological states, when by definition there is a perfect coupling between oxygen supply and demand, but also in pathological conditions determining a matched reduction and/or a mismatch between these two parameters.

4.3 Regional Flow–Function Relationship in Myocardial Ischemia

Ischemia may occur either at rest for a progressive coronary stenosis or during stress in the presence of a critical obstruction. A close association between mean transmural blood flow and regional wall thickening can be observed (Fig. 4.7).

Above normal perfusion levels, the functional response to a twofold to fourfold increase in flow is flat [9]. Conversely, when perfusion is below normal values, regional thickening appears to be almost linearly related to flow: in particular, the subendocardial flow determines regional thickening, which is mainly due to the

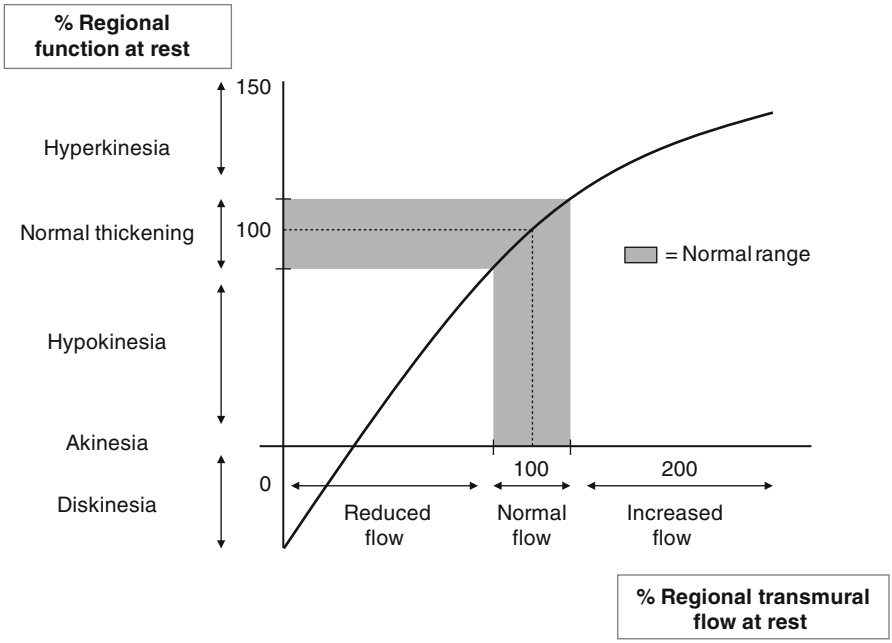

Fig. 4.7 Relationship obtained in anesthetized dogs between transmural flow (measured by microsphere) and regional function (assessed with 2D echocardiography) (Redrawn and modified from Kaul [9])

subendocardial layer. On average, a reduction in subendocardial blood flow of about 20 % produces a 15–20 % decrease in left ventricular wall thickening; a 50 % reduction in subendocardial blood flow decreases regional wall thickening by about 40 %, and when subendocardial blood flow is reduced by 80 %, akinesia occurs. When the flow deficit is extended to the subepicardial layer, dyskinesia occurs [9]. For minimal flow reductions, abnormalities of regional systolic function are subtle and certainly below the threshold of detection by echocardiography. The detection of a regional dysfunction by 2D echocardiography requires a "critical ischemic mass" of at least 20 % of transmural wall thickness and about 5 % of the total myocardial mass [10]. Thus, relatively milder and more localized forms of myocardial ischemia do not leave echocardiographic fingerprints – at least when radial strain and regional systolic thickening or (regional or global) ejection fraction are considered. However, initial forms of contractile dysfunction can more selectively affect longitudinal and circumferential strain, both at baseline [11] and during stress-induced ischemia of mild degree [8].

4.4 Postischemic Recovery of Contractile Function

The postischemic recovery of myocardial function is related to two main variables: the duration of the ischemic attack and the efficacy of postischemic reperfusion. In animals, doubling ischemia time quadruples recovery time. For a given duration and

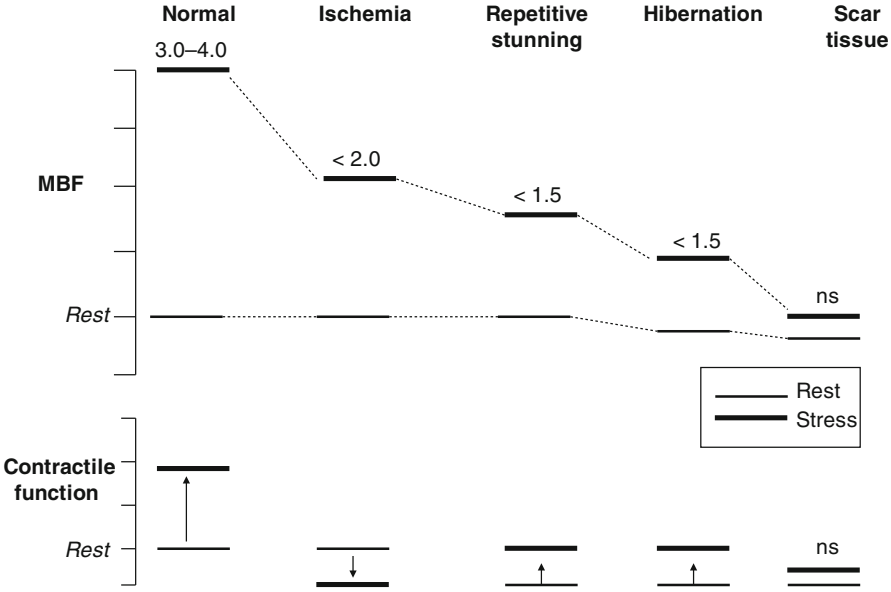

Fig. 4.8 Schematic representation of ischemia, repetitive stunning, hibernation, and scar as points of a spectrum of myocardial dysfunction. In the *upper panel*, myocardial blood flow (*MBF*). In the *lower panel*, the corresponding regional contractile function at baseline (rest) and during stress (Adapted and modified from De Castro and Pandian, Ref. [13])

severity of ischemia, the recovery of contractile function will be faster with a more complete coronary reflow. In the experimental model, the reopening of a coronary artery previously occluded for a few seconds or minutes is followed by a complete reactive hyperemia and prompt recovery of contractile function, transiently even above baseline levels. In man, the resolution of transient transmural ischemia is also accompanied by a short postischemic rebound in the previously ischemic areas [12]. In contrast, a severe coronary stenosis will significantly slow reperfusion and thus the recovery of contractile function (Fig. 4.8).

Thus, the experimental evidence confirms that a slower, at times partial, recovery of regional function may be associated with a longer period of ischemia and/or with markedly diseased coronary vessels. In all these conditions, flow and function vary symmetrically in rest, ischemia, and recovery states. However, there is a "point of no return," beyond which the restoration of flow is unable to restore regional function due to irreversible myocardial cell damage. There is a blurred transition zone between fully reversible ischemia and ischemia lasting more than 20 min and invariably associated with necrotic phenomena. In this border zone, ischemia is too short to cause myocardial necrosis, but long enough to induce a persistent contractile dysfunction (lasting for hours, days, and even weeks) after flow restoration – the so-called myocardial stunning [14]. The stunned myocardium is different from "hibernated" myocardium, where the myocardial perfusion is chronically reduced (for months or years), but remains above the critical threshold indispensable for

keeping the tissue viable (although with depressed performance) [15]. While in the stunned myocardium a metabolic alteration causes an imbalance between the energy supply and work produced, the hibernating myocardial cell adapts itself to a chronically reduced energy supply, and its survival is guaranteed by a reduced or abolished contractile function. This adaptation is incomplete, and degeneration of terminally differentiated myocytes occurs, with loss of contractile proteins and deposition of glycogen granules. Over time, apoptotic cell death eventually occurs with replacement fibrosis and thus progressive loss of potential for contractile function recovery. The ventricular dysfunction persists until flow is restored, but if revascularization is delayed by several months, left ventricular function no longer improves [15]. Unlike the infarcted myocardium, the postischemic viable tissue retains a contractile reserve. The necrotic myocardium is unresponsive to any inotropic stimulus, whereas the viable myocardium typically responds with a transient increase in regional function which predicts the functional recovery [16].

4.5 Determinants of Regional Dysfunction

In chronic infarction the transmural extent of myocardial damage is correlated to the severity of the regional dyssynergy. A necrosis confined to less than 20 % of myocardial thickness is associated with only mild hypokinesia [17]. Dyskinesia is associated with a more transmural extent of necrosis, involving at least 30–40 % of myocardial thickness in the vertical (endocardium–epicardium) direction. These experimental data have a clinical correlate: in non-Q myocardial infarction, stable changes of the ST–T segment, with prolonged chest pain and an increase of necrosis enzymes, can be accompanied in 20 % of cases by a perfectly normal echocardiogram [18].

Ischemia, infarction, stunning, and hibernation are not the only possible causes of regional asynergy [19]. A series of other factors, both intrinsic and extrinsic to the ischemic region, can mimic or mask the signs of ischemia on the myocardial wall or disrupt the linearity of the regional flow–function relationship. Fibrosis of nonischemic origin obviously induces a stable regional dysfunction, for instance, in dilated cardiomyopathy. Septal wall motion abnormalities – usually with normal systolic thickening – can be observed in conditions associated with abnormal ventricular depolarization, such as left bundle branch block, Wolff–Parkinson–White type B syndrome, and right ventricular paced rhythm [20] (Fig. 4.9).

Following onset of electrical depolarization, there is a downward motion of the interventricular septum or early systolic downward dip or beaking. The abnormal early systolic septal motion with left bundle branch block [6] and with ventricular pacing [21] is secondary to an early rise in pressure in the right ventricle. The abnormal depolarization produces contraction of the right ventricular chamber prior to the left ventricular chamber, thus producing an earlier rise in right ventricular pressure. This differential in pressure then produces the abnormal septal motion. The download displacement is reversed as soon as the left ventricle begins to contract and raises the left ventricular pressure. Almost all patients with left bundle

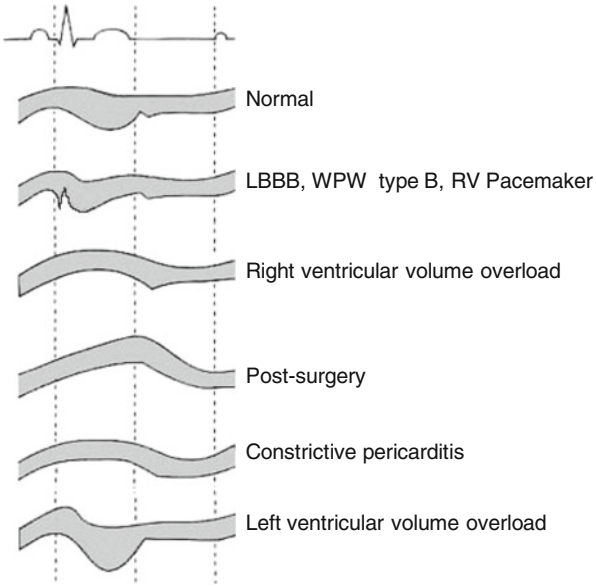

Fig. 4.9 Different types of nonischemic septal wall motion changes. Abnormal (paradoxical) septal motion can be found in a variety of conditions, including (*from top to bottom*) abnormal electrical activation (left bundle branch block, Wolff–Parkinson–White type B, paced right ventricular rhythm), right ventricular volume overload, and/or elevated right ventricular end-diastolic pressure, postoperative status. A septal "bounce" is consistent with constriction. On the other hand, left ventricular volume overload may cause vigorous, supernormal septal motion (Adapted and modified from De Castro and Pandian, Ref. [13])

branch block and right ventricular paced rhythm have early beaking of the interventricular septum, but septal motion is paradoxical in only some of them. In left bundle branch block, the paradoxical wall motion is more frequent with a markedly abnormal activation sequence (QRS >150 ms) and/or septal fibrosis (see also Chap. 28) [22]. In right ventricular pacing, a paradoxical septal motion is more frequent with pacing from right ventricular outflow or right ventricular inflow [22, 23] (see also Chap. 15). Other nonischemic causes of altered septal motion include right ventricular volume overload and/or elevated right ventricular end-diastolic pressure and postoperative status [17]. A septal "bounce" is consistent with constriction [20]. The regional function can be modulated by factors extrinsic to the wall. In left ventricular volume overload, septal motion is exaggerated (Fig. 4.9) and might mask signs of ischemic dysfunction. Two potentially important causes of "normal" wall motion following acute myocardial infarction are the ventricular septal rupture and acute mitral insufficiency: the hemodynamic unloading of the left ventricle tends to lessen the regional abnormality induced by ischemia or infarction. The increase in heart rate and systolic blood pressure can reduce regional systolic thickening independently of ischemia [24, 25]. At high heart rate and high blood pressure values, regional function may also decrease in normal healthy subjects [13].

Table 4.2 Coronary and noncoronary causes of regional dysfunction

Coronary	Noncoronary
Ischemia	Myocardial fibrosis
Infarction	Systolic blood pressure and heart rate increase
Stunning	Electrical activation (LBBB, WPW, RV pacing)
Hibernation	Right ventricular overload, cardiac surgery

LBBB left bundle branch block, *RV* right ventricular, *WPW* Wolff–Parkinson–White

Finally, during acute ischemia, the extent of mechanical alterations exceeds that of metabolic or flow abnormalities. In fact, there is a border zone where the muscle is normally perfused but shows reduced thickening, representing the continuity between ischemic and hypercontractile myocardium. The phenomenon of adjacent dysfunction is spatially limited to the regions immediately close to the ischemic area and seems to be due to a purely passive mechanism (tethering) by which the ischemic region acts as a parallel resistance, limiting the function of the contiguous myocardium (Table 4.2).

4.6 Global Left Ventricular Function in the Stress-Echo Lab

The description of global left ventricular function with a number is usually obtained in the daily routine through gross proxies such as ejection fraction and wall motion score index (see Chap. 7, Table 7.2). Left ventricular ejection fraction is universally used to identify disease, titrate its severity, establish prognosis, and guide therapy, since based on cut-off values for ejection fraction, we recommend valve operations and device implantation. There is one problem: the ejection fraction does not tell the whole story on left ventricular function. This is due not only to practical limitations, such as occasionally poor image quality (more frequently observed with end-diastolic than end-systolic frames) and technical limitations due to geometric assumptions and limited reproducibility. Ejection fraction has some inherent conceptual problems which limit its value as a guide in clinical decision-making, due to its dependence not only on contractility but also on afterload, preload, heart rate, and synchronicity (Table 4.3). All these extra-contractility variables change substantially, and unpredictably, during stress. Ejection fraction can increase, although contractility falls, due to development of massive mitral insufficiency decreasing afterload during stress, or conversely it may paradoxically decrease although true contractility rises with a marked hypertensive response determining a disproportionate increase in afterload. Increase in heart rate can also reduce ejection fraction due to a decline in left ventricular filling occurring with small and stiff ventricles. Increase in dyssynchrony during stress (for instance, with appearance of reversible left bundle branch block) can reduce ejection fraction, simply because the septum and the lateral wall reach the maximum inward and outward motion at different times. Of these many factors, the most important is afterload, i.e., the resistance against which the left ventricle contracts. It corresponds to the load lifted in a

Table 4.3 Indices of global left ventricular function with conventional ultrasound

Ejection fraction	Pressure–volume relationship
Afterload dependence yes	No
Preload dependence yes	No
Raw echo data EDV, ESV	ESV
Use established	Investigational

EDV end-diastolic volume, *ESV* end-systolic volume of the left ventricle

training center, if the muscle strength is left ventricular contractility. Ejection fraction will estimate your strength from the muscle contraction measured by an observer blinded to the weight of the lift. However, the true strength of an athlete is different when he lifts a light or a heavy weight. If the external observer wants to really establish the true muscle strength, the weight lifted should also be considered.

However, it is possible to obtain a more rigorous (yet still appealingly simple) assessment of global left ventricular function through the dynamic (rest–stress) evaluation of the simplified pressure–volume relationship (PVR) [26], which provides a preload and afterload independent assessment of left ventricular contractility [27] usually performed in the catheterization laboratory with the attending risks of invasivity, contrast injection, and radiation exposure [28]. In the cath lab, the stress is pacing, the pressure is obtained by a catheter in the aortic root, and the volumes are derived from a conductance catheter placed in the left ventricle. In the stress-echo lab, the methodological scenario is dramatically simplified with no substantial loss in accuracy: the stress can be the one currently used for diagnostic purposes (exercise, dobutamine, dipyridamole, or noninvasive pacing), the end-systolic volume is obtained with 2D (or, better, real-time 3-dimensional) imaging, and the pressure is from noninvasively measured systolic arterial pressure (by tonometry or cuff sphygmomanometry) through a standardized correction factor (0.9 times systolic blood pressure) [29]. The pressure–volume ratio is measured at baseline and again at intermediate stage and peak stress (Fig. 4.10).

From a clinical decision-making viewpoint, PVR falls into three broad levels of clinical importance: normal upsloping (with stress values two times or more higher than resting values, meaning that during stress progressively higher systolic pressures are developed with smaller end-systolic volumes), abnormal biphasic (with early rise during stress followed by return toward baseline for higher levels of stress), and markedly abnormal flat response (with fixed blood pressure and volume response during stress). The expected normal increase in PVR is higher for stresses increasing myocardial oxygen demand through a substantial contractility increase such as exercise [29, 31, 32] and dobutamine [33–36] but is present – although to a lower extent – also for pacing [37] and vasodilators [38, 39]. In patients with negative stress echo by conventional wall motion criteria, a lower increase in PVR is associated with a worse prognosis, with better prognostic stratification capability than changes in ejection fraction [30, 33]. Although the clinical and scientific impact of stress echo is based, for many good reasons, upon the merits of regional wall

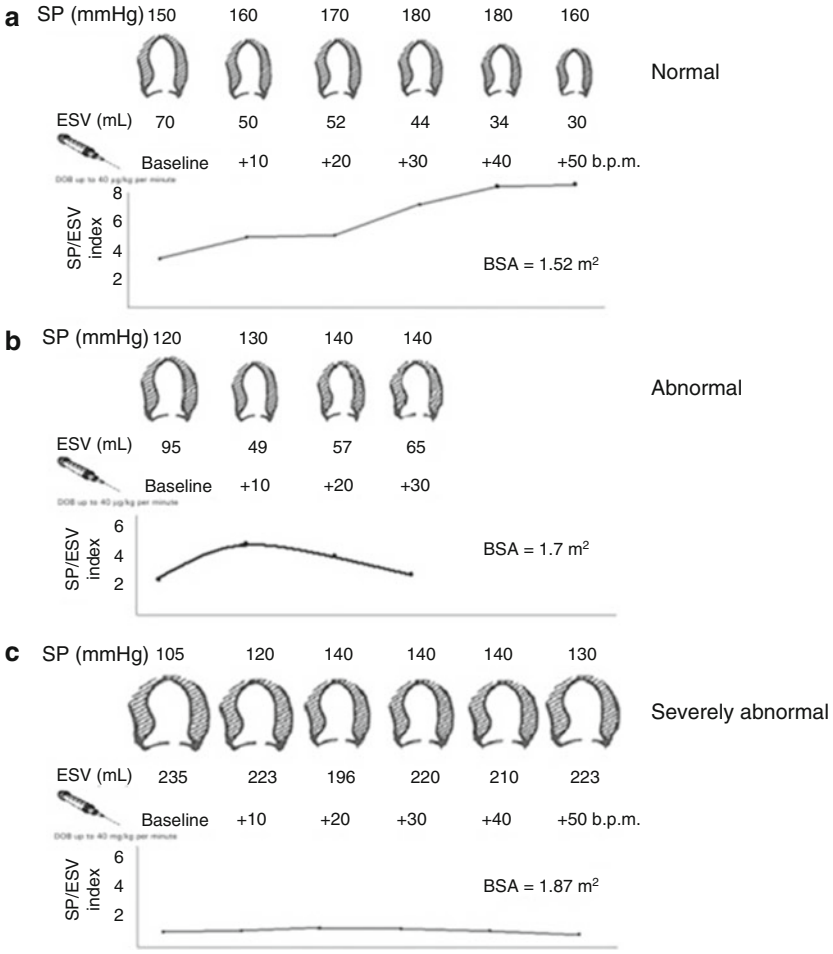

Fig. 4.10 Methodology of the PVR assessment in the stress-echo lab with a normal (*upper panel*), abnormal (*middle panel*), and severely abnormal (*lower panel*) response (Adapted and modified from Bombardini [30]). The end-systolic volume is reduced at peak stress in normal, but dilated in markedly abnormal responses. The systolic arterial pressure (SP) rises in normal and falls in markedly abnormal responses

motion abnormalities over insensitive global indices of left ventricular function such as ejection fraction, the appealingly simple PVR approach stirred new interest in the information present in the entire left ventricle, which is absent in regional function. Global contractility assessment through PVR may be clinically useful for identifying patients with suboptimal prognosis in spite of negative stress echo by wall motion criteria in patients with both very early and very advanced stages of disease. In fact, initial cardiomyopathy (due to diabetes or hypertension or cardiotoxic chemotherapy in oncology patients) can be associated with normal resting and

stress regional left ventricular function, yet with an abnormal contractile reserve during stress [30]. At the opposite end of the disease spectrum, patients with severe resting left ventricular dysfunction and no change in segmental wall motion score (fixed response at viability testing) can still have a contractile reserve mirrored by the increase in PVR during stress, which portends a better long-term prognosis [30].

4.7 Clinical Guidelines

Wall motion and regional thickening abnormalities are at the basis of cardiac stress testing with SE and stress CMR. Both techniques can also apply – in the same setting – simultaneous assessment of perfusion and coronary flow reserve. The ability of regional systolic dysfunction to detect the presence, site, and extent of ischemia obviously cleared the way to extensive clinical applications of stress echocardiography for the diagnosis and risk stratification of coronary artery disease [40, 41]. In the near future, the challenge ahead will be to implement – with the help of advanced technologies such as speckle tracking and real-time 3-dimensional echocardiography [42] – a more quantitative assessment of regional and global cardiac function during stress, with focus on regional longitudinal function and global left ventricular contractility reserve with dynamic assessment of PVR.

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