Echocardiographic Signs of Ischemia

6

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The response of left ventricular function to ischemia is monotonous and independent of the stress employed [1]. The same echocardiographic signs can be found in transient ischemia and acute infarction. The difference lies in the time sequence, and from an echocardiographic viewpoint, myocardial ischemia is a "reversible" myocardial infarction. The cardinal sign of ischemia is the transient, regional wall motion abnormality – the cornerstone of diagnosis. There are other ancillary signs of severity which may occasionally help in disease severity stratification, such as left ventricular cavity dilation, acute severe mitral insufficiency, fall of stroke volume, and the appearance of ultrasound B-lines in the chest. In cutting-edge stress echocardiography environments, today wall motion analysis can be coupled during vasodilator stress with assessment of coronary flow reserve – further expanding our diagnostic and prognostic information during stress echocardiography.

Contrast myocardial perfusion imaging, although technically more complicated and requiring the injection of contrast media, is also potentially clinically useful for diagnosis and prognosis, but to date, its use has remained mostly confined to research (Table 6.1).

6.1 The Main Sign of Ischemia: Regional Wall Motion Abnormalities

Normal myocardium shows systolic thickening and endocardial movement toward the center of the cavity. The hyperkinesia indicates an increase in normal movement and thickening (Table 6.2).

The hallmark of transient myocardial ischemia is regional asynergy (or dyssynergy) in its three degrees: hypokinesia (decreased movement and systolic thickening), akinesia (absence of movement and systolic thickening), and dyskinesia (paradoxical outward movement and possible systolic thinning). Obviously, this description is arbitrarily focused on three points of a continuous spectrum of mechanical modifications induced by ischemia. From a clinical point of view, the

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Table 6.1 Signs of ischemia

	Simplicity	Usefulness	Meaning
Regional wall motion	++	+++	Diagnosis/prognosis
Ancillary signs:			
LV cavity dilation	+++	±	Prognosis
Severe MI			
B-lines			
PASP increase			
CFR	+	++	Prognosis/diagnosis
Contrast myocardial perfusion	±	++	Diagnosis/prognosis

CFR coronary flow reserve, *LV* left ventricular, *MI* mitral insufficiency, *PASP* pulmonary artery systolic pressure

Table 6.2 Regional wall function

	Systolic thickening	Endocardial motion
Hyperkinesis	Increased	Increased
Normokinesis	30–80 (%)	5–10 mm
Hypokinesis	Reduced	Reduced (< 5 mm)
Akinesis	Abolished	Abolished (< 2 mm)
Dyskinesis	Systolic thinning	Outward systolic movement

reliability of hypokinesia is reduced because of a greater intra- and interobserver variability. In contrast, akinesia and dyskinesia reflect more marked modifications of regional mechanics with smaller interobserver discordance. From a pathophysiological viewpoint, the severity of dyssynergy is correlated to the severity and transmural extension of the flow deficit [2]. Virtually all approaches and all projections can be utilized to document regional dyssynergy. From each projection, an M-mode line of view can help document the asynergy, thanks to the better axial resolution and the easier quantification of the time-motion tracings when compared with the B-mode images. The M-mode tracing must be perpendicular to the ischemic region and geometrically controlled from the bidimensional image. The evaluation of a segmentary dyssynergy is easier in a ventricle with normal baseline function than in a ventricle with a resting asynergy. In the latter case, the stress can induce a homozonal ischemia in the infarcted area: for instance, a hypokinetic zone becomes akinetic. The stress-induced worsening of a baseline dysfunction (so-called homozonal ischemia) indicates a residual critical stenosis in the infarct-related coronary artery and the presence of jeopardized myocardium in the infarcted area. Homozonal residual ischemia may also involve a segment adjacent to the necrotic area but belonging to the distribution territory of the same coronary artery. In contrast, heterozonal ischemia develops in an area remote from the necrotic segment and supplied by a different coronary artery. Heterozonal ischemia is very specific for multivessel coronary disease. The reduced regional systolic thickening is theoretically more sensitive and specific than wall motion [2]. In fact, the latter – unlike the thickening – can remain unmodified during ischemia due to a passive movement transmitted by neighboring regions where perfusion and contraction are normal.

In practice, regional movement and systolic thickening tend to be symmetrically affected with the exception of a few pathological situations (i.e., postsurgical septum after bypass intervention, left bundle branch block, or right ventricular pacing) in which the two parameters may dissociate, with alterations of movement and normal thickening. In these cases, it is essential to evaluate only the systolic thickening both in resting conditions and during stress.

6.2 Stress Echo in Four Equations

All stress echocardiographic diagnoses can be easily summarized in four equations centered on regional wall function and describing the fundamental response patterns: normal, ischemic, viable, and necrotic (Table 6.3). The possible mechanical patterns are schematically shown in Fig. 6.1 along with their myocardial and coronary correlates.

The corresponding stress echocardiography patterns are displayed in Fig. 6.2.

In the normal response, a segment is normokinetic at rest and normal–hyperkinetic during stress. In the ischemic response, the function of a segment worsens during stress from normokinesis to dyssynergy. In the viable response, a segment with resting dysfunction improves during stress. In the necrotic response, a segment with resting dysfunction remains fixed during stress. A resting akinesia that becomes dyskinesia during stress reflects a purely passive, mechanical phenomenon of increased intraventricular pressure developed by normally contracting walls and should not be considered a true active ischemia [3]. It is conceptually similar to the increase in ST-segment elevation during exercise in patients with resting Q waves.

In the jeopardized pattern, a segment with resting hypokinesis becomes akinetic or dyskinetic during stress. A viable response at low dose can be followed by an ischemic response at high dose; the "biphasic" response is suggestive of viability and ischemia, with jeopardized myocardium fed by a critically stenosed coronary artery [4].

6.3 False-Negative Results

A stress echocardiography examination can be normal in the presence of angiographically assessed coronary artery disease (Table 6.4). This happens more frequently with submaximal stresses which do not test the coronary circulation efficiently. With maximal stress, a false-negative response is found more frequently

Table 6.3 Stress echocardiography in four equations

Rest	+	Stress	=	Diagnosis
Normokinesis	+	Normal–hyperkinesis	=	Normal
Normokinesis	+	Hypokinesis, akinesis, dyskinesis	=	Ischemia
Akinesis	+	Hypokinesis, normokinesis	=	Viable
Akinesis, dyskinesis	+	Akinesis, dyskinesis	=	Necrosis

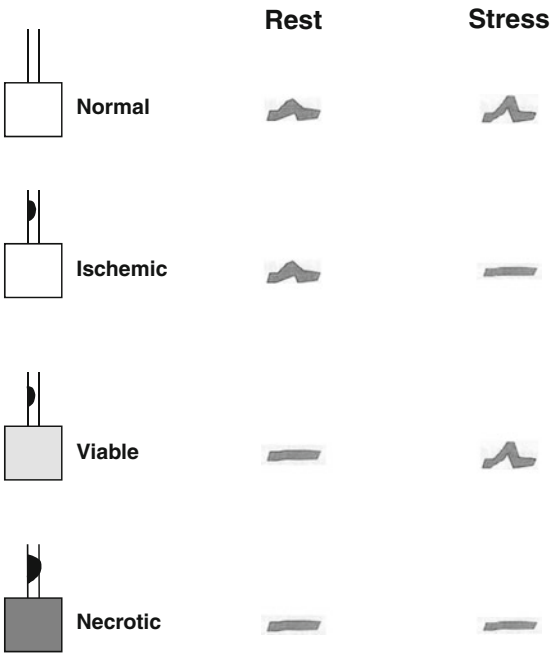

Fig. 6.1 Stress echographic patterns of normal (*upper row*), ischemic (*second row*), viable (*third row*), and necrotic (*fourth row*) responses are schematically represented. On the *left side*, the corresponding schemes of the coronary artery (*parallel lines*) and the myocardium (*box*) are shown. A normal myocardium is represented as a *white box*, a necrotic myocardium as a *black box*, and a viable myocardium as a *gray box*. In a normal segment fed by a normal coronary artery, the segment is normokinetic at rest and normal–hyperkinetic during stress (*upper row*). In a normal myocardium fed by a critically stenosed coronary artery, the segment is normokinetic at rest and hypokinetic, akinetic, or dyskinetic during stress (*second row*). A viable segment (*third row*) is akinetic at rest and normal during stress. A necrotic segment shows a fixed wall motion abnormality at rest and during stress (*lower row*)

in the presence of less extensive (single-vessel disease) or less severe (50–75 % stenosis) coronary disease and especially on the left circumflex coronary artery [5]. Not all coronary stenoses were created equal and – when a maximal stress is administered – those with a negative stress echocardiography response are less severe from the anatomic [6], functional [7], and prognostic [8] points of view. Antianginal therapy lowers the sensitivity of exercise echocardiography as it does with vasodilator stresses [9, 10]. Dobutamine stress results are much less affected by calcium-channel blockers and nitrate therapy [11, 12]. In some cases, true ischemia occurs but may go undetected by stress echocardiography, especially in less well-imaged segments, such as the inferior wall, because of the inherent limitations of subjective analysis and lack of quantitative criteria. In these cases, cine-magnetic resonance imaging (MRI) documents a true impairment in regional systolic thickening [13]. Contrast echocardiography, applied to achieve better wall motion assessment alone, or even more when taking advantage of myocardial perfusion imaging, increases the

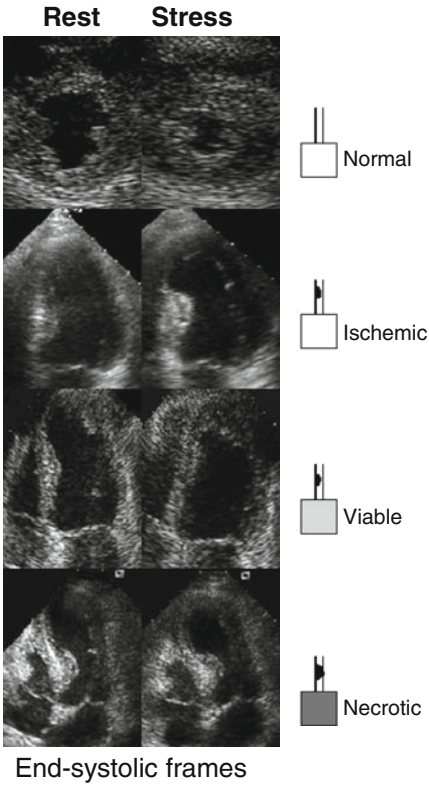

Fig. 6.2 Echocardiographic examples of normal (*upper row*), ischemic (*second row*), viable (*third row*), and necrotic (*fourth row*) responses. On the *left side*, the end-systolic frames of a rest (*left part*) and a stress (*right part*) study are shown. In a viable myocardium with resting dysfunction and fed by a coronary artery with noncritical coronary stenosis, the segment is hypokinetic or akinetic at rest and normokinetic during stress (*third row*). Necrotic tissue shows unchanged function throughout the test, regardless of the underlying anatomical condition of the infarct-related vessel (*fourth row*)

Table 6.4 Sources of false-negative results

1. Submaximal stress
2. Limited (single-vessel) coronary artery disease
3. Mild (50–75 %) coronary artery disease
4. Left circumflex coronary artery disease
5. Patients studied under anti-ischemic therapy
6. Inadequate imaging/inadequate reading

sensitivity for the diagnosis of coronary stenosis, at lower cost and logistic complexity than MRI [14–16].

6.4 False-Positive Results

A transient alteration of regional function represents a very specific sign of myocardial ischemia. Nevertheless, false-positive results in stress echocardiography do exist and occur with (Table 6.5) or without (Table 6.6) true induced ischemia. Even with a nonsignificant stenosis at coronary angiography, a stress test for coronary artery disease can induce true ischemia and asynergy by triggering a coronary

Table 6.5 Sources of false-positive results (with true ischemia)

1. Spasm on a nonsignificant fixed stenosis
2. Inadequate angiographic imaging of a fixed, significant stenosis
3. Severe reduction in flow reserve with mild, nonsignificant stenosis
4. Occult, or unrecognized, cardiomyopathy
5. Hemodynamic changes (excessive increase in systolic blood pressure and/or heart rate)

Table 6.6 Sources of false-positive results (without true ischemia)

1. Human error
2. Heterogeneity of contraction
3. Artifactual asynergies
4. Altered electrical activation (intermittent LBBB)

LBBB Left bundle branch block

vasospasm in susceptible patients. Stress-induced coronary vasospasm has been described with exercise [17], dobutamine [18, 19] (Fig. 6.3), or dipyridamole (more frequently during or following aminophylline) [20].

Coronary spasm is easily recognized when it is associated with transient ST-segment elevation during stress, but frequently it also occurs with ST-segment depression or even with no obvious changes on the ECG. True ischemia can also be found in patients with an angiographic stenosis below the "magic" 50 % but with a physiologically important reduction in flow reserve. In this case, the regional dysfunction during stress echocardiography is a "false-positive" vs the angiographic standard but a "true positive" vs a more accurate descriptor of anatomy such as intracoronary ultrasound [21]. True stress-induced ischemia may occur in the presence of occult cardiomyopathy [22]. The incipient muscle disease may not be overt at rest, but a chronotropic and afterload challenge associated with stress can unmask a true regional dysfunction – destined to progress over time to frank cardiomyopathy. An extreme reduction in coronary flow reserve usually associated with left ventricular hypertrophy [23, 24] may also provoke stress-induced ischemia. As described in Chap. 30, microvascular angina typically occurs with chest pain, ST-segment depression, and perfusion abnormalities without wall motion change [25]. However, in extreme left ventricular hypertrophy and especially in aortic stenosis, in which there is a critical contribution of increased end-systolic wall stress of the left ventricle, true extensive subendocardial hypoperfusion can develop [26] with real wall motion abnormalities [24]. Finally, an excessive systolic blood pressure rise during exercise may increase disproportionately the afterload determining a wall motion abnormality [27] – often severe and in multiple regions – in the left ventricle (Fig. 6.4).

Stress-induced high heart rate [28] and high blood pressure [29] may reduce regional systolic thickening in normal subjects as well. False-positive results may occur in the absence of a true ischemic asynergy, due to a mistake in the acquisition and/or interpretation and/or analysis. Human error determining a false-positive

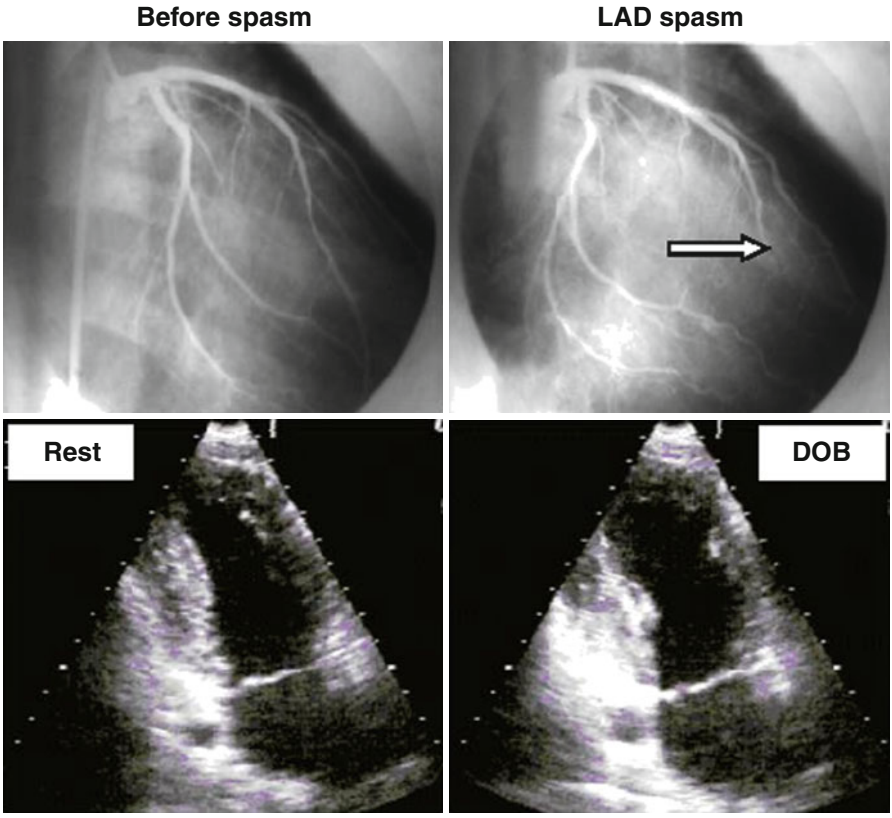

Fig. 6.3 Normal coronary angiogram (*left upper panel*), spontaneous spasm of the left anterior descending coronary artery of the same patient (*right upper panel, indicated by arrow*), and end-systolic frames of the patient in two-chamber view at rest (*left lower panel*) and at peak stress (*right lower panel*) with clear akinesia of the apex (Modified from Varga et al. [19])

result is more frequent with aggressive reading criteria (for instance, lack of hyperkinesia) and with stressors polluting image quality and determining marked increase in heart rate and contractility, which inflate the number of indeterminate or ambiguous results. In fact, a relative lack of hyperkinesis, or even a true hypokinesia, can be a part of the physiological response by a completely normal ventricle to an inotropic stress [30, 31]. False-positive results and angiographically defined stenosis are also more frequently found when using contrast myocardial perfusion imaging, due to its inherent ability to detect minor reductions in the expected normal increase in myocardial blood flow after a given stressor. In fact, these reductions are also seen in microvascular disease, initial cardiomyopathy, and several other conditions, independently from the presence of flow-limiting epicardial coronary artery disease [32].

Last but not least, no left ventricle can be called free of artifactual asynergies. Spurious off-axis projections can create artifactual asynergies – more frequent in basal and inferoposterior regions.

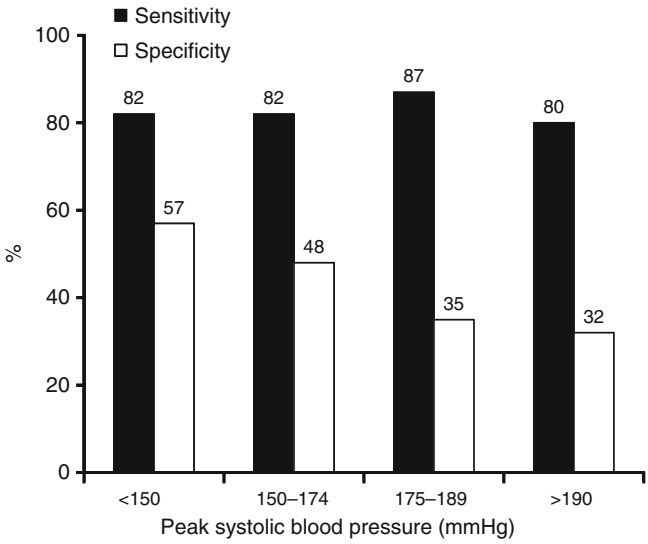

Fig. 6.4 Sensitivity (*empty bars*) and specificity (*full bars*) of exercise echocardiography according to peak systolic blood pressure response during exercise (Modified from Ha et al. [27])

6.5 The True Meaning of "False" Stress Echo Results

Even the best laboratory will have a "physiological" percentage of false-positive and false-negative results. Obviously, this percentage of stress echocardiography "lies" will be higher with inexperienced readers and with stresses polluting image quality (exercise and dobutamine more than dipyridamole). Patients with variant angina, severe left ventricular hypertrophy, and uncontrolled hypertension have a greater chance of false-positive responses; patients studied under full anti-ischemic therapy will have a greater chance of false-negative responses. If the rate of false responses exceeds the expected average of 20 %, the method should be reassessed. The "angiographic lies" of stress echocardiography can turn out to be striking "prognostic truths" in the long run, overruling the prognostic stratification provided by the anatomic gold standard of coronary angiography. Therefore, in the anatomically defined subset of patients with single-vessel disease, patients with negative stress echocardiography findings ("false negative") have a good prognosis, better with medical therapy rather than with anatomy-guided revascularization [8]. Patients with angiographically normal coronary arteries and with stress echocardiography positivity (false-positive result) have a greater chance of adverse events in the long run [33].

6.6 Ancillary Signs of Ischemia

With stress scintigraphy, left ventricular cavity dilation and lung tracer uptake reflect late signs of global pump dysfunction and increase in pulmonary wedge pressure with interstitial lung edema. Also during stress echocardiography, we can

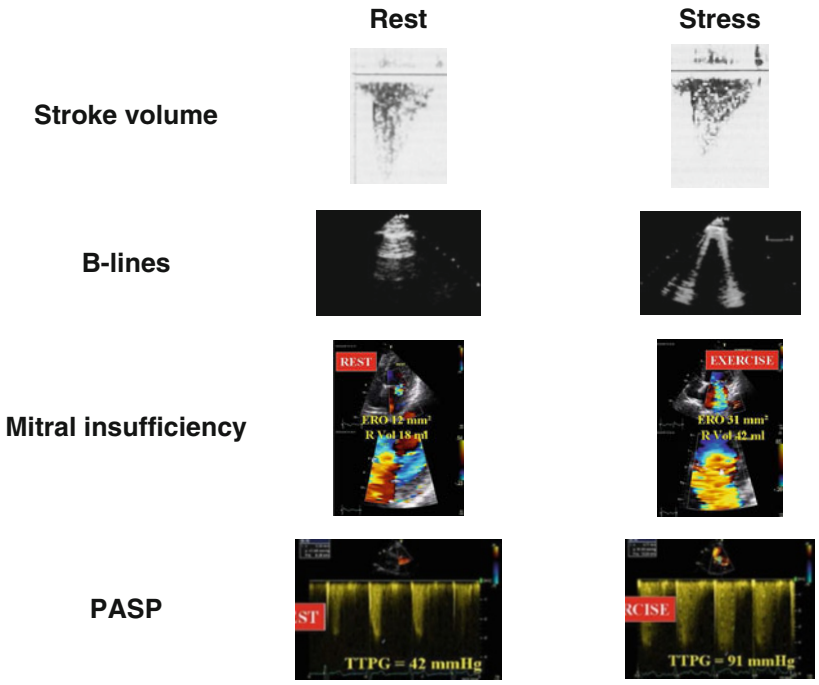

Fig. 6.5 Ancillary signs of ischemia: fall in stroke volume, increase in B-lines, acute severe mitral insufficiency, and rise in pulmonary artery systolic pressure. Each of these signs has an ominous prognostic meaning

Table 6.7 The ancillary severity signs of myocardial ischemia

Sign	Technique	Meaning	Cutoff value
LV ESV	2D (RT3D)	LV global dysfunction	>20 % (stress–rest)
MR	Color Doppler	MV dysfunction	>1 Grade
B-lines	LUS	Pulmonary edema	>20 % (>15)
PASP	CW Doppler	Pulmonary hypertension	>20 % (60 mmHg)

sometimes observe poorly sensitive but highly specific signs of extensive ischemia, severe underlying coronary artery disease, and ominous prognostic outcome (Fig. 6.5): a stroke volume fall [34, 35]; a transient dilation of the left ventricular cavity (>20 % from baseline of end-systolic diameter) [36]; the development of severe acute mitral insufficiency [37, 38]; an increase in B-lines, a sign of extravascular lung water accumulation (detectable with lung ultrasound by placing the cardiac echocardiography probe on the third right intercostal space) [39, 40]; and the rise in pulmonary artery systolic pressure [41].

The main ancillary signs of severity and their frequently used cutoff values are summarized in Table 6.7.

6.7 Beyond Regional Wall Motion: Coronary Flow Reserve

In the last decade, the old dream of combining wall motion with a simultaneous assessment of coronary flow reserve became a reality in the echocardiography laboratory. There are conceptual and methodological differences between myocardial perfusion and coronary flow reserve, since perfusion requires contrast opacification of the myocardium and coronary flow reserve assesses the vasodilating capacity of the coronary artery (see Chap 9). However, both mirror information on coronary vasodilating capability, which requires the full integrity of the epicardial (proximal, upstream) and microcirculatory (distal, downstream) components of the coronary circulation. In the nuclear medicine and cardiovascular magnetic resonance stress laboratory, perfusion is usually evaluated. In the stress echocardiography laboratory, more than a decade of attempts with myocardial contrast echocardiography led to disappointing results, due to the long learning curve required to perform and interpret contrast myocardial perfusion imaging [42]. On the contrary, the diffusion of assessment of coronary flow reserve in the left anterior descending coronary artery was rapidly accepted in the clinical arena and led to a remodeling of our diagnostic equations. There are differences between wall motion and reduction of coronary flow reserve as diagnostic markers, since only the former requires true ischemia, is affected by antianginal therapy, and is sensitive to epicardial stenosis and much less sensitive to purely microvascular coronary impairment (Table 6.8).

As a consequence, the diagnostic signs shown in Fig. 6.1 can be expanded to include coronary flow reserve as shown in Fig. 6.6. Normal function with normal coronary flow reserve (in the left anterior descending and right coronary artery) expresses the absence of anatomic and functionally significant stenosis of the epicardial artery and microcirculatory integrity. On the contrary, a normal wall motion with abnormal coronary flow reserve is associated with either a mild-to-moderate hemodynamically significant epicardial stenosis or significant microcirculatory disease [46]. The two markers are also prognostically complementary, since wall motion abnormalities identify troublemakers in the short run (months) and coronary flow reserve reduction – in the absence of wall motion disturbances – identifies

Table 6.8 Wall motion and myocardial perfusion in the stress echo lab

	Wall motion	Coronary flow reserve	Contrast myocardial perfusion
Technique	2D	Color pulsed-wave Doppler	Low-mechanical index 2D setting
Ischemia required	Yes	No	No
Therapy reduces sensitivity	Yes	No	Probably yes[a] [43]
Sensitivity	++	+++	+++ (and not confined to LAD)
Specificity	+++	++	++
Prognostic value	+++	++	++ [44, 45]
Troublemakers	Short run	Long run	Long run

[a]Extending SPECT data

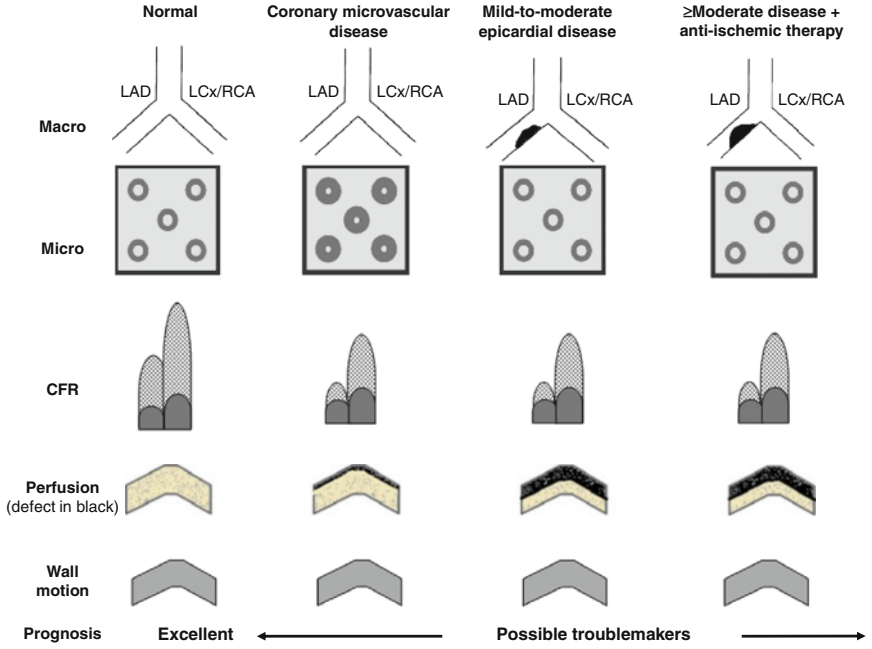

Fig. 6.6 Pathophysiological and prognostic heterogeneity behind normal wall motion response during stress. In the *upper panel*, we show epicardial coronary arteries: normal in the *first two columns*, with moderate disease in the *third column* and moderate-to-severe disease but concomitant, effective anti-ischemic therapy in the *last column*. The myocardium is shown as a *square box,* with small vessels as *circles*. Coronary small vessel disease is shown (*second column*) as *bold circle*s (structural or functional impairment). All four very different pathophysiological conditions show the negativity of wall motion response. The abnormal coronary flow reserve (*CFR*) response is present in the *last three columns*, with abnormality of micro- or macrocirculation. Reversible myocardial perfusion defects behave similarly to CFR, since in fact they reflect myocardial blood flow reserve, with the advantage that myocardial perfusion imaging can indifferently assess all of the three coronary territories. In case of microvascular disease, the strictly subendocardial perfusion defects typically extend across the boundaries of a single coronary territory (Modified from Rigo et.al. [46])

troublemakers in the long run (years). With the abovementioned limitation of significant technical complexity, the addition of contrast myocardial perfusion imaging to stress echocardiography has also demonstrated diagnostic and prognostic advantages over stand-alone wall motion assessment, similar to Doppler coronary flow reserve in the left anterior descending artery, but with the additional advantage of full coverage of the three coronary artery territories [14–16, 44].

6.8 Contrast Perfusion Stress Echocardiography

Stress echocardiography has been revolutionized by the availability of stable gas-filled microbubbles, which via a simple peripheral venous injection may offer the following multifaceted advantages:

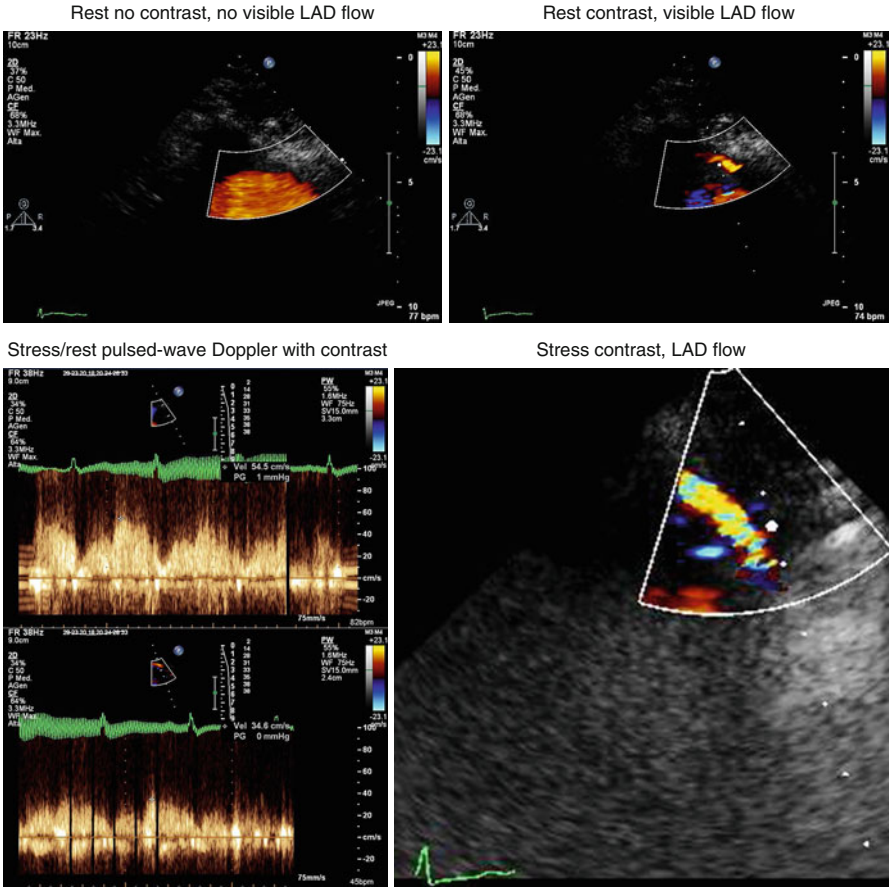

Fig. 6.7 The use of contrast for the enhancement of the LAD color flow in technically difficult cases, in which rest coronary flow is difficult to localize. Figure (lower part) also shows the downside of noisier pulsed-wave Doppler tracings, although quality is usually sufficient for the measurement of diastolic peak velocities

(a) Opacification of heart chambers (Fig. 6.7), making wall motion assessment of the left ventricle:
   - More *reproducible* among different readers [47]
   - Slightly but significantly more *accurate* [48] and
   - More *feasible* for almost the totality of patients, including the small but existing percentage of technically inadequate patients in whom stress echocardiography was previously precluded and stress MRI was considered as the only alternative for wall motion assessment

(b) Enhancement of color Doppler imaging of the mid-distal left anterior descending artery, increasing feasibility of coronary flow reserve measurement for non-experts or in very difficult patients (Fig. 6.8). The downside of color Doppler contrast enhancement is that PW Doppler tracing technical quality may degrade.

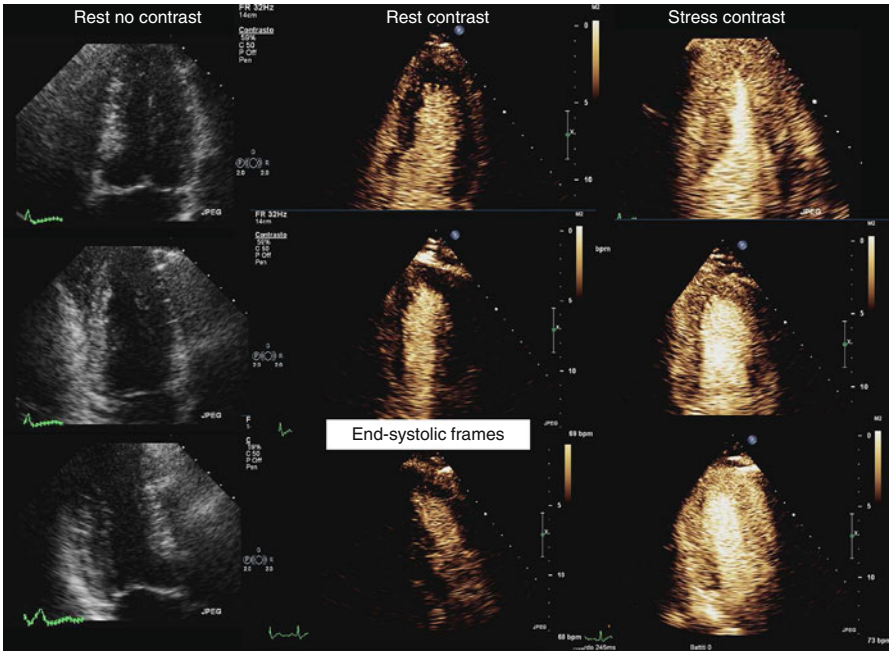

Fig. 6.8 The appearance of four-chamber, two-chamber, and three-chamber end-systolic frames, both at rest (*mid*) and stress (*right*) phases, when using low-mechanical index real-time imaging in conjunction with contrast. The same setting is used for myocardial perfusion imaging, as shown in Fig. 6.9, with the addition of flash-replenishment sequences to assess myocardial replenishment after microbubble-destructive impulses

(c) Assessment of myocardial perfusion (Fig. 6.9) which, although technically demanding and adequate for most but not all 17 segments of the left ventricle, boosts sensitivity very significantly to diagnose coronary artery disease in all coronary territories, although with a minor loss in specificity, compared with isolated.
(d) Assessment of wall motion [14–16, 48]; myocardial perfusion also demonstrates incremental accuracy for prognostication [44, 45].

The microbubbles that constitute contrast agents are biologically inert and safe: they remain entirely within the vascular space and have an intravascular rheology that is similar to that of erythrocytes [49–52]. An important aspect is that all ultrasound contrast agents are pure intravascular tracers, which is almost unique among commonly used tracers in cardiac imaging (see Chap. 24). The key technical advance was online signal processing of ultrasound signal from insonified microbubbles, which made it possible to separate bubble signals (nonlinear) from myocardial tissue backscatter (linear), with no need for time-consuming offline processing [53]. With the use of signal processing/filtering techniques, the nonlinear signals (non-multiple frequencies or amplitudes) produced by microbubbles can be selectively amplified, while the linear signals from myocardial tissue can be filtered out by cancellation pulse sequences; this results in a prevalent visualization

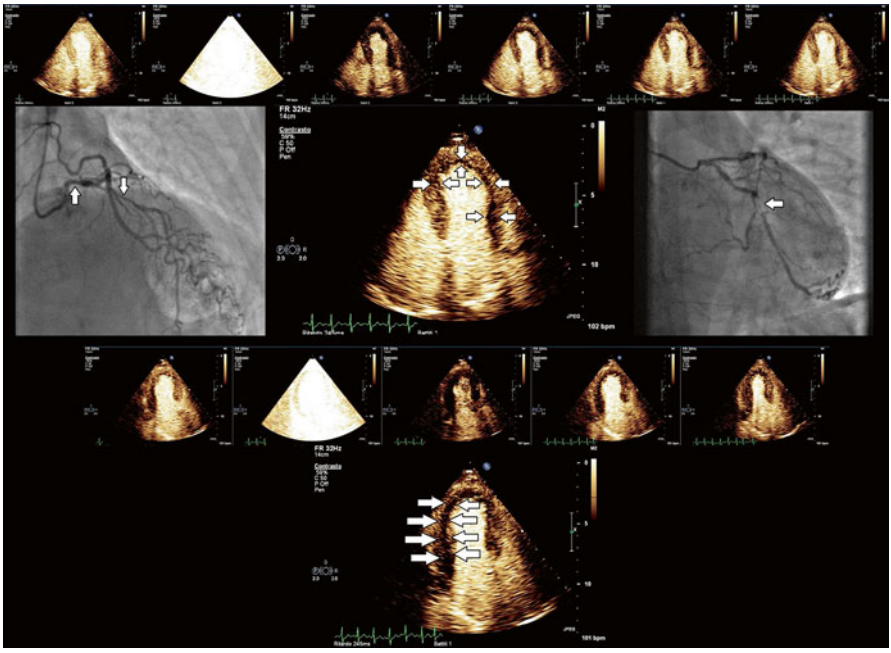

Fig. 6.9 Stress phase in a patient who underwent contrast dipyridamole echocardiography (0.84 mg/kg/6 min). The upper part of figure shows four-chamber contrast flash-replenishment sequence (from left to right), which demonstrates black areas in the subendocardial region of the true apex and apical–septal, apical, mid, and basal lateral segments (*arrows*) up to four cycles after microbubble destruction, representing perfusion defects. Lower part shows the three-chamber view (contrast flash-replenishment sequence from left to right), similarly demonstrating the perfusion defect (*arrows*), in this case almost transmural, in the inferolateral segments. Angiogram on the left side of the figure shows left main disease (50–60 % stenosis, arrow) and LAD disease (*arrow*), while the angiogram on the right shows the very severe stenosis of the left circumflex artery (*arrow*), which in fact caused a more profound reduction in myocardial blood flow, with inferolateral transmural perfusion defect. Myocardial perfusion defects may underscore the presence of "balanced disease" in which regional differences in wall motion may often be absent or difficult to detect, at any severity of coronary artery disease (mild or severe); subendocardial stress perfusion defects in several territories are apparent in these cases, due to epicardial/endocardial "vertical" steal phenomenon, although the horizontal would mostly go undetected

of returning signals from the microbubbles. Ultrasound imaging hardware/software that selectively receives the nonlinear responses produces a much better signal-to-noise ratio and more sensitive detection of microbubbles than would occur using conventional imaging software. The major hurdles for clinical use of myocardial contrast echocardiography are regulatory, financial, and technical. No agent has received FDA approval. There is lack of reimbursement in most settings. The technique is still a bit too complex and misses clinical cutoffs easy to handle for busy physicians. These limitations may explain why the technique is not yet routinely employed in most stress echo laboratories despite extensive scientific evidence [54].

Table of Contents Video Companion

See stress echo primer, case 6 (intracoronary contrast stress echo).
See also in section "Illustrative cases: Case numbers 26, 27, and 28" (by Nicola Gaibazzi, MD, Parma, Italy).
Springer Extra Materials available at http://extras.springer.com/2015/978-3-319-20957-9

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