Eugenio Picano

Stress Echocardiography

Sixth Edition

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Springer

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Preface

This book has a past. Its various editions and increasing diffusion parallel the growth of stress echocardiography within the scientific community and the clinical arena. The first edition in 1991 consisted of 100 pages, which gradually increased to more than 700 in this sixth edition.

Stress echocardiography is no longer a promising innovation used by isolated pioneers (i.e., desperate researchers surrounded by universal disbelief working with the technique at a time when it clearly could not work), but it is now an established, mainstream technique used every day, in every part of the world, by busy clinicians well aware of the huge potential of stress echocardiography to resolve the present paradox of saving health-care money while at the same time improving diagnostic standards. In a societal and economic climate of increasing pressure for appropriate, justified, and optimized imaging, stress echocardiography offers the great advantages of being radiation-free, relatively low cost, and with a staggering versatility: we can get more (information) with less (cost and risk).

For a long time, the scope and application of stress echo remained focused on coronary artery disease. In the last 10 years, it has exploded in its breadth and variety of applications. From a black-and-white, one-fits-all approach (wall motion by 2D echo in the patient with known or suspected coronary artery disease), now we have moved on to an omnivorous, next-generation laboratory employing a variety of technologies (from M-mode; to 2D and pulsed, continuous, color, and tissue Doppler; to lung ultrasound and real-time 3D echo, 2D speckle tracking, and myocardial contrast echo) on patients covering the entire spectrum of severity (from elite athletes to patients with end-stage heart failure) and ages (from children with congenital heart disease to the elderly with low-flow, low-gradient aortic stenosis).

The book was totally single authored in the first edition, up to the record number of 50 contributors in this edition. They come from 22 countries spanning four continents and represent, in my opinion, some of the best available knowledge and expertise in their respective fields. I am proud and honored that they have accepted the invitation to be a part of this project. At the same time, I aimed to avoid the fragmentation, gaps, and inconsistencies of a multiauthor text; therefore, I drafted the first version of each chapter – then asked for corrections, revisions, cuts,

additions, and integrations from more knowledgeable contributors. To all of them and to the junior and senior colleagues who have worked with me over the last 35 years – far too many to be mentioned here – *grazie*.

Pisa-Astana
2015

Eugenio Picano, MD, PhD

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Stress echo Primer and tutorial (from Pisa stress echo school 2000)

Coronary artery territories and myocardial segments
Regional wall motion scoring
Stress echo signs
Index: cases 1 to 7 (dipyridamole); case 8 (dobutamine and dipyridamole); cases 9–12 (dobutamine); cases 13–16 (ergonovine). Each case with clinical information and reading test

Illustrative cases

- *Ischemic heart disease*: cases 1 to 8 (dipyridamole); case 9 and 10 (exercise); case 11 (dobutamine); case 12 (ergonovine). Maria Joao Andrade, Aleksandar Neskovic, Bogdan Popescu, Jesus Peteiro
- *The added value of coronary flow velocity reserve*: cases 13, 14, 15 and 16 (dipyridamole); 17 and 18 (adenosine). Ana Djorkievic-Dikic, Quirino Ciampi
- *The added value of new technologies*: case 19 to 25 (dipyridamole, coronary flow velocity reserve and 2-D strain map). Jorge Lowenstein
- *Special interest, heart failure*: cases 29 (exercise echo and diastolic dysfunction); case 30 (exercise and acute severe mitral regurgitation); case 31 (exercise echo and B-lines). Maria Joao Andrade
- *Special interest, valvular heart disease*: cases 32, 33, 34 and 35 (dobutamine echo and low flow, low gradient aortic stenosis: true severe aortic stenosis and pseudo-severe aortic stenosis). Maria Joao Andrade

- *Special interest, heart transplant*: case 36 (dobutamine and wall motion); case 37 and 38 (dipyridamole and coronary flow velocity reserve); case 39 (dipyridamole-transesophageal stress echo for aged donor heart recruitment); case 40 (transthoracic dipyridamole stress echo for aged donor heart recruitment). Layla Elif Sade (case 36, 37 and 38) and Tonino Bombardini (case 39 and 40)
- *Special interest, hypertrophic cardiomyopathy*: case 41 (exercise and left ventricular outflow obstruction in orthostatic position). Carlos Cotrim
- *Special interest, noninvasive pacing*: case 42 (noninvasive pacing and real time 3-dimensional stress echo). Edyta Plonska
- *When stress echo fails, stress CMR*: cases 43 to 45 (dipyridamole stress-CMR with wall motion and perfusion). Vicente Bodi-Peris

The way we were: Nuovo Cinema Paradiso remastered

- *Myocardial viability: a moonlight serenade (1998)*- with Albert Varga (and Giuliano Kraft)
- *The roaring of the lamb (2000)* – with Albert Varga (and Giuliano Kraft)
- *Rocky Horror stress echo picture show (2002)* – with Albert Varga (and Giuliano Kraft)
- *A novel silver heart from National Research Council (2012)* – with Tonino Bombardini
- *Left ventricular contractility: from molecules to man (2013)* – with Tonino Bombardini (and Monica Zoppè - narrator voice, Ms Alison Frank)

Selected presentations (year):

- Pharmacological and myocardial effects of adenosine and dipyridamole (2004)
- Stress echo: math and geography (2001)
- Stress echo reading: the doctor factor (2001)
- Stress echo and myocardial perfusion imaging: How I ate my father (2005)
- Tests for myocardial ischemia: Angels in the stress echo lab (2003)
- The appropriate and justified use of medical radiation (2014)
- Stress echo for ischemia detection (2006)
- Ultrasonic Tissue characterization of myocardial ischemia and the atherosclerotic plaque (2013)
- Stress echo complications and catastrophes: heart of darkness (2005)

Stress echo book and video-companion dream team 2015

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Geographic map
Charts and contributions

General information for users

Contents

Part II Stresses: How, When and Why

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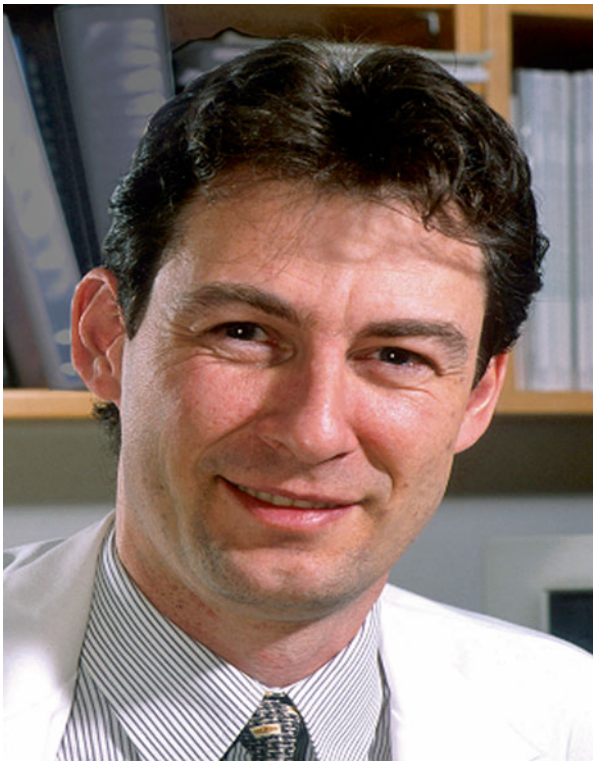

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Part I

Basic Principles, Methodology and Pathophysiology

Stress Echocardiography: A Historical Perspective

1

Patricia A. Pellikka and Eugenio Picano

Stress echocardiography (SE) provides a dynamic evaluation of myocardial structure and function under conditions of physiologic or pharmacological stress [1, 2]. Both specialty recommendations [3, 4] and general cardiology guidelines [5, 6] recommend SE as a primary tool for evaluating patients with established or suspected coronary artery disease (CAD). However, the ultrasound images obtained during conventional SE provide far more information. From an SE era with a one-fits-all approach (wall motion by 2D echo in the patient with known or suspected coronary artery disease), now we have moved on to a highly diverse, next-generation laboratory employing a variety of technologies (from M-mode to 2D and pulsed, continuous, color and tissue Doppler, to lung ultrasound and real-time 3D echo, 2D speckle tracking, and myocardial contrast echo) on patients covering the entire spectrum of severity (from elite athletes to patients with end-stage heart failure) and ages (from children with congenital heart disease to the elderly with low flow, low gradient aortic stenosis) (Fig. 1.1) [7].

The about 35 years-long history of the technique laid the solid experimental, pathophysiological, technological, and clinical foundations of SE. Current state-of-the-art applications with leading-edge expertise and technology rely on an integrated, simultaneous assessment of left ventricular wall motion and coronary flow reserve. The perspective of SE in the near future is to eliminate current pitfalls (dependence on acoustic window and operator expertise, with SE-based clinical management driven by consensus rather than hard evidence) and exploit to the fullest the advantages of this technique, i.e., versatility, portability, connectivity, and sustainability.

E. Picano, *Stress Echocardiography*, DOI 10.1007/978-3-319-20958-6_1

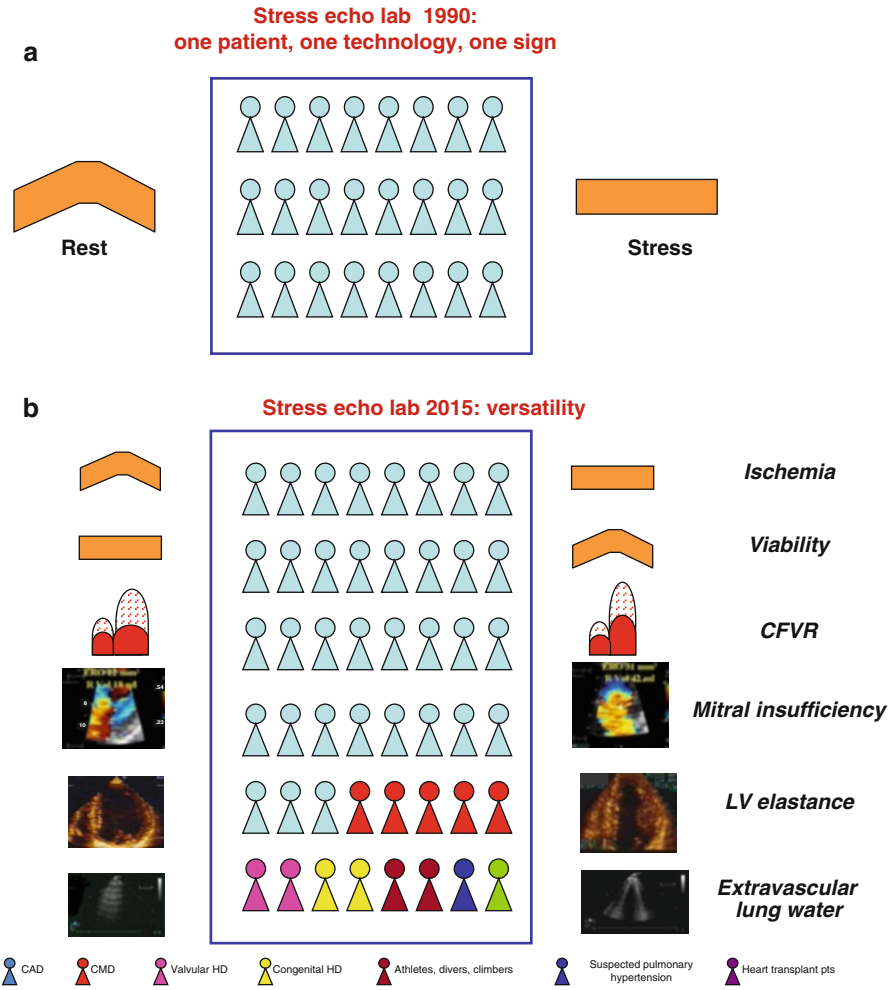

Fig. 1.1 SE as it was (*upper panel*), (**a**): one technology (2D echo), one sign (segmental wall motion abnormalities), and one type of patient (with known or suspected coronary artery disease). SE as it is today (*lower panel*), (**b**): many different technologies (from 2D echo to real-time 3D echo, tissue Doppler imaging, color Doppler, lung ultrasound), many signs (from mitral insufficiency to B-lines to pulmonary hypertension), all patients (from cardiomyopathies to valvular and congenital heart disease)

1.1 The Past Stress Echocardiography Era: From Experimental Studies to the Two-Dimensional Approach

In 1935, Tennant and Wiggers showed that coronary occlusion resulted in almost instantaneous abnormality of wall motion [8]. Experimental studies performed some 40 years later with ultrasonic crystals during acute ischemia [9] and two-dimensional echocardiography on a canine model of myocardial infarction [10]

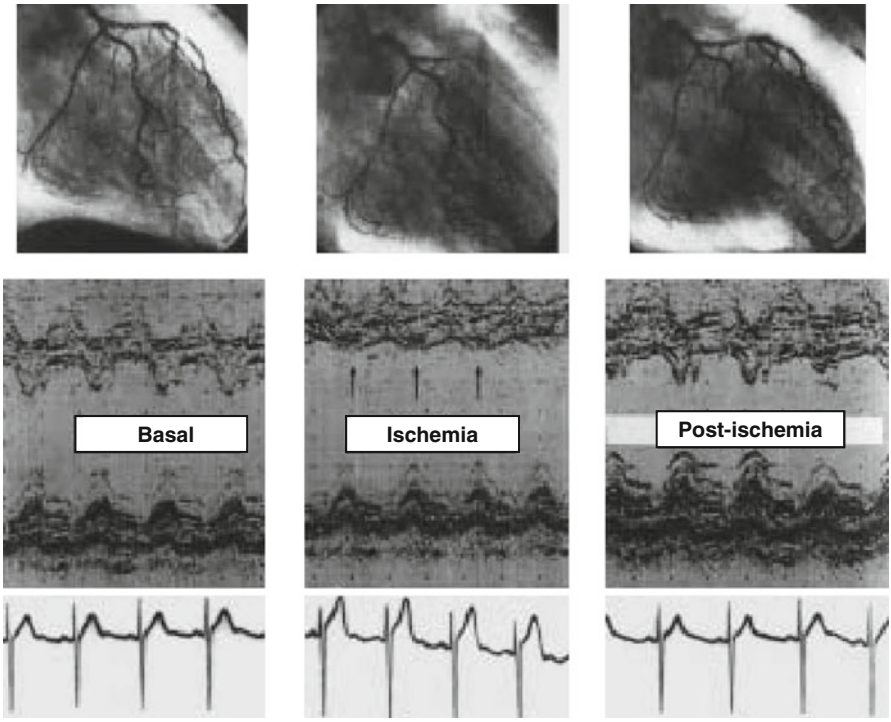

Fig. 1.2 Coronary angiographic (*upper panels*) and 2D targeted M-mode tracings (*lower panels*) during attacks of variant angina induced by ergonovine maleate. At baseline, left anterior descending coronary artery shows a tight stenosis (*left panel*); the artery is totally occluded by a complete vasospasm during ischemia (*middle panel*), and it is again open in the recovery phase (*right panel*). The corresponding three frames of an original *M*-mode recording document a fully reversible sequence of myocardial ischemia. The septum moves normally at rest (*left panel*) and is obviously akinetic during ischemia (*middle panel*). During the recovery phase (*right panel*), the previously ischemic wall exhibits hyperdynamic motion and systolic thickening (From Distante et al. [12])

showed that reductions in regional flow are closely mirrored by reductions in contractile function, setting the stage for the clinical use of ultrasonic methods in ischemic heart disease. The feasibility of using echocardiography to identify stress-induced wall motion abnormalities was first demonstrated with M-mode recordings during exercise-induced (subendocardial) or ergonovine-induced (transmural, vasospastic) ischemia [11, 12]. The M-mode technique was the only one available to cardiologists in the 1970s and nowadays appears largely inadequate for providing quality information when diagnosing myocardial ischemia. The time-motion technique sampling, according to an "ice-pick" view, greatly limited exploration to a small region on the left ventricle. Although this feature could hardly be reconciled with the strict regional nature of acute and chronic manifestations of ischemic heart disease, for the first time the M-mode technique outlined echocardiography's potential in diagnosing ischemia, clearly showing that a reversible segmental wall motion abnormality is an early, sensitive, specific marker of transient ischemia, much more accurate than electrocardiogram changes and pain (Fig. 1.2). The practical impact of these observations had to await the development of two-dimensional

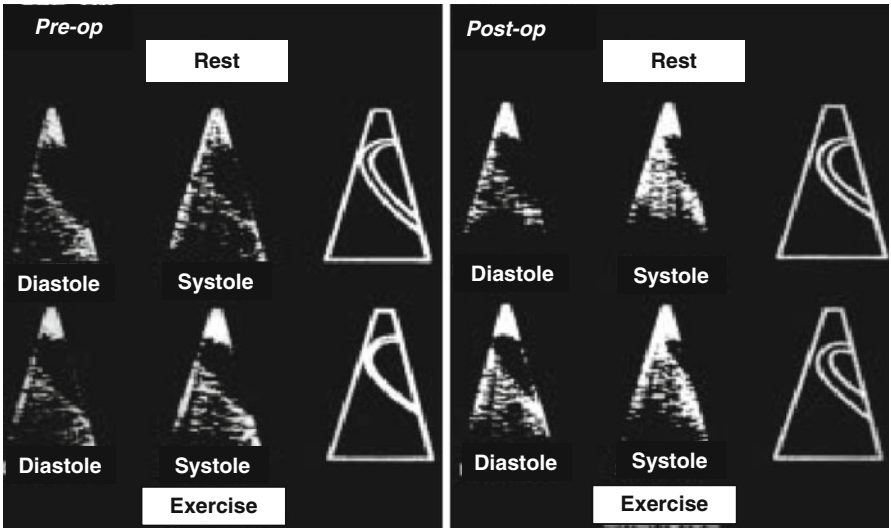

Fig. 1.3 SE in its infancy: not easy on the eyes. Exercise echocardiograms are shown before (*left panel*) and after (*right panel*) coronary artery bypass surgery. At that time (1979), image quality was so poor that even obtaining a single "typical example" for publication purposes was a challenge (From Wann et al. [13])

echocardiography, which allowed exploration of more segments of the left ventricle with excellent spatial and temporal resolution, and was thus ideally suited for detecting the regional and transient manifestations of myocardial ischemia. In addition, the technical difficulties and degraded quality of echocardiographic imaging during exercise – due to excessive chest wall movement, hyperventilation, and tachycardia – were minimized with two different approaches. Post-treadmill imaging, pioneered by Feigenbaum's group in Indianapolis, is still the standard in the USA today [13], based on the realization that stress-induced wall motion abnormalities produce stunned myocardium permitting immediate post-treadmill echoes to be clinically useful (Fig. 1.3). An alternative approach, more popular in Europe, was the introduction of pharmacological SE as an exercise-independent approach for detecting myocardial ischemia with vasodilators (introduced by the Pisa group in 1985) (Fig. 1.4) or dobutamine (first proposed by the Liege group in 1986) [14, 15].

Additionally, the method's clinical relevance was increased by the introduction of digital recording techniques and split screen displays so that the same views on rest and stress images could be acquired and viewed synchronously side by side [16]; this initially required stand-alone computers, but ultrasound systems now have direct digital output, and quad-screen display is standard on most systems. The advent of new technologies such as harmonic imaging of tissue [17] or contrast use for endocardial border recognition and left ventricular cavity opacification improved image resolution [18]. The introduction of native tissue harmonic imaging, which increases lateral resolution and signal-to-noise ratio, clearly improved endocardial border detection. Intravenous contrast echocardiography with second-generation

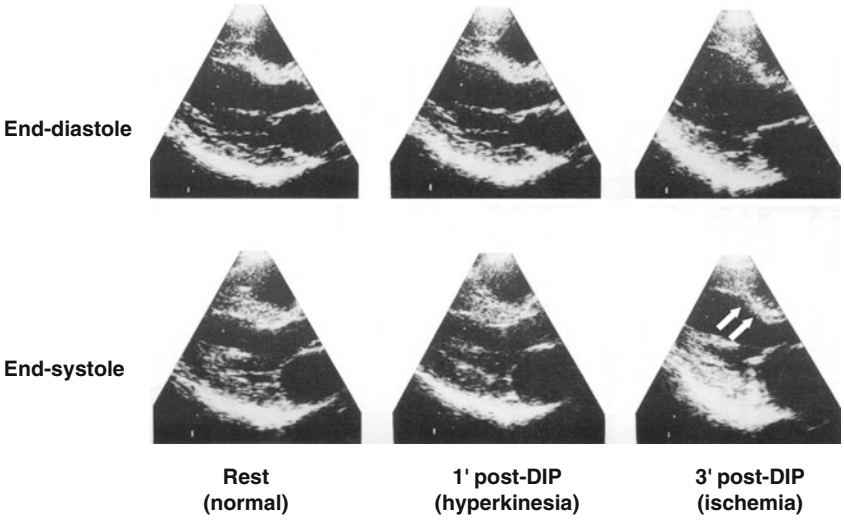

Fig. 1.4 The birth of pharmacological SE. End-diastolic (*upper panels*) and end-systolic (*lower panels*) frames at baseline (*left panel*), during early hyperkinetic phase (*middle panel*, 1 min post-dipyridamole infusion), and 3 min post-dipyridamole infusion at peak ischemic effect (*right panel*) showing septal akinesia. The quality of the image (compared to Fig. 1.3) is dramatically improved, thanks to the evolution of technology and the use of pharmacological instead of post-treadmill exercise echo (Original images from Picano et al. [14])

lung-crossing agents for endocardial border recognition allowed cardiologists to study otherwise "acoustically hostile" patients and segments.

The validation of stress echocardiography involved demonstration of its accuracy for detection of coronary artery disease and its prognostic value. The sensitivity and specificity of stress echocardiography to detect angiographic coronary artery disease were documented by multiple groups of investigators [19]. Such evidence already existed for the earlier established nuclear perfusion techniques. Meta-analyses, as well as direct comparison with tomographic nuclear perfusion imaging, demonstrated a comparable accuracy of stress echocardiography and SPECT perfusion imaging. The next step was to establish evidence of the prognostic utility of stress echocardiography. This evidence was collected by multiple investigators studying large consecutive series of patients, including men and women [20], the elderly [21], patients with diabetes mellitus [22], chronic kidney disease [23], and peripheral vascular disease [24]. The safety of stress echocardiography, even when supervised by registered nurses rather than physicians [25], was also documented. Stress echocardiography was then accepted as a valid tool that could be used to study safety of drugs and devices [26] and appropriate for the assessment of many types of patients [27]. The dosing schedules of pharmacologic agents have been validated, even in patients of widely varying size [28]. The technique was upgraded from research toy to clinical tool, receiving wide-scale support and credibility from prospective multicenter studies and international registries providing effectiveness [29] and safety [30] data in the real world – beyond the

experience of a few research-oriented centers. At the beginning of the new millennium, and after some 20 years of experience, the technique was finally ready for widespread clinical use [31].

1.2 State-of-the-Art Stress Echocardiography

The rise of SE in the last 30 years has been continuous and remarkable. SE is now widely available. Moreover, the feasibility of diagnostic quality images with selective use of current generation contrast agents for endocardial border enhancement currently exceeds 95 % and allows one to obtain diagnostic images even in acoustically hostile patients (such as those with morbid obesity and severe lung disease). In addition, a flexible use of exercise, vasodilators, and dobutamine stress in every echo lab maximizes the feasibility of performing a stress test, avoids specific contraindications of each, provides a second choice when the preferred test has produced submaximal (and therefore rarely useful) results, and makes it possible to tailor the most appropriate stress for the individual patient (for instance, exercise for evaluating hemodynamic changes in heart failure, vasodilators to assess coronary flow reserve, and dobutamine for contractile reserve). However, a utilization gap remains in comparison with nuclear stress imaging, which at least in some areas is still used – in spite of higher cost, radiation exposure, lack of online reading, and multiple large studies documenting its comparable diagnostic and prognostic accuracy [32, 33]. The validation of SE in three areas remains incomplete: tissue characterization of the myocardial structure (scar vs normal tissue), myocardial perfusion with myocardial contrast echocardiography (allowing perfusion to be coupled with function in the same stress), and regional wall motion quantification with new technologies (turning the diagnosis of regional wall motion from an opinion into a quantifiable number) [34]. At first, each of these targets appeared to be within reach, based on strong experimental data and encouraging clinical experiences, but they did not pass the test of multicenter studies [34], in the case of contrast myocardial perfusion echocardiography, have not garnered US Food and Drug Administration approval, and to date have not had any substantive clinic impact. However, in the last 10 years, a major innovation changed the face and the diagnostic content of SE in many parts of the world: dual imaging of wall motion and coronary flow reserve with pulsed-Doppler imaging of the mid-distal left anterior descending coronary artery [35, 36]. Imaging coronary flow reserve expands the prognostic potential of SE, since in the absence of wall motion positivity, the patient subset with reduced coronary flow reserve has a less benign outcome and in patients with wall motion abnormality, those with reduced coronary flow reserve also have a more malignant prognosis (Fig. 1.5) [37]. In the same setting, with the same stress, it is now possible to image function and flow simultaneously and therefore catch two "birds" (flow and function) with one "stone" (vasodilator stress). Although coronary flow reserve is a technology in progress, it is recommended by the European Association of Echocardiography whenever technology and expertise are available since "it provides critical prognostic value when added to conventional wall motion analysis" [4].

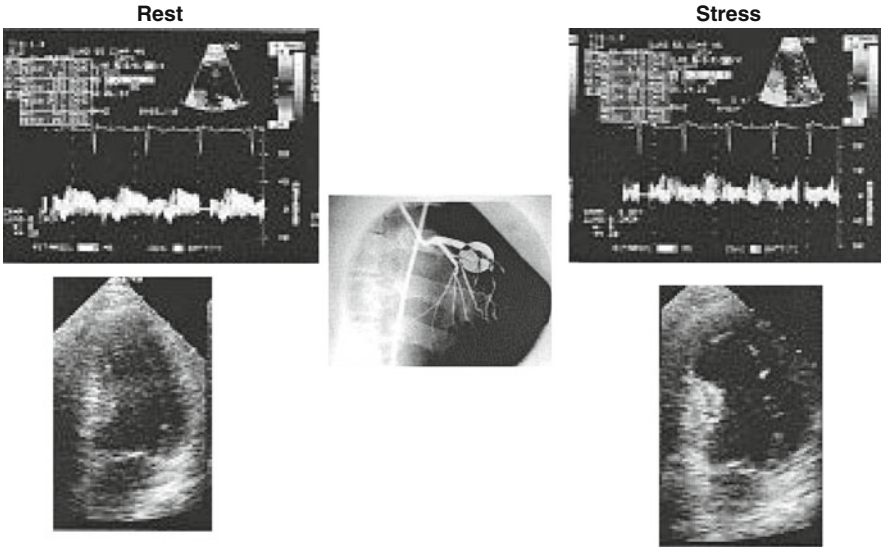

Fig. 1.5 A typical example of a 2-dimensional (2D) regional wall motion (*lower panel*) and coronary flow velocity reserve (*upper panel*) pattern from a patient with a tight proximal stenosis of the left anterior descending (LAD) artery (*central panel*). On the left, rest, and on the right, stress findings. The end-systolic frames from the apical 4-chamber view show a normal thickening at rest (*lower left panel*) and akinesia of the apex during stress (*lower right panel*). Pulsed-wave (PW) Doppler shows no significant increase in Doppler peak diastolic flow velocity from baseline (*upper left panel*) to peak dipyridamole (*upper right panel*). (By courtesy of Fausto Rigo, Venice, Italy [21])

1.3 The Future: Next-Generation Stress Echocardiography

The next challenge for SE is to fix its weaknesses: dependence on operator expertise and, despite numerous large studies that have documented the predictive value of the test in various populations [3], lack of outcome data (also missing for other stress and imaging tests) to document how and when it should be used to improve patient outcomes. SE must also take full advantage of its strategic strengths: low cost, widespread access, richness of information, and radiation-free nature.

1.3.1 Objectivity of Reading

SE is relatively simple and widely available, but training recommendations should be followed [7, 8]. In general, many parameters used in SE applications beyond CAD can be more difficult to acquire but are easier to measure and more amenable to quantification than regional wall motion assessment; therefore, these applications may be less dependent upon the subjectivity of interpretation and experience [9]. However, for regional wall motion – which is still the core of SE activity – the interpretation remains subjective and heavily dependent on operator skill. The development of an objective, quantitative method for wall motion analysis during stress testing would

overcome these limitations, translating the inducible wall motion abnormality from an opinion into a number. Different waves of ultrasound technologies have been proposed in the last 20 years – from tissue characterization, color kinesis, and tissue Doppler imaging to strain rate and speckle tracking – but at present there is no routine place for these techniques in the clinically driven practice of SE [34]. Although intriguing and potentially useful, these measurements are also complicated and time-consuming, and results may differ for different ultrasound systems. The best hope for the future is the non-Doppler-based imaging with speckle tracking echocardiography – once the limiting problem of inter-vendor comparability of strain values is settled – especially attractive for detection of subtle global and regional abnormalities in LV longitudinal strain, not otherwise detectable with regional wall motion analysis and linked to minor degrees of subendocardial ischemia [38]. Real-time three-dimensional echocardiography also has proven benefits in accuracy and reproducibility, but its methodology is time-consuming, and frame rates are at times still too low for optimal transthoracic imaging. Its impact in stress echo could be critically important, with continued improvements in image quality, and with the advent of automated quantification software tools that can be used immediately as the images are acquired.

1.3.2 Evidence-Based Use

Prospective large-scale and randomized (SE-guided vs standard) outcome studies are needed to support more evidence-based treatment strategies. Guidelines, restricted to the rigors of evidence-based data, may underemphasize the utility of SE in many clinical contexts. Nevertheless, it is also true that most of the guidelines and society recommendations are based on a level of evidence C, that is, the consensus of the writing committees in the absence of a firm evidence base [39]. In most circumstances, there is a lack of convincing evidence that the results of stress testing lead to clinical decisions that result in better outcomes. This is especially important in light of results that run counter to prevailing wisdom, showing, for instance, that viability (detected by SE or SPECT) is not per se an indication for revascularization in patients with left ventricular dysfunction and stable CAD enrolled in the randomized STICH (Surgical Treatment for Ischemic Heart Disease) trial [40]. Prospective large-scale and (when possible) randomized (medical vs interventional treatment) outcome studies are needed at this point to support more evidence-based rather than consensus-based treatment strategies, based on SE results, in CAD and non-CAD patients [41].

1.3.3 Versatility

In the last few years, the tremendous technological and conceptual versatility of this technique has been increasingly applied in challenging diagnostic fields. Today, in the echocardiography lab, we can detect not only ischemia from coronary artery stenosis but can also recognize abnormalities of the coronary microvessels,

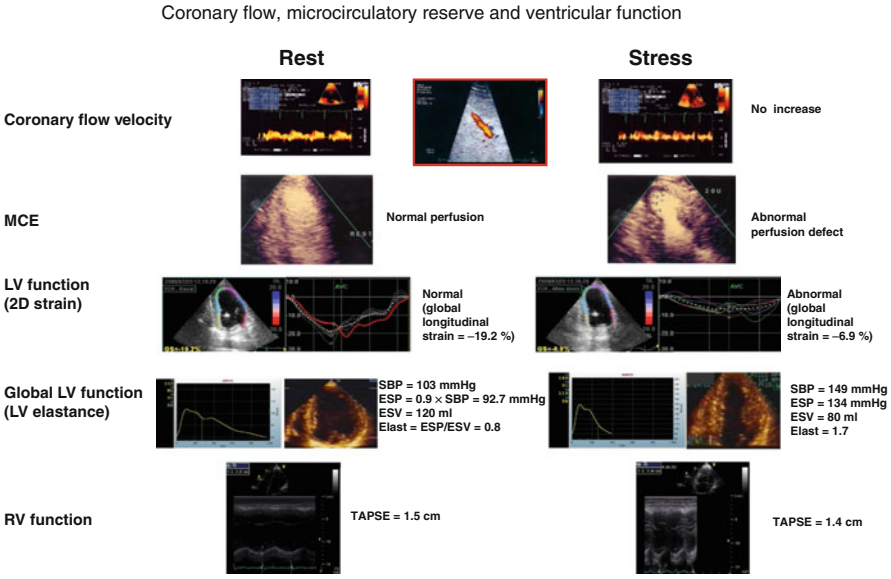

Fig. 1.6 Assessment of coronary flow and ventricular systolic function. *From top to bottom*: coronary flow velocity reserve (with pulsed Doppler showing a near-absent increase in coronary flow velocity as shown by coronary time velocity integrals) or myocardial microcirculatory reserve (MCE, second row): regional function (by 2D strain), global LV function (with end-systolic LV volume and arterial tonometry to calculate LV elastance), and right ventricular function (with blunted increase in TAPSE in a patient with repaired tetralogy of Fallot). *Abbreviations*: *LV* left ventricle, *MCE* myocardial contrast echocardiography, *TAPSE* tricuspid annular plane systolic excursion

myocardium, heart valves, pulmonary circulation, alveolar-capillary barrier, and right ventricle. Thus, we evaluate coronary arteries as well as coronary microvascular disease (associated with diabetes and hypertension), suspected or overt dilated cardiomyopathy, systolic and diastolic dysfunction [42] and heart failure, hypertrophic cardiomyopathy, athletes' hearts, valvular heart disease, congenital heart disease, incipient or overt pulmonary hypertension, and heart transplant patients for early detection of chronic or acute rejection as well as potential donors for better selection of suitable donor hearts. As with CAD, in these diseases as well, the application of exercise or pharmacological stress under controlled conditions can unmask structural defects which – although occult in the resting or static state – may occur under real-life loading conditions and lead to dysfunction detected by echocardiography [3]. For each patient, we can tailor a dedicated stress protocol with a specific method to address a particular diagnostic question (Figs. 1.6, 1.7, and 1.8).

Provided that the acoustic window is acceptable and the necessary expertise available, SE is useful and convenient in many situations, from valvular to congenital heart disease, and whenever there is a mismatch between symptoms during stress and findings at rest.

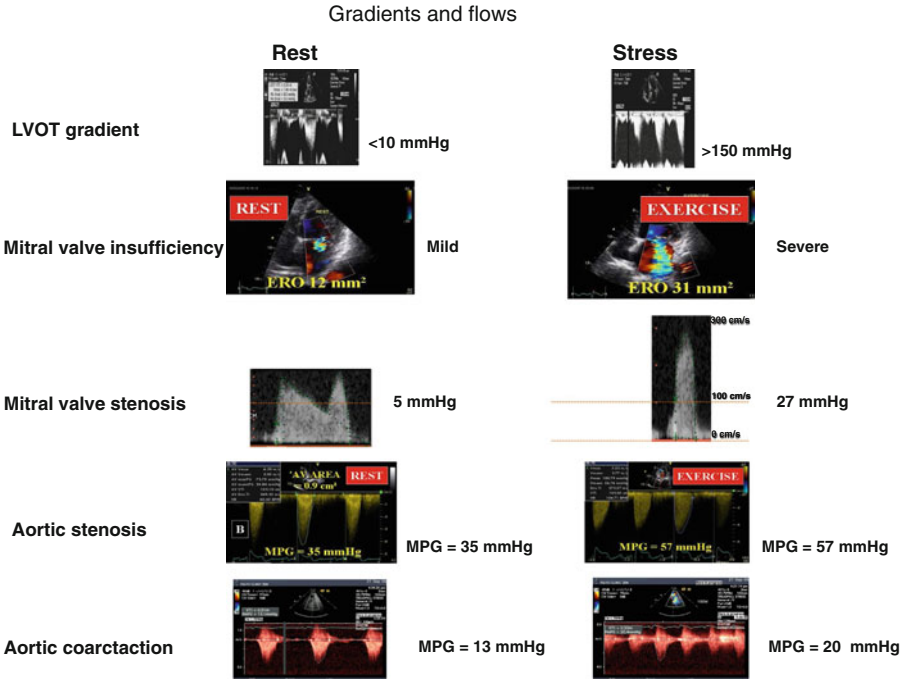

Fig. 1.7 Assessment of intraventricular and transvalvular gradients and flows. *From top to bottom*: LV outflow tract gradient (in HCM), mitral valve insufficiency, mitral valve stenosis, aortic stenosis, and aortic coarctation. Doppler signs of disease were absent to mild at rest and increased during stress

1.3.4 Portability

Scanner miniaturization is underway, and our imaging devices will become smaller and smaller with laptops and even smartphones being used, if only for display. Although their image quality cannot rival that of high-end systems, this miniaturization will allow diagnosis anytime, anywhere, and of virtually anything (from left ventricular function to pulmonary edema). This technological innovation is especially promising in the SE field, since it holds the potential of a paradigm shift from the artificial reality of the cardiac stress testing lab to the real world of real-life stress testing, under the actual physiological conditions encountered in everyday life, where extreme psychological, environmental, and physical challenges cannot be reproduced in the cardiac stress laboratory with any physical and (much less so) pharmacological stress. A prototype of this cultural and methodological transition from an artificial, indoor to an ecological, outdoor stress is represented by lung ultrasound in extreme physiology settings, such as deep underwater apnea diving [43], or high-altitude trekking [44], or marathon running in the desert [45]. The theater is no longer the large and comfortable SE lab, crowded with nurses, doctors, and fellows in training, armed with last-generation, high-end, costly, and heavy ultrasound instruments with all sorts of technological options. In this artificial

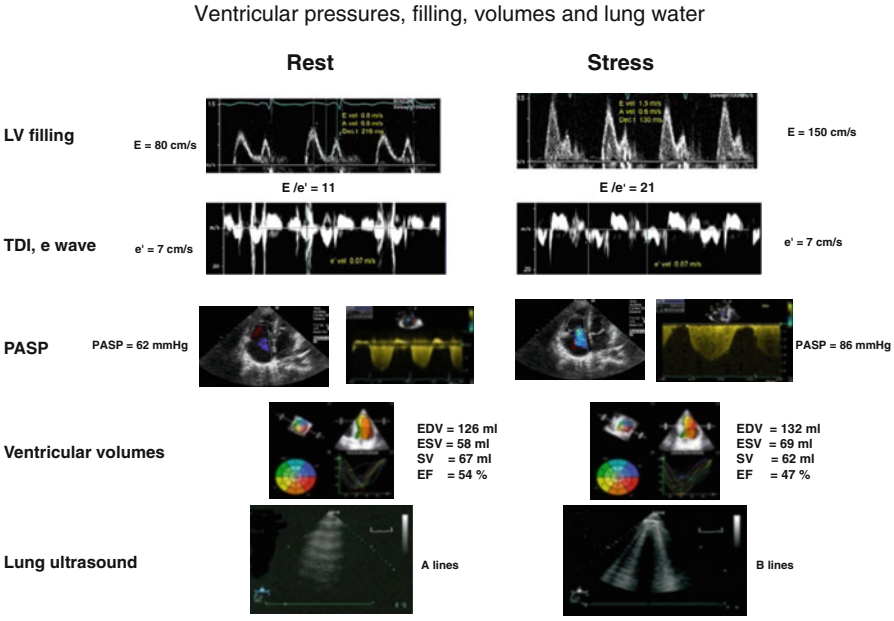

Fig. 1.8 Assessment of intracavitary pressures, filling, ventricular volumes, and extravascular lung water. *From top to bottom*: LV transmitral flow velocity (with increase in E wave during stress), tissue Doppler imaging of mitral annulus (e′ unchanged, with E/e′ increase during stress to >15), PASP (increasing during stress), LV size (with end-systolic volume increase), and lung ultrasound (with B-lines during stress, absent at rest, indicating interstitial pulmonary edema)

world, patients are scanned while lying quietly in the most suitable position for ultrasound imaging and with all equipment and personnel readily available for treating any sort of complications. The new theater for ecological stress is a hostile environment, often with very limited space and time available for meaningful image acquisition with a pocket-size machine, usually with the doctor playing the role of cardiologist, nurse, and technician at the same time. Yet, the information available is probably much greater with ecological stress outdoors than in a controlled setting in the hospital, where some conditions – for instance, mental stress, psychological discomfort, environmental aggression with urban pollutants, or extreme physiological conditions – cannot be reproduced. In the next years, SE "no-thrills" will go outdoors, and a new physiological and clinical window of opportunity will be wide open for SE.

1.3.5 Connectivity

In the wireless connection world, we can acquire stress images in a neuro-reanimation unit in a brain-dead potential heart donor [46] or in the emergency room for a work-up of chest pain [47] and have instantaneous access to an expert

second opinion reading, in some settings critical also from a legal point of view – for instance, when the qualitative response of SE is required to give the green light to organ explant for heart donation. Remote expert interpretation can provide backup support to point-of-care diagnosis by nonexperts when read on a dedicated tablet-based application, and mobile-to-mobile consultation may improve access in previously inaccessible locations to accurate interpretation by experienced cardiologists [48, 49], ultimately allowing ultrasound imaging – via mobile device – virtually anywhere and anytime [50]. Ordinary remote consultation for questionable cases in a technique still highly dependent upon subjectivity of reading will progressively gain space and popularity as smartphone-based connectivity becomes simpler and more pervasive.

1.3.6 Sustainability

The time when the best physician was the one who was doing the greatest number of the most expensive exams is over. Having less money will not necessarily lower the quality of care, since too much of a good thing (like imaging or stenting) can be dangerous. The first generation of stress echocardiographers was raised in the climate of an affluent society, with virtually unlimited resources devoted to health care: the more, the better! We performed too many scans and too many stresses, applying too many appealing, fancy, colorful new technologies which later proved to be of limited clinical value [34]. As a result, cardiac stress imaging is one of the top five most inappropriately performed cardiology examinations in the *Choosing Wisely* campaign in the USA [51]. Today, we are aware that every useless exam is a risk, a cost, and even a disturbing diagnostic noise. We can no longer afford the culture of waste. Less is more, also in stress cardiac imaging. The best physician is not the one prescribing the greatest number of expensive examinations but the one doing the most appropriate examinations with the lowest risk, since even very small costs and risks – multiplied by billions of examinations – become significant population burdens. This is especially true for radiation risk [52], but any unnecessary testing can lead to additional testing that increases risk. Increasing societal concern regarding cost, environment, and risks of medical imaging will lead to a preferential application of ultrasound over competing techniques, due to its unsurpassed versatility, portability, absence of radiation, safety, and low cost [53].

In conclusion, to be cost-effective and competitive, SE must be a definitive examination, feasible in nearly all patients, anytime and anywhere, quantitative and objective whenever possible, sufficiently flexible and versatile to be tailored in the individual patient, and supported by solid evidence guiding stress echo-based changes in management (see Table 1.1).

We are still far from this ideal test, but in the last 35 years, we have come a very long way, and hopefully we are still moving in the right direction.

Table 1.1 The next-generation stress echo lab

	What we have	What we need
Feasibility	Difficult windows in <5 %	Contrast, image upgrade
Reading	In-site	Also remote
Interpretation	Qualitative, subjective	Objective, quantitative
Location	Indoors	+ Outdoors
Patient	CAD	+ DC, VHD, CHD, etc.
Sign	WM + CFR	+ PASP, B-lines, MI, etc.
Available studies	Observational retrospective	Randomized prospective
Management changes	Consensus based	Evidence based
Stress setting	Laboratory (artificial)	+ Ecological (real life)

CAD coronary artery disease, *CFR* coronary flow reserve, *CHD* congenital heart disease *DC* dilated cardiomyopathy, *MI* mitral insufficiency, *PASP* Pulmonary artery systolic pressure, *WM* wall motion

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Anatomical and Functional Targets of Stress Testing

2

Branko Beleslin and Eugenio Picano

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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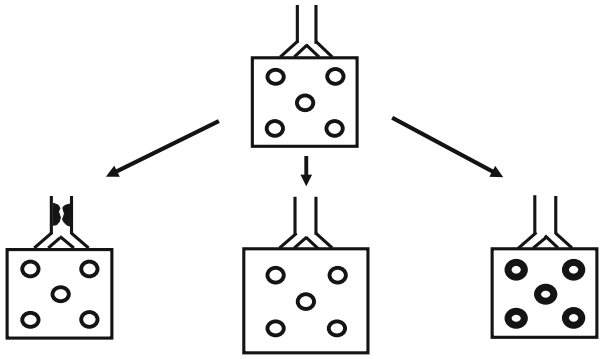

Fig. 2.1 The pathways of ischemia. *Upper panel*: The fundamental anatomical components of the normal heart are shown: epicardial coronary arteries (*parallel lines*), myocardium (*square box*), and small vessels (*circles*). *Lower panel*: The three main pathophysiological conditions that may provoke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

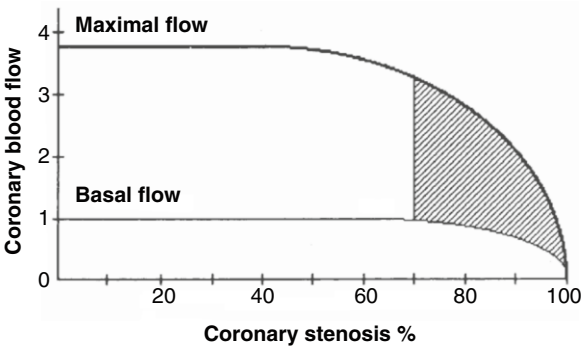

Fig. 2.2 Coronary blood flow curve (*on the ordinate*) for increasing levels of coronary stenosis (*on the abscissa*) experimentally obtained in resting conditions (*lower curve*) and at maximal post-ischemic vasodilation (*upper curve*). Coronary reserve – i.e., the capacity of the coronary circulation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

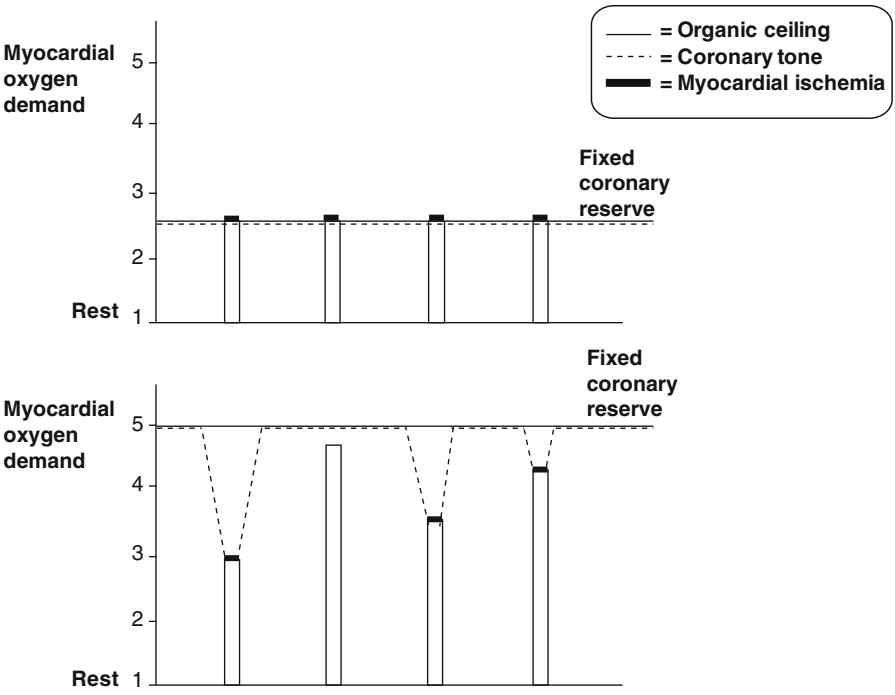

Fig. 2.3 In the presence of a fixed hemodynamically significant stenosis, there is a pathologically reduced "ceiling" of flow reserve (*continuous transverse line*) which induces ischemia when myocardial oxygen demand exceeds a definite threshold (*upper panel*). In the presence of a dynamic stenosis (*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

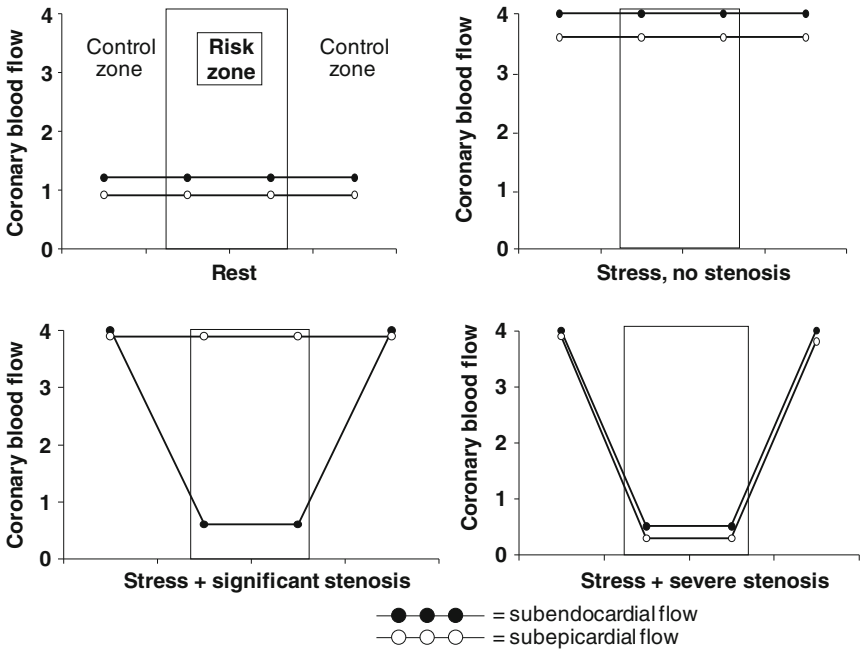

Fig. 2.4 Distribution of flow in the subendocardial and subepicardial layers under different hemodynamic conditions. *Upper left panel*: In resting conditions, the subendocardial and subepicardial flows overlap. *Upper right panel*: During stress, the flow increases homogeneously in both layers without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

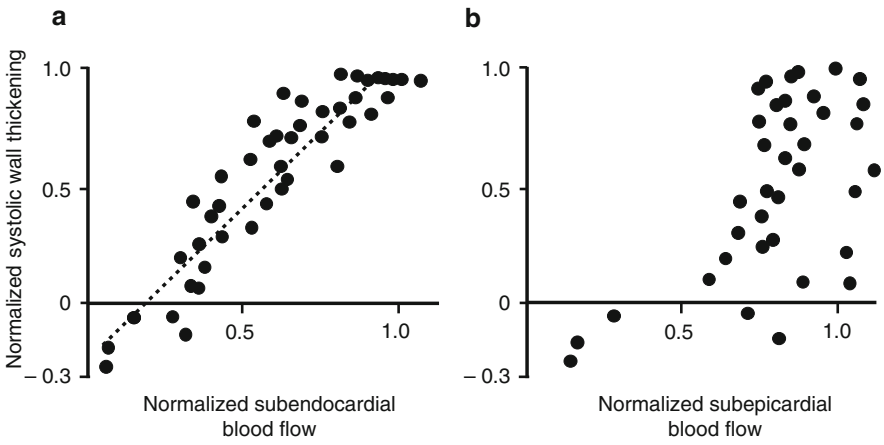

Fig. 2.5 The relationship between regional blood flow and systolic wall thickening in resting conscious dogs subjected to various degrees of circumflex coronary artery stenosis. Flow is expressed as a decimal fraction of that in a normal region of the ventricle, and percentage wall thickening (*%WTh*) 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

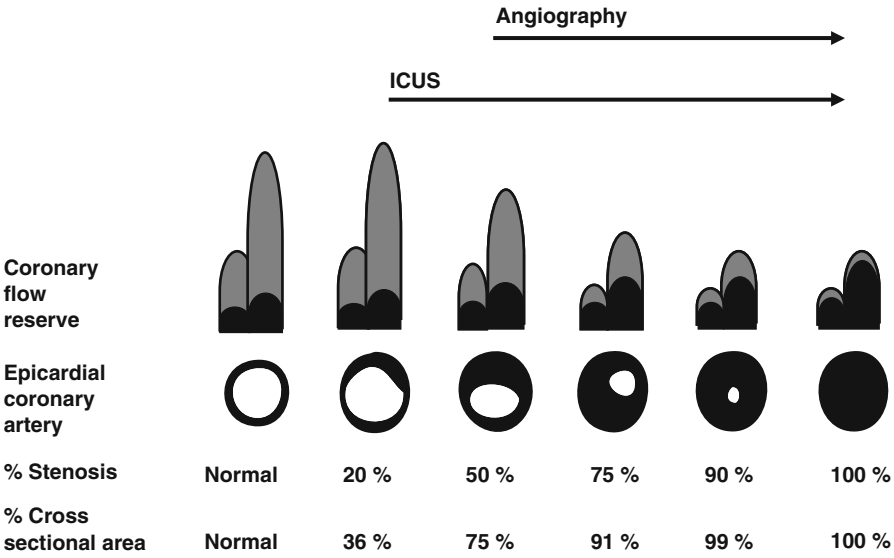

Fig. 2.6 Invasive diagnostic tests for the detection of coronary artery disease. Invasive tests include the luminogram of coronary angiography and the direct visualization of the coronary arterial wall by intracoronary ultrasound (*ICUS*). The percentage of a stenosis can be expressed in angiographic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

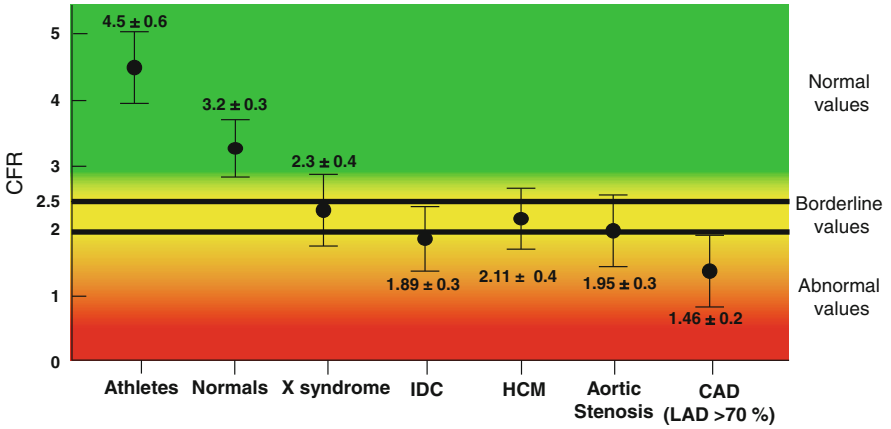

Fig. 2.7 The spectrum of clinical conditions with normal coronary arteries and reduced CFR on the left anterior descending artery by transthoracic vasodilatory stress echocardiography (Redrawn and modified from Rigo [33]). *CAD* coronary artery disease, *CFR* coronary flow reserve, *HCM* hypertrophic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

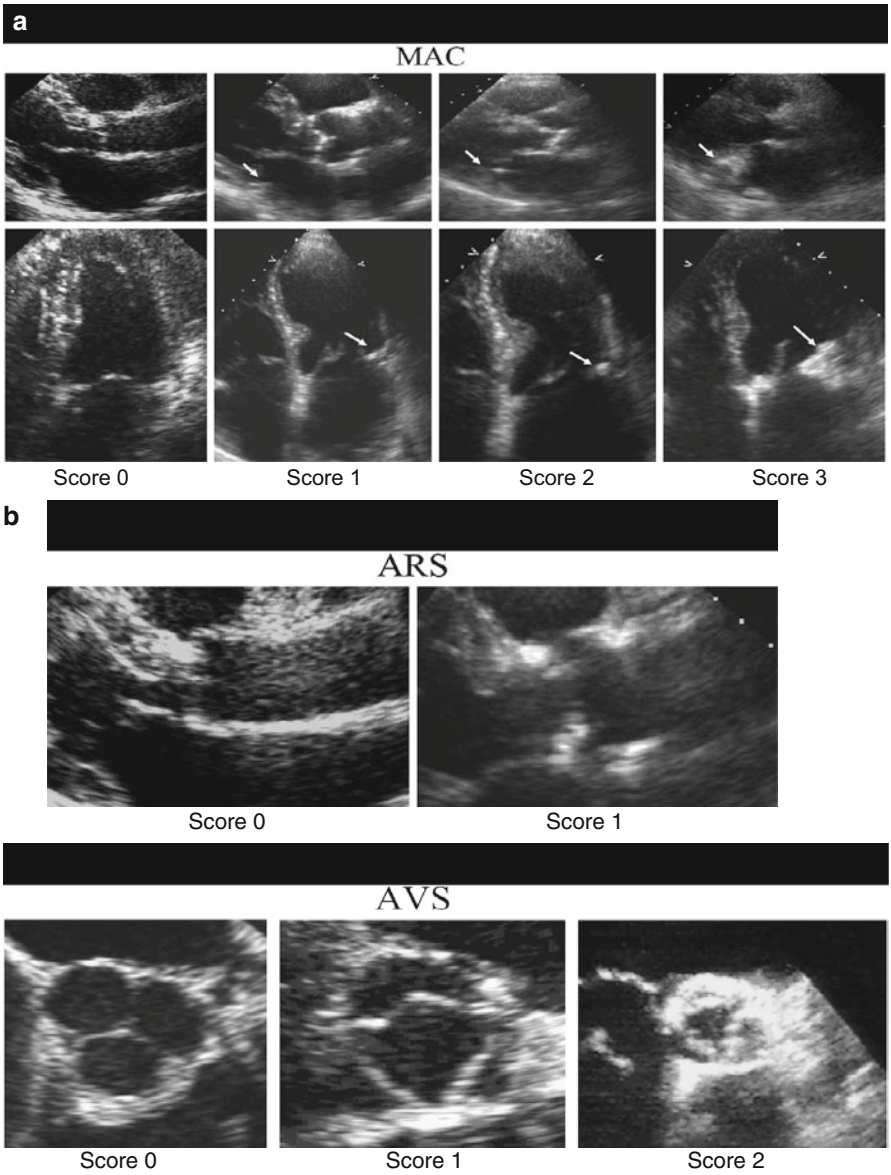

Fig. 2.8 A simple assessment of cardiac calcification through scoring of mitral annulus calcification (*upper panel* **a**, from 0 = no calcium, to 3 = extensive calcification), aortic root (*lower panel* **b**, from 0 = absent, to 1 =, present), and aortic valve leaflets (from 0 = no calcium, to 3 = 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

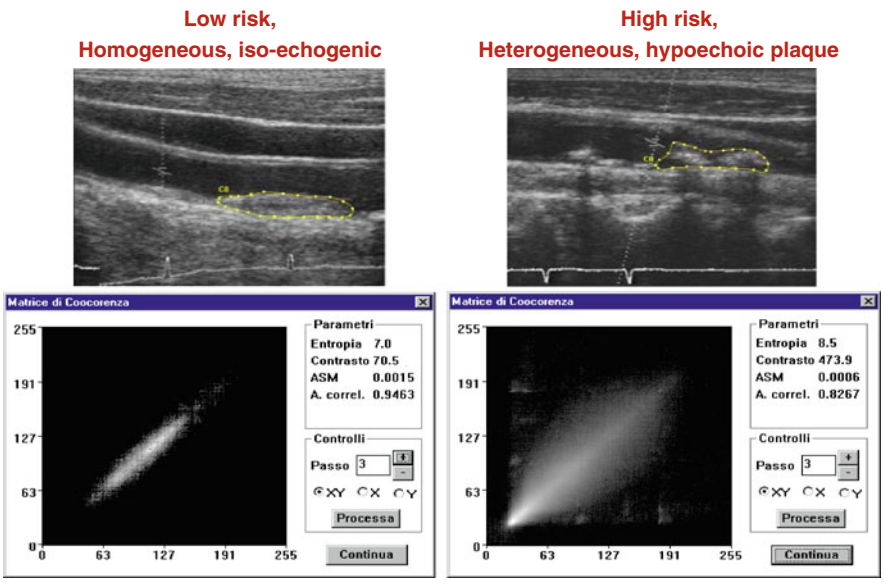

Fig. 2.9 A visual and videodensitometric assessment of carotid plaque morphology. Unstable, soft, lipid-rich plaques are less echogenic and more dishomogeneous than stable, fibrotic plaques. These texture features can also be more objectively described with simple textural analysis with quantitative 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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Symptoms and Signs of Myocardial Ischemia

3

Vicente Bodì Peris and Eugenio Picano

A transient regional imbalance between oxygen supply and demand usually results in myocardial ischemia, the signs and symptoms of which can be used as a diagnostic tool [1]. Myocardial ischemia results in a typical "cascade" of events in which the various markers are hierarchically ranked in a well-defined time sequence [2]. Flow heterogeneity, especially between subendocardial and subepicardial perfusion, is the forerunner of ischemia, followed by metabolic alterations, diastolic dysfunction, induced systolic dysfunction, and only at a later stage electrocardiographic changes, global left ventricular dysfunction, and pain (Fig. 3.1). The ideal marker of ischemia should provide absolute values of sensitivity and specificity, as well as a diagnosis of the site and severity of ischemia, an accurate prediction of the patient's outcome and reliable guidance in the decision-making process. Unfortunately, such a marker does not exist; in contrast, we have a number of imperfect markers that if associated can provide a reasonably good noninvasive estimation of the presence, extent, and severity of myocardial ischemia. The pathophysiological concept of the ischemic cascade is translated into a gradient of sensitivity of different available clinical markers of ischemia, with chest pain being the least sensitive and regional malperfusion the most sensitive (Fig. 3.2).

3.1 Chest Pain

Chest pain is, in general, the reason the patient seeks medical care. As in any other field of medicine, a correct and comprehensive clinical history is the most important step to achieving a correct diagnosis and making the most appropriate decisions. However, many chest pain syndromes are not ischemic in origin and are due to extra-cardiac causes (such as anxiety or reflux esophagitis), and about 25 % of deaths due to coronary artery disease (CAD) are observed to occur in patients who had never complained of chest pain. Typical or definite angina pectoris can be defined as (1) substernal chest pain or discomfort that is (2) provoked by exertion or emotional stress and (3) relieved by rest and/or nitroglycerin. Atypical or probable

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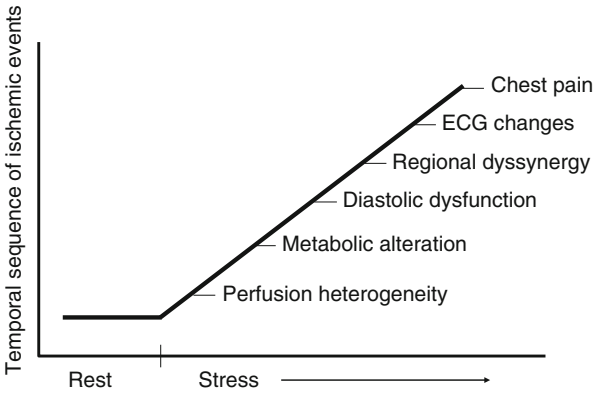

Fig. 3.1 The classic ischemic cascade, triggered by coronary vasospasm and/or epicardial stenosis. The various markers are usually ranked according to a well-defined time sequence

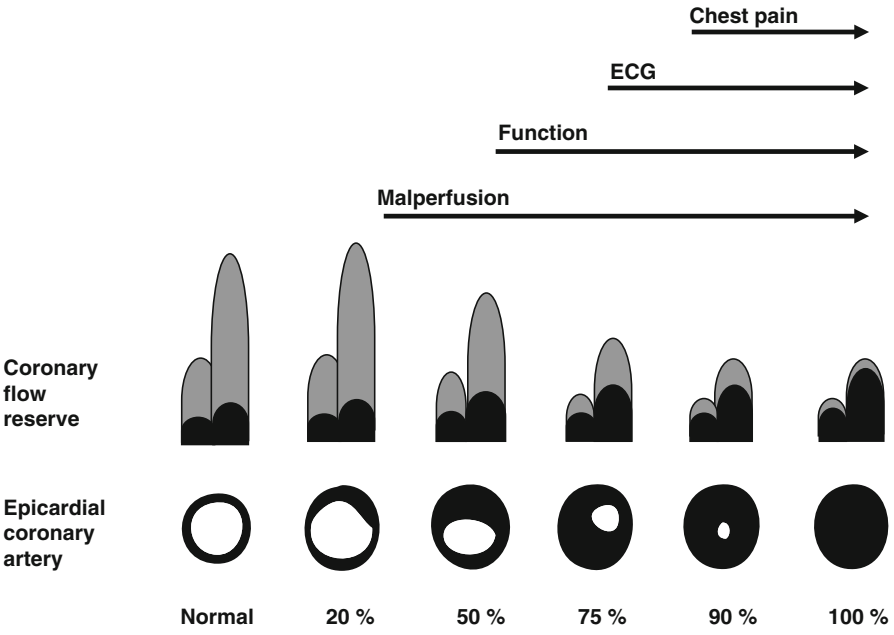

Fig. 3.2 The sensitivity of different diagnostic markers of ischemia ranked according to the underlying coronary anatomy and physiological impairment in coronary flow reserve. Electrocardiographic changes appear late during stress testing and provide only a modest sensitivity, barely superior to that of chest pain. The sensitivity of wall motion abnormalities is markedly superior to that of ECG changes. Malperfusion is more sensitive than wall motion abnormalities in detecting minor but flow-limiting levels of coronary artery stenosis

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

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

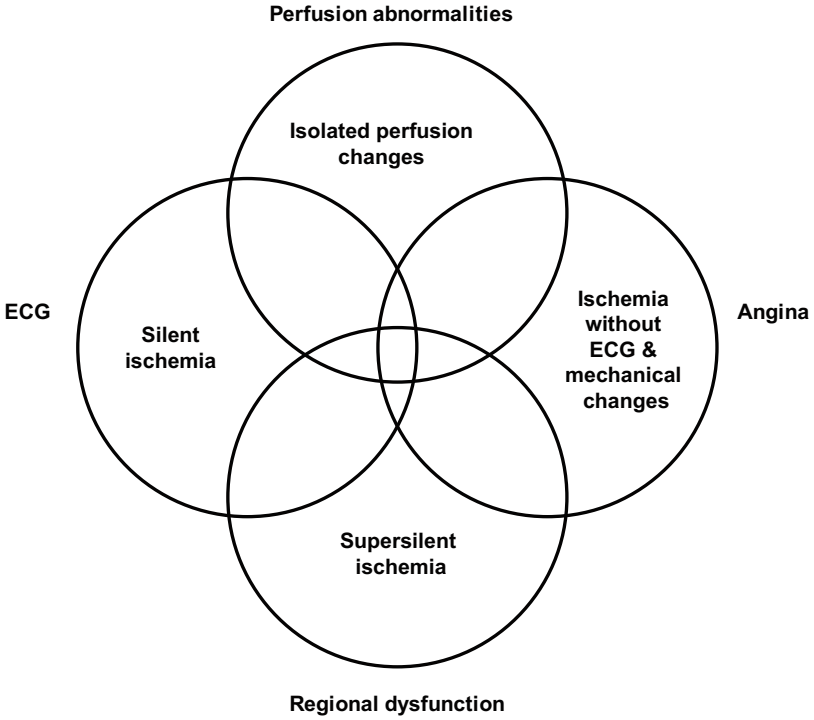

Fig. 3.3 Relative sensitivity of electrocardiography, pain, perfusion, and wall motion changes in diagnosing myocardial ischemia. In the domain of electrocardiography, there is the entity of silent ischemia; in the domain of echocardiography, there is the entity of the so-called supersilent ischemia

(Fig. 3.3). More than 60 % of ischemic episodes observed on Holter monitoring are silent, and about 20 % of transient dyssynergies detected by echocardiography are supersilent. Thus, chest pain is an important clinical symptom, but it is also a simple diagnostic optional feature.

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

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

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

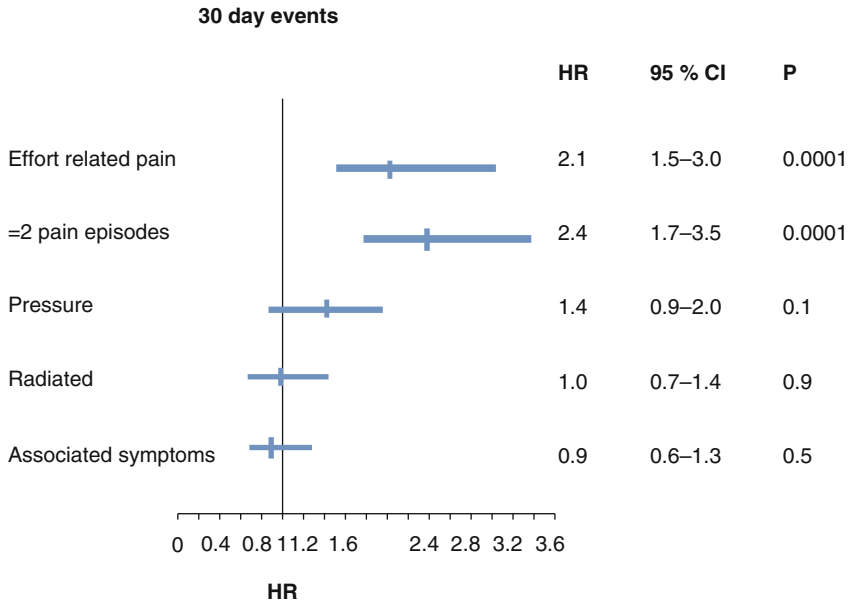

Fig. 3.4 Predictive value of chest pain characteristics for prediction of cardiac events (death, readmission for acute coronary syndrome, or unplanned revascularization) at 30 days in a population of 789 patients with acute chest pain without ECG changes and normal troponin (Modified from Sanchis et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

3.2 Electrocardiographic Changes

Electrical alterations provoked by ischemia can easily be detected by the 12-lead electrocardiogram (ECG). The electrocardiographic signs of subendocardial ischemia are represented by ST-segment shift or T-wave changes; by contrast, transmural ischemia is generally associated with transient ST-segment elevation. The site of ST-segment elevation is correlated with the site of ischemia, while this agreement does not hold in the more frequently found ST-segment depression. However, ST-segment shifts and T-wave changes are often an equivocal marker of ischemia because the line dividing normal from abnormal is not sharp, and a series of factors (electrical, metabolic, pharmacological, neurohumoral, hemodynamic) can induce ischemia-like ST–T changes [6]. Therefore, the electrocardiographic marker – alone or associated with chest pain – is not always capable of detecting the presence of myocardial ischemia and usually cannot predict its site and extent. Moreover, in clinical practice, out of the context of acute coronary syndromes, it is unusual for patients to complain of chest pain during clinical evaluation. Thus, in stable CAD, baseline ECG seldom contributes definitive proof regarding the presence and location of myocardial ischemia.

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

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

3.3 Alterations in Left Ventricular Function

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

Myocardial ischemia causes left ventricular regional dyssynergy (an early, sensitive, and specific marker of ischemia) and global dysfunction (a late and nonsensitive sign). Various techniques have been proposed for the imaging of left ventricular function: echocardiography, radioisotopic ventriculography (at first pass or equilibrium), fast computed tomography, and stress cardiac magnetic resonance (stress CMR) [3]. To date, echocardiography has been the technique of choice for the assessment of ventricular function, both in resting conditions and even more so during stress, in spite of the dependence of echocardiographic imaging on the patient's acoustic window and on the experience of the cardiologist interpreting the study. The advantages of feasibility, safety, reliability, and unsurpassed temporal and spatial resolution allow the documentation under optimal conditions of a regional dysfunction that can be extremely localized in space and transient in time. Stress CMR, attending to its extraordinary spatial resolution and its capability to simultaneously evaluate a variety of relevant parameters in CAD, is an excellent alternative to stress echo.

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

3.4 Metabolic Abnormalities

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

3.5 Perfusion Abnormalities

An epicardial coronary artery stenosis reduces the maximal flow achievable in the related territory, although the blood flow in resting condition can be equal to that observed in regions supplied by normal coronary arteries. During hyperemia (either during exercise or after dipyridamole or adenosine), perfusion heterogeneity will occur with lower blood flow increase in the regions supplied by the stenotic artery [13]. The criterion of positivity is the presence of a regional flow heterogeneity or malperfusion between different zones of the left ventricle (Fig. 3.5). Perfusion imaging is routinely performed with gamma-camera scintigraphy, but it can be also obtained – with higher accuracy and at substantially greater cost – by means of positron emission tomography. Other techniques with potential for perfusion imaging are contrast echocardiography and magnetic resonance imaging with injection of specific contrast agents. Echocardiography and magnetic resonance imaging do not use radiation; this is a significant advantage taking into account the expected exponential growth in the use of radiation throughout the lifespan of patients as well as its well-known deleterious effects [14].

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

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

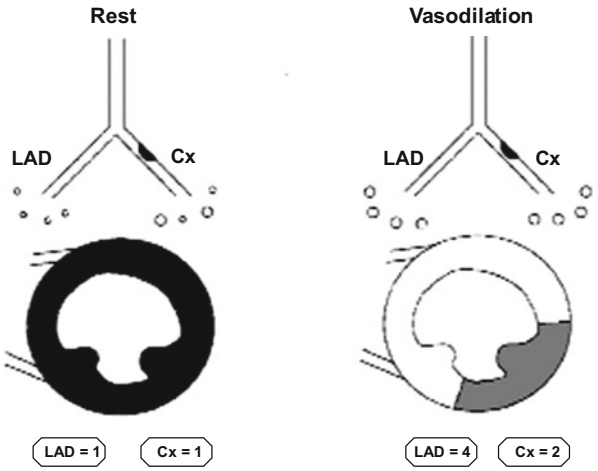

Fig. 3.5 Schematic illustration of the principle underlying myocardial perfusion imaging for the diagnosis of coronary artery disease. At rest, myocardial perfusion is homogeneous, with no differences between the territory of the normal coronary artery (*LAD*, left anterior descending artery) and that of the diseased coronary artery (*Cx*, left circumflex, with 80 % stenosis). The resting flow image (obtained, for instance, with thallium-201 scintigraphy or with contrast echocardiography) does not show any interregion variation. However, perfusion in the territory of the stenotic coronary artery is maintained at the price of a partial exhaustion of coronary reserve, with partial dilatation of the arteriolar bed – represented by *larger circles* located downstream from the epicardial coronary arteries. The normal arteriolar tone is represented by *smaller circles* (normally vasoconstricted arterioles). During vasodilation obtained with a metabolic stimulus such as exercise or with a pharmacological stimulus such as dipyridamole, the arteriolar tone is lost, determining an increase in flow that will be greater in the normal coronary artery (which at rest has a preserved tone in the entire arteriolar district) than in the stenotic coronary artery (with lower coronary reserve). Perfusion imaging will show the stenosis "mirrored" in the myocardium as a region with relative underconcentration of flow tracer when compared with the normal contralateral region. The septal and anterior wall appear "*brighter*" (due to greater echocontrast concentration) when compared with the "*darker*" inferoposterior wall (lower echocontrast concentration)

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

3.6 The Paradigm Challenged: The Alternative Ischemic Cascade

In diagnostic practice with stress imaging, not all patients follow the reassuring paradigm proposed by the "ischemic cascade." ECG changes may often occur with typical chest pain, in the absence of echocardiographic changes, and are often

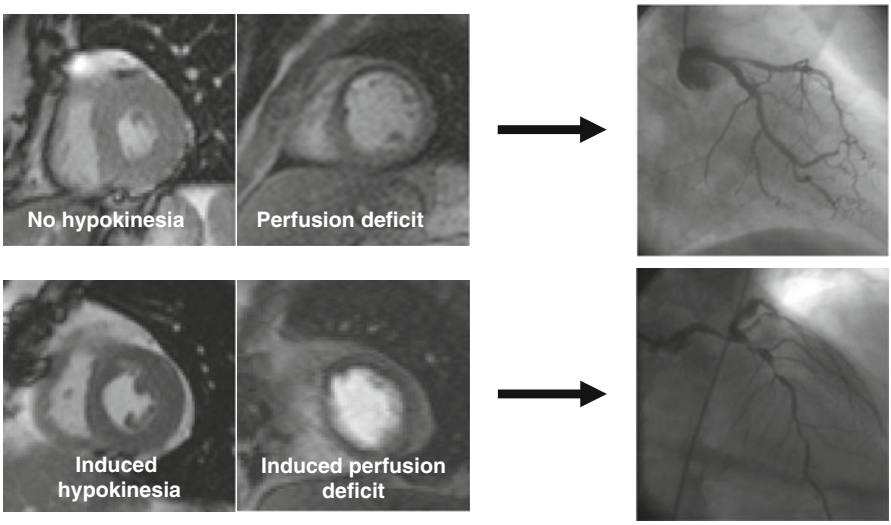

Fig. 3.6 Vasodilator stress imaging: "Two birds with one stone." In stress imaging using vasodilators (such as dipyridamole or adenosine, which are maximal hyperemic stresses with potential to induce true ischemia), induction of isolated perfusion abnormalities (an early step in the ischemic cascade)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

accompanied by real, not artifactual [17], reversible perfusion defects. In fact, the typical behavior of microvascular disease during stress testing is the frequent induction of chest pain, ST-segment depression, and perfusion abnormalities without regional or global wall motion changes [18]. The sequence of events is therefore strikingly different from the classic ischemic cascade described in Fig. 3.1 and in the right-hand panels of Fig. 3.8 as well as from that found during stress testing in the presence of a coronary stenosis. This alternative ischemic cascade is illustrated in the left-hand panel of Fig. 3.8 and derives from real clinical experience [18]. The classic ischemic cascade was a clear laboratory phenomenon described as early as 1935 by Tennant and Wiggers [19], who demonstrated that the immediate result of a coronary occlusion was an instantaneous abnormality of wall motion. The alternative ischemic cascade was a clear clinical finding disclosed by cardiac imaging techniques and it still requires a good laboratory model. It was initially described in cardiac syndrome X by Kemp et al. in 1973 with pacing left ventriculography [20] and later observed with stress echocardiography [21–23]. The left ventricle is

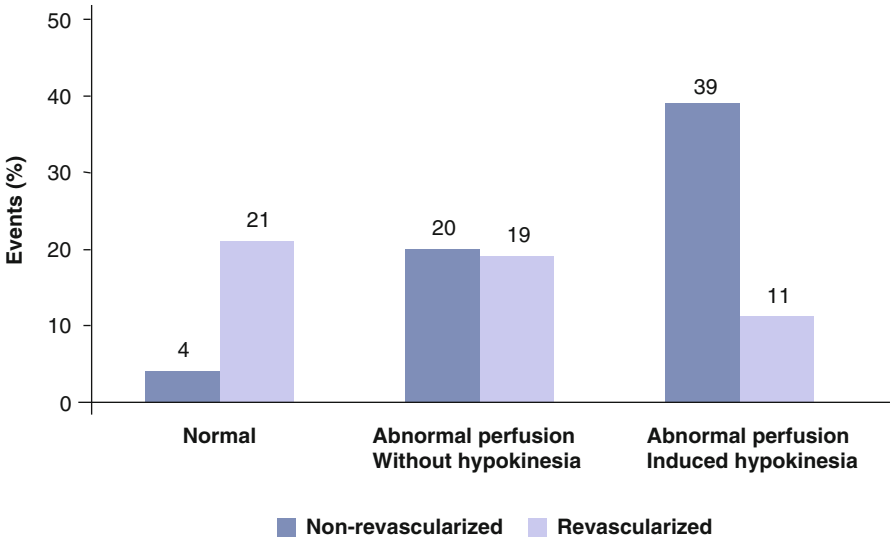

Fig. 3.7 Implications of stress imaging in the decision-making process. In a series of 601 patients with known or suspected ischemic heart disease studied with dipyridamole stress CMR and follow-up for a median of almost 3 years, patients without evidence of ischemia (normal study) who underwent revascularization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

hyperdynamic during stress, in spite of the frequent occurrence of chest pain and ST-segment depression: it is "too good to be ischemic," [24] at least when the usual pattern of classic ischemia due to coronary artery stenosis is considered. The alternative cascade refers to a sequence of clinical events, during which the occurrence of ischemia usually cannot be proven [18], although in a subset of patients a reduction in coronary flow reserve [24, 25, 26, 27], and/or metabolic evidence of inducible ischemia [28, 29], and/or a strictly subendocardial stress-induced hypoperfusion [30] has been described. Thus, while few would argue that induced myocardial dysfunction is an accurate marker of regional ischemia, the occurrence of ECG changes and demonstration of regional abnormal vasodilator reserve may or may not be associated with ischemia [13]. In this debate, one should consider that the absence of stress-induced dysfunction does not rule out the ischemic nature of the electrocardiographic abnormalities. It is well-known that under ideal imaging conditions even a subendocardial infarction characterized by prolonged chest pain, a rise in serum enzymes, and ST-segment and T-wave changes can be accompanied in 20 % of cases by a perfectly normal echocardiogram [31]. Several conditions can be clustered together with cardiac syndrome X in coronary microvascular disease, characterized by normal coronary arteries and reduced coronary flow reserve,

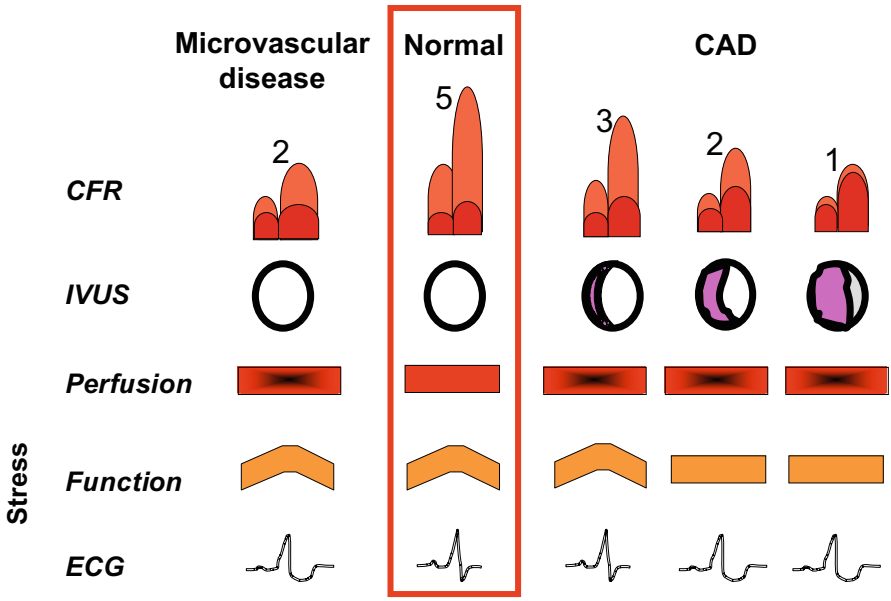

Fig. 3.8 A concise view of the different pathophysiological situations of the classic (*CAD*) and alternative (microvascular) ischemic cascade. In normal conditions (*framed*, *second column from left*), there are a normal coronary flow reserve (*CFR*, *first row*, *with intracoronary Doppler ultrasound*), normal coronary anatomy (*IVUS*, *second row*, *with intravascular ultrasound*), normal perfusion pattern with scintigraphy (*perfusion*, *third row*), and normal contraction during stress (*function*, *fourth row*). ECG is shown in the *last row*. Coronary flow reserve is pictorially expressed with a Doppler tracing before, during, and after a coronary occlusion. With the classic ischemic cascade, perfusion defects are present with mild (*third column from the right*), moderate (*second column from the right*), and severe (*first column from the right*) coronary stenosis, mirroring reductions in coronary flow reserve and accompanied (for moderate-to-severe stenoses) by regional wall motion abnormalities, which are usually absent for mild degrees of stenosis, capable of limiting coronary flow reserve without inducing ischemia. In microvascular disease (*first column from the left*), the depressed coronary flow reserve is associated with a normal coronary anatomy, the frequent occurrence of stress-induced perfusion defects (often with ST-segment depression), and normal left ventricular function (Modified from Picano et al. [18])

without epicardial coronary artery vasospasm [17]. In each of them, an echocardiographically silent ST-segment depression has been described as the typical pattern during stress testing. Among others, they include arterial hypertension (with normal coronary arteries, with or without left ventricular hypertrophy), hypertrophic cardiomyopathy, and diabetes [18, 32]. It is entirely likely that our monolithic view of ischemia mirrored in the classic ischemic cascade should integrate awareness of the reverse or alternative ischemic cascade best describing microvascular disease, with ECG changes coming first and perfusion abnormalities second and with echocardiographic changes usually absent during physical or pharmacological stress. Not all forms of myocardial ischemia are the same, and milder, patchy degrees of myocardial ischemia – like those possibly induced in microvascular angina – remain silent in its mechanical functional manifestations and may represent a physiological

scotoma of stress echocardiography (Fig. 3.8). "Anatomic lies" on the ECG may well be turned into "physiological truths," when coronary flow reserve or systemic endothelial function is considered, or even into correct prognostic predictions – possibly identifying troublemakers in the long run [24].

3.7 Equations in the Diagnosis of Ischemia

On the basis of the classic markers of ischemia, i.e., chest pain and ECG changes, diagnostic equations have been proposed and are reported in Table 3.1.

In view of the limitations of these traditional hallmarks of acute transient myocardial ischemia, "*new practical objective criteria* (*other than ECG changes and pain*) *for the diagnosis of transient myocardial ischemia are needed*" as pointed out by Maseri in 1980 [33]. The classic equations ignore the variable of wall motion and perfusion changes, both available today in the stress-echo and stress-CMR labs. It is known that the four most commonly used markers of ischemia (chest pain, electrocardiographic changes, wall motion abnormalities, and perfusion changes) identify at least partially superimposed diagnostic fields (Fig. 3.3). Considering the low diagnostic and prognostic accuracy of the traditional hallmarks of acute transient ischemia, namely, pain and ST-segment depression, the standard diagnostic equations can be profoundly remodeled by introducing new variables, such as transient wall motion abnormalities and/or perfusion changes detected during stress (Table 3.2). Regional wall motion has been present in the echo lab from the very beginning, but coronary flow reserve is a relative newcomer, brought into the lab with the advent of coronary flow reserve evaluated by pulsed Doppler transthoracic echocardiography in the stress echocardiography laboratory [34]. It is an ideal complement of regional wall motion in the stress echocardiography diagnostic one-stop shop [35]. The equations of ischemia become more robust with the integration of the two markers, one (regional wall motion) assessing mainly anatomic epicardial coronary artery disease and the other (reduced coronary flow reserve) also mirroring

Table 3.1 Classic markers of ischemia during stress

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

Table 3.2 The imaging markers of ischemia during stress

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

the functional condition of coronary microcirculation. The spectrum of responses will range anywhere from very abnormal (induced wall motion abnormalities and reduced coronary flow reserve, indicating epicardial stenosis and abnormal microcirculatory response) to completely normal (no inducible wall motion abnormalities and normal coronary flow reserve), indicating absence of hemodynamically significant macroepicardial upstream and micro, distal, downstream arteriolar coronary alterations. The stress response can be stratified into a severity code, mirroring the experimental ischemic cascade: no evidence of abnormality (normal wall motion and normal coronary flow reserve) associated with very low risk, isolated perfusion or coronary flow reserve abnormality (without inducible wall motion) associated with intermediate risk, and inducible wall motion abnormalities (usually with a perfusion or coronary flow reserve reduction) associated with the highest risk, in patients who will benefit most from ischemia-driven revascularization.

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

Conclusions

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

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

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Rational Basis of Stress Echocardiography

4

Masaaki Takeuchi, Tonino Bombardini, and Eugenio Picano

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

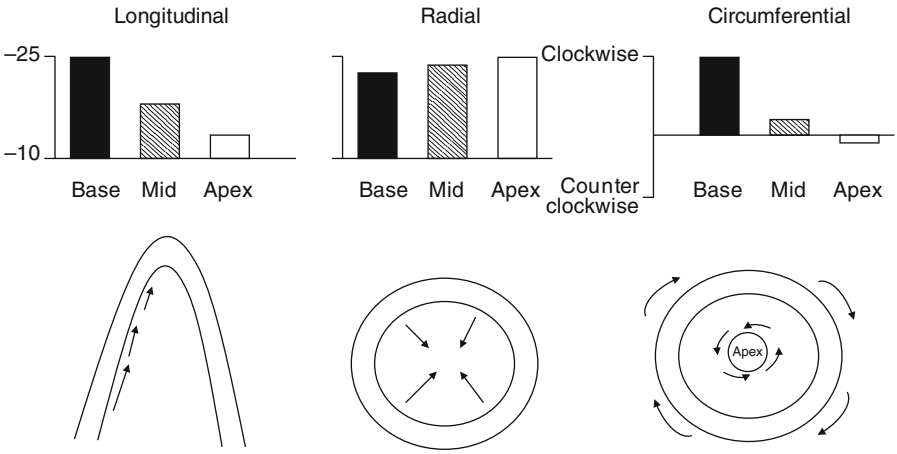

Fig. 4.1 Base-to-apex heterogeneity in radial (*middle panel*), longitudinal (*left panel*), and circumferential (*right panel*) function

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

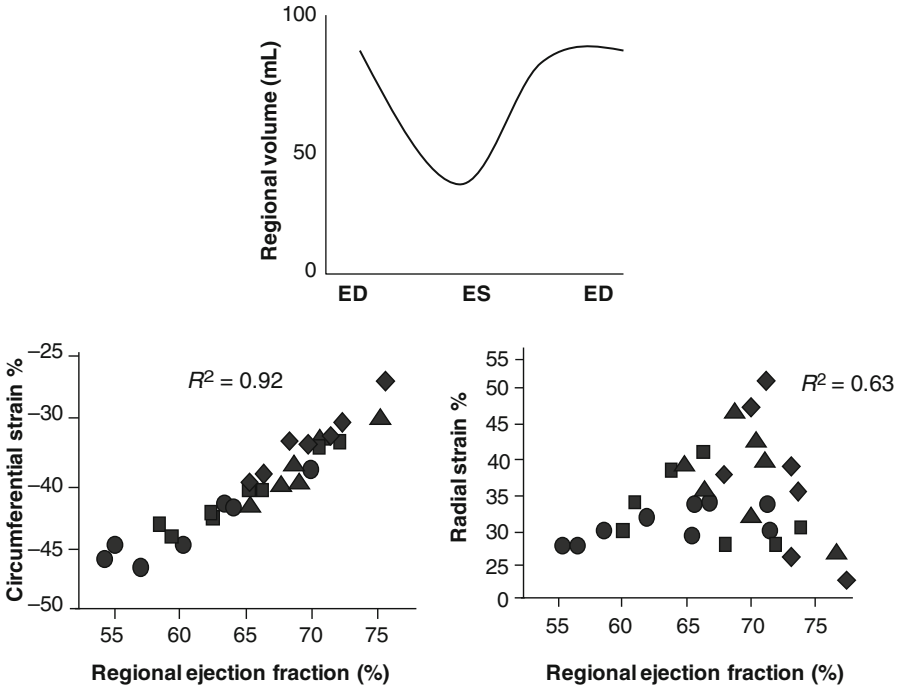

Fig. 4.2 Regional ejection fraction can be obtained with real-time 3D imaging in the echocardiography laboratory (*upper panel*). It is correlated only weakly with % systolic thickening (*lower right panel*) and tightly with circumferential strain (*lower left panel*) (Redrawn and adapted from original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

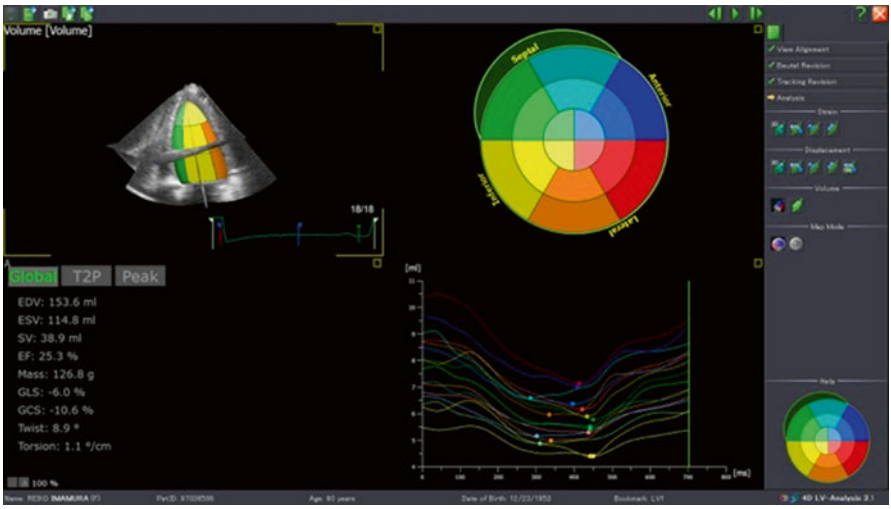

Fig. 4.3 Regional heterogeneity in left ventricular function mirrored by different peak values of regional ejection fraction by real-time 3D echocardiography in a patient with diffuse, global left ventricular dysfunction (ejection fraction = 25 %). Also the timing of contraction shows considerable dyssynchrony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

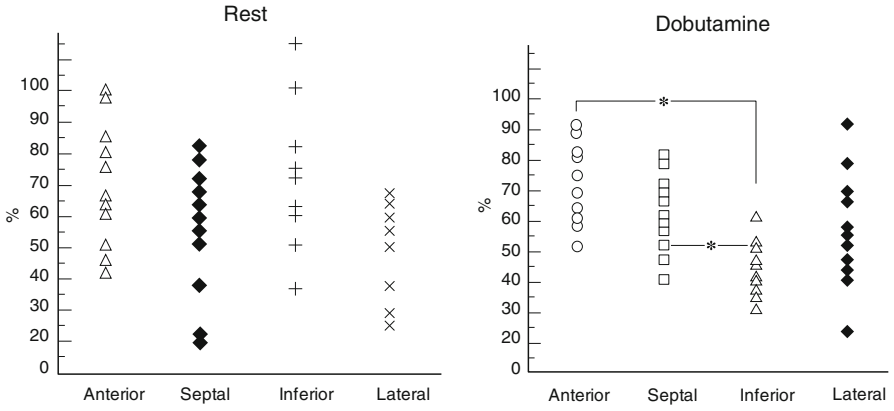

Fig. 4.4 Circumferential heterogeneity in radial strain (% systolic thickening) magnified during stress (*right panel*) in healthy subjects (From Borges et al. [5])

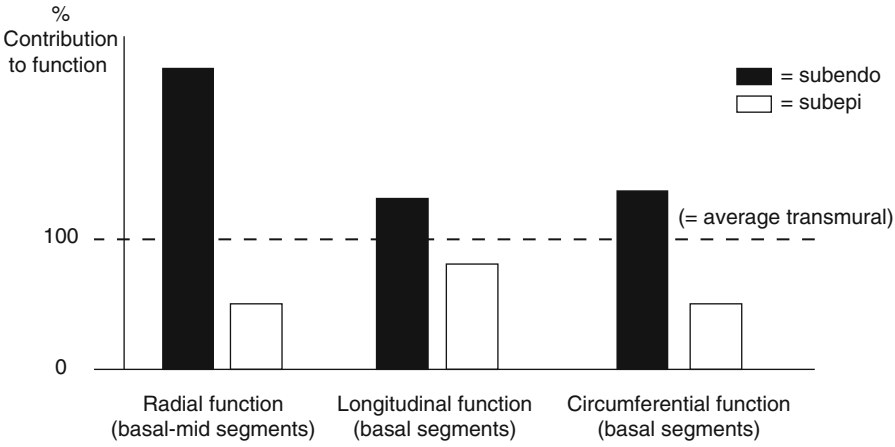

Fig. 4.5 Physiological, transmural heterogeneity determined as % systolic thickening (radial strain, *left panel*), longitudinal strain (*middle panel*), and circumferential strain (*right panel*) (Adapted from [7, 8])

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

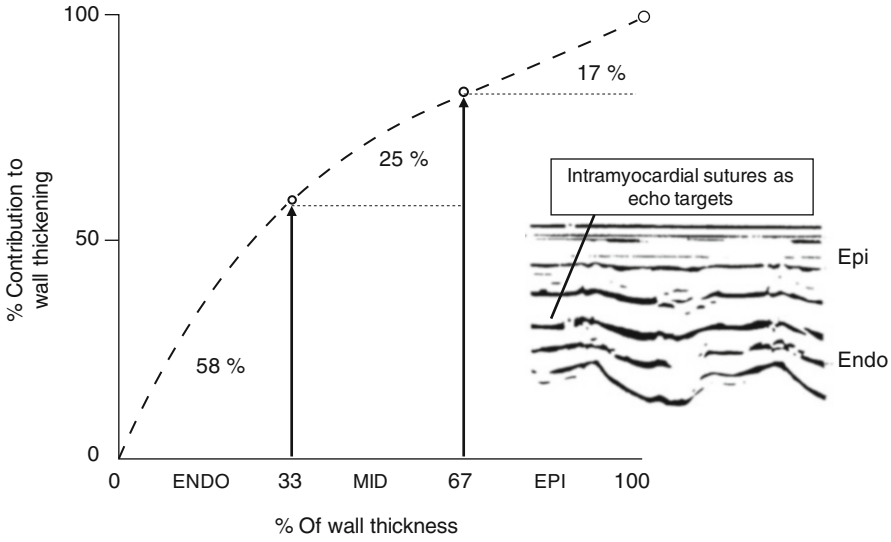

Fig. 4.6 A gradient of thickening (radial function) exists across the myocardial wall, with the inner, middle, and outer thirds of the myocardial wall contributing to 50, 25, and 17 % of total wall thickening, respectively. In the *right part* of the graph, the echocardiographic tracing obtained with 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

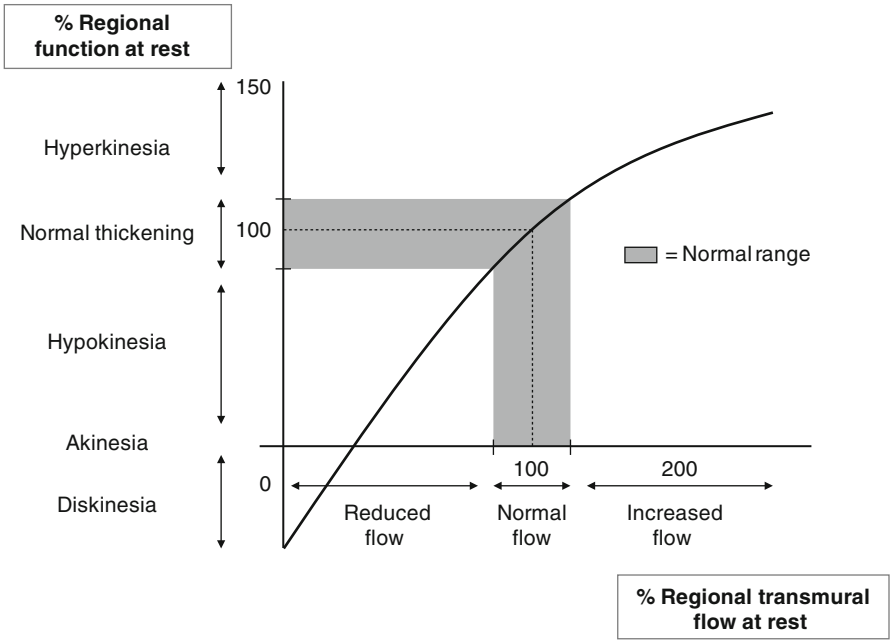

Fig. 4.7 Relationship obtained in anesthetized dogs between transmural flow (measured by microsphere) and regional function (assessed with 2D echocardiography) (Redrawn and modified from Kaul [9])

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

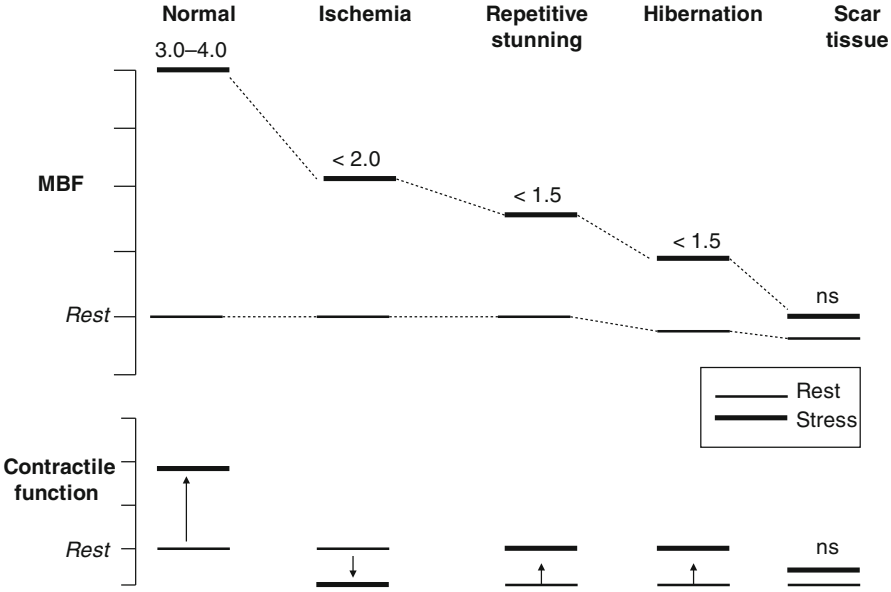

Fig. 4.8 Schematic representation of ischemia, repetitive stunning, hibernation, and scar as points of a spectrum of myocardial dysfunction. In the *upper panel*, myocardial blood flow (*MBF*). In the *lower panel*, the corresponding regional contractile function at baseline (rest) and during stress (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

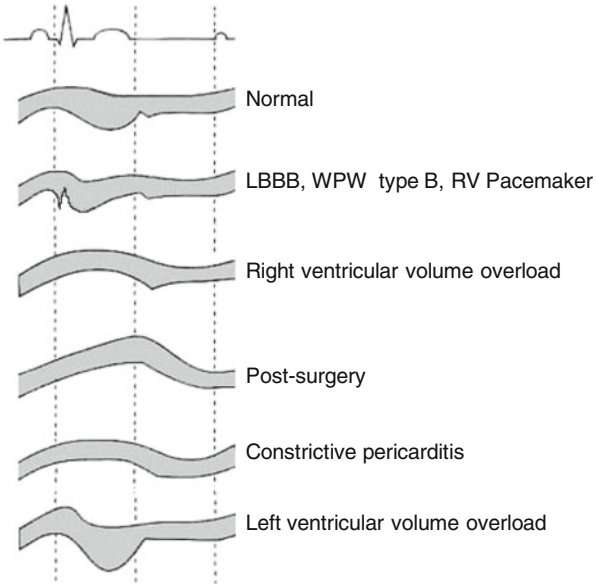

Fig. 4.9 Different types of nonischemic septal wall motion changes. Abnormal (paradoxical) septal motion can be found in a variety of conditions, including (*from top to bottom*) abnormal electrical activation (left bundle branch block, Wolff–Parkinson–White type B, paced right ventricular rhythm), right 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

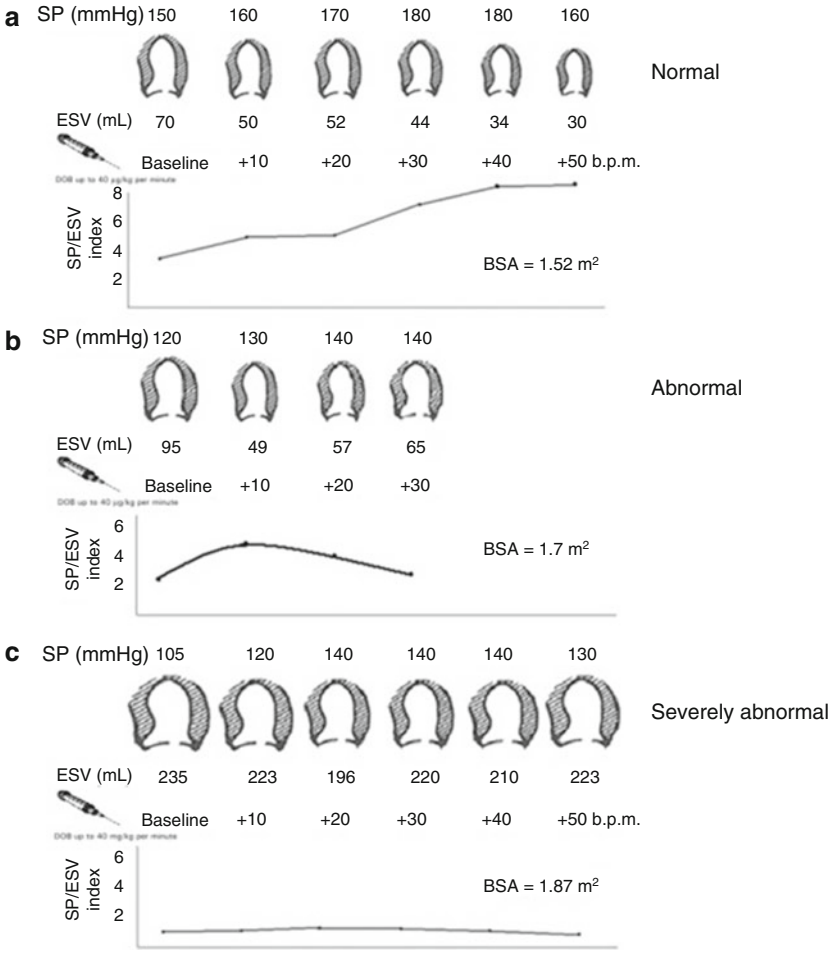

Fig. 4.10 Methodology of the PVR assessment in the stress-echo lab with a normal (*upper panel*), abnormal (*middle panel*), and severely abnormal (*lower panel*) response (Adapted and modified from Bombardini [30]). The end-systolic volume is reduced at peak stress in normal, but dilated in markedly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

5

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For a rational use of stress tests and an appropriate interpretation of their results, it may be useful to adopt a pathogenetic classification, taking into account the diagnostic end point of the test. Tests inducing vasospasm (ergonovine infusion and hyperventilation) explore the functional component. Tests trying to unmask coronary stenosis (exercise, dipyridamole, adenosine, dobutamine, pacing) mostly explore the ceiling of coronary reserve as defined by organic factors (Fig. 5.1). Some of these stressors (such as exercise) may also induce variations in coronary tone which can be superimposed on the organic factors, thus blurring the correlation between coronary anatomy and test positivity.

5.1 Ischemia and Vasospasm

Since coronary vasospasm can coexist with any degree of coronary stenosis, the presence of angiographically normal coronary arteries does not rule out the possibility of vasospastic myocardial ischemia; on the other hand, a "significant" coronary stenosis at angiography does not automatically establish a cause–effect relationship between organic disease and myocardial ischemia. In the past 20 years, we have come to appreciate the fact that the endothelium serves not only as a nonthrombogenic diffusion barrier to the migration of substances into and out of the blood stream but also as the largest and most active paracrine organ in the body, producing potent vasoactive, anticoagulant, procoagulant, and fibrinolytic substances. Normal endothelium produces two vasoactive and platelet-active products, prostacyclin and nitric oxide (NO), which act in concert to inhibit platelet adhesion and aggregation and relax vascular smooth muscle [1]. Normal endothelium also opposes a variety of vasoconstrictive stimuli, including catecholamines, acetylcholine, and serotonin, and it enhances the vasorelaxant effects of dilators, such as adenosine nucleotides. In the presence of a dysfunctional endothelium, vasodilatory stimuli – such as adenosine or dipyridamole – may become less potent, and vasoconstrictive stimuli much more effective [1]. The mechanisms of coronary spasm are still unclear. No

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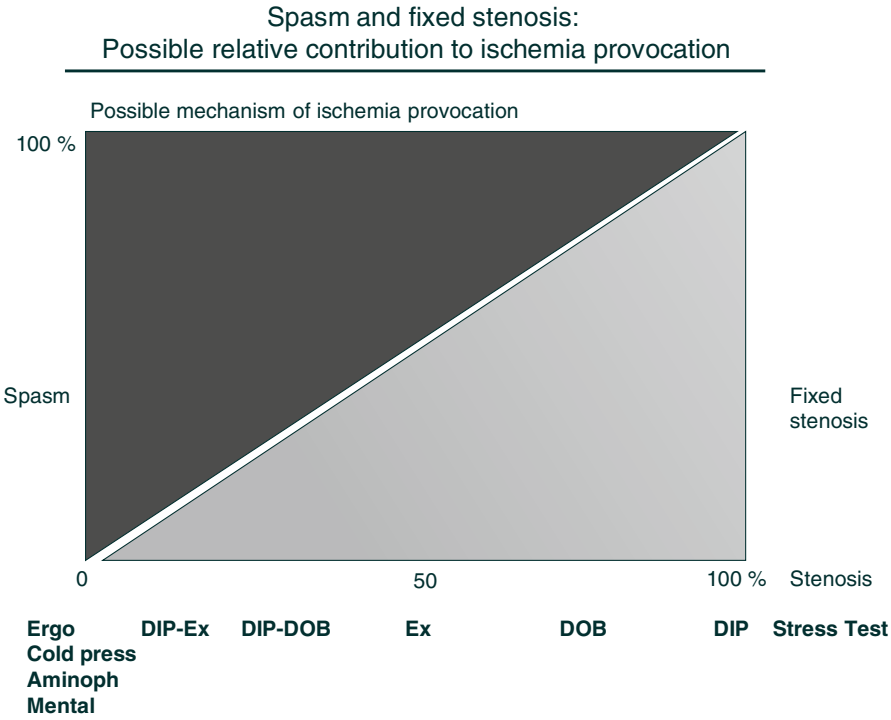

Fig. 5.1 Conceptual allocation of the tests employed in combination with echocardiography to induce ischemia via coronary vasospasm (*left*), coronary stenosis (*right*), or both mechanisms. *Aminoph* aminophylline after dip, *Cold press* cold pressor, *DIP* dipyridamole, *DOB* dobutamine, *Ergo* ergonovine, *Ex* exercise

specific receptor subtypes appear to be involved, since a variety of physical and pharmacological stimuli can provoke spasm and no specific antagonist has proved capable of preventing it. The smooth muscle cell in the medial layer of coronary epicardial arteries reacts to several vasoconstrictive stimuli, coming centripetally from the adventitial layer (such as α-mediated vasoconstriction) or centrifugally from the intima–blood interface (such as endothelin and serotonin). In fact, serotonin has a vasodilatory effect on normal human myocardial arteries, which is mediated by nitric oxide; when the endothelium is damaged, as in coronary artery disease, serotonin has a direct, unopposed vasoconstrictive effect [1]. Clinically, coronary vasospasm can be elicited by ergonovine maleate, an ergot alkaloid which stimulates both α-adrenergic and serotonergic receptors and therefore exerts a direct constrictive effect on vascular smooth muscle [2]. Hyperventilation induces spasm through systemic alkalosis. Physiologically, a powerful calcium-antagonistic action is exerted by hydrogen ions, which appear to compete with calcium ions for the same active sites both in the transmembrane calcium transport system and in the myofibrillar ATPase. Thus, vasoconstriction occurs if either calcium ion concentration increases or hydrogen ion concentration decreases. Exercise can also induce an

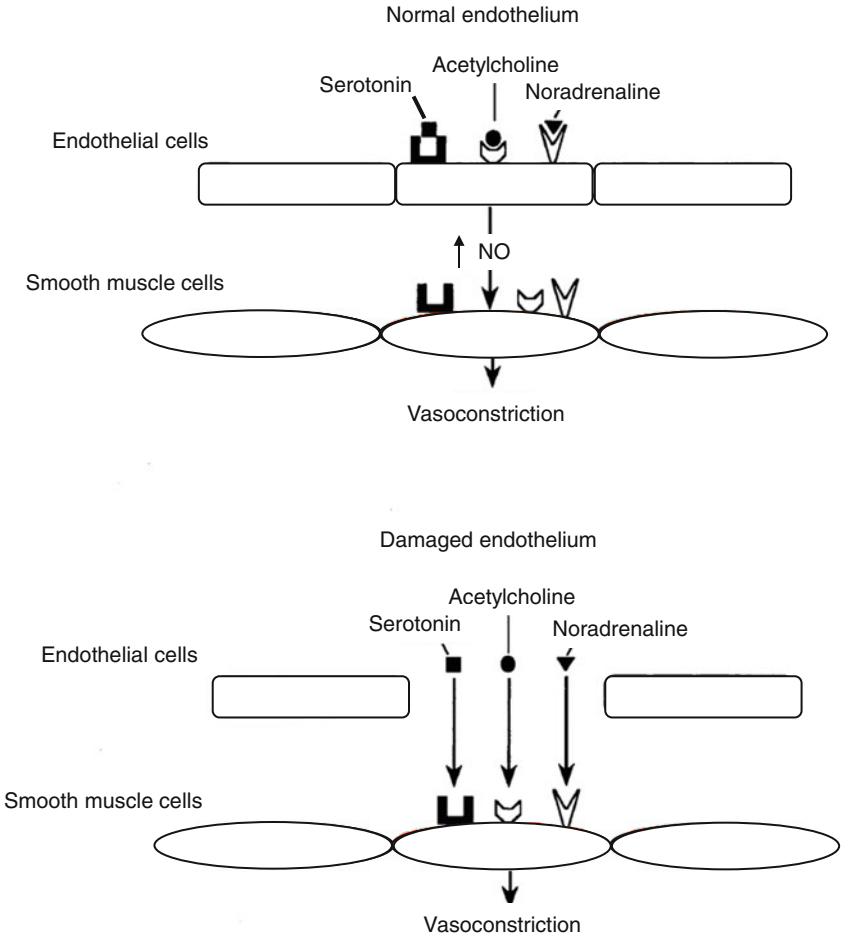

Fig. 5.2 *Top*: endothelial and smooth muscle cells in coronary vessels in the presence of intact endothelium. Mediators such as serotonin, acetylcholine, and noradrenaline stimulate the corresponding receptors present on the endothelial surface, which induce smooth muscle cell relaxation and vasodilation via nitric oxide release. *Bottom*: when endothelium is damaged, the same mediators act directly on the corresponding receptors present on the smooth muscle membrane, causing vasoconstriction

increase in coronary tone, up to complete vasospasm, through α-sympathetic stimulation [3]. Dobutamine has a vasospastic and coronary vasoconstrictive effect mediated by α-adrenergic stimulation [4, 5]. Dipyridamole has no coronary constrictive effects per se; however, interruption of the test by aminophylline (which blocks adenosine receptors but also stimulates α-adrenoreceptors) can evoke coronary vasospasm in one-third of patients with variant angina [6]. Tests exploring organic fixed (without spasm) coronary stenosis can induce ischemia by means of two basic mechanisms: (a) an increase in oxygen demand, exceeding the fixed supply, and (b)

flow maldistribution due to inappropriate coronary arteriolar vasodilation triggered by a metabolic/pharmacological stimulus. The main pharmacodynamic actions of dobutamine and dipyridamole stresses are summarized in Tables 5.1 and 5.2, respectively. Dobutamine has complex dose-dependent effects on β_1-, β_2-, and α_1-adrenoreceptors [7], whereas the principal targets of adenosine and dipyridamole are adenosine receptors, both A_1 and A_2, present both in myocardium and in coronary vessels [8]. In particular, stimulation of A_2A receptors produces marked dilation of coronary resistance vessels, determining arteriolar vasodilation, whereas A_2B receptors mediate vasodilation in conductance vessels. Myocardial A1 adenosine receptors mediate the negative chronotropic and dromotropic effects of adenosine and the direct algogenic effect. A_3 receptors are found on the surface of mast cells and may play a role in mediating bronchospasm and hypotension. Exogenous and endogenous adenosine may profoundly dilate coronary arterioles with minimal effect, if any, on systemic circulation, probably because A_2A receptors are more abundant in coronary arterioles than in any other vascular area [8]. A_1 and A_3 receptors also have a potential role in mediating preconditioning [8].

Adenosine is produced inside the cell via two pathways (Fig. 5.3), but it does not exert its effects until it leaves the intracellular environment and interacts with A_1 and A_2 adenosine receptors on the cell membrane [9]. As illustrated by the scheme in Fig. 5.3, dipyridamole acts by blocking the uptake and transport of adenosine into the cells, thereby resulting in a greater availability of adenosine at the receptor site.

Table 5.1 Pharmacodynamics of dobutamine

	Receptor populations		
	α_1	β_1	β_2
Myocardium	Increased inotropy	Increased chronotropy, increased inotropy	–
Vasculature	Vasoconstriction	–	Vasodilation

Table 5.2 Pharmacodynamics of adenosine and dipyridamole

	Receptor populations			
	A_1	A_2A	A_2B	A_3
Myocardium	Decreased chronotropy Decreased dromotropy Chest pain Preconditioning			
Vasculature		Coronary arteriolar vasodilation	Conductance vessel vasodilation	
Mast cells/ Mononuclear cells			Bronchoconstriction due to mast cell degranulation	Antinflammatory effect

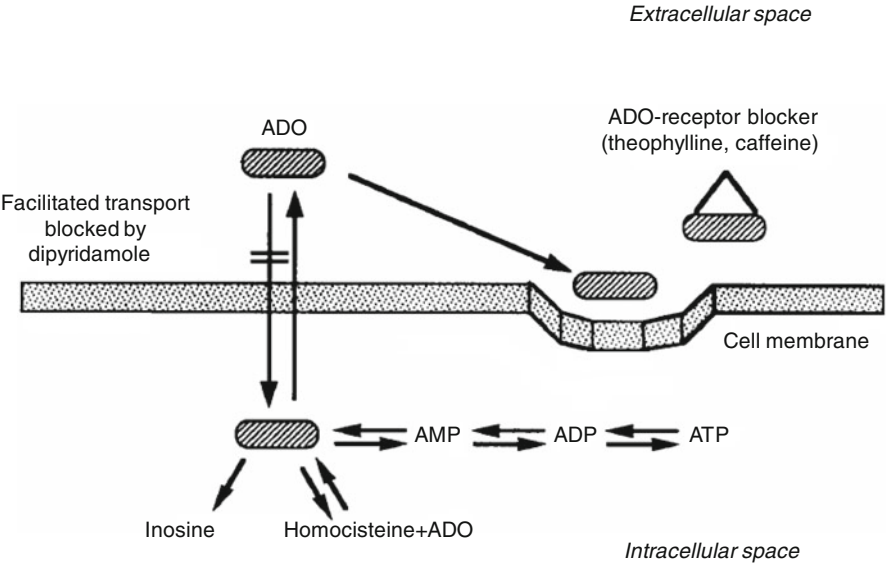

Fig. 5.3 Metabolism and mechanisms of action of adenosine in the coronary arteries. *ADO* adenosine, *AMP* adenosine monophosphate, *ADP* adenosine diphosphate, *ATP* adenosine triphosphate (Modified from Verani [9])

Both these mechanisms can provoke myocardial ischemia in the presence of a fixed reduction in coronary flow reserve due to organic factors (involving the epicardial coronary arteries and/or myocardium and/or microvasculature).

5.2 Increased Demand

This mechanism can be easily fitted into the familiar concept framework of ischemia as a supply–demand mismatch, deriving from an increase in oxygen requirements in the presence of a fixed reduction in coronary flow reserve. The different stresses can determine increases in demand through different mechanisms (Fig. 5.4).

In resting conditions, myocardial oxygen consumption is dependent mainly on heart rate, inotropic state, and left ventricular wall stress (which is proportional to the systolic blood pressure and left ventricular radius) [10]. Following dipyridamole or adenosine administration, due to their vasodilatory action, there are some decrease in the blood pressure with the compensatory increase of the sympathetic tone and consequent increase in contractility and heart rate [11].

During exercise, the increase in heart rate, blood pressure, and inotropic state accounts for the overall increase in myocardial oxygen consumption (Fig. 5.4) [12]. To a lesser degree, pacing and dobutamine also increase myocardial oxygen demand [13]. During pacing, the increase is mainly due to the increased heart rate. Dobutamine markedly increases contractility and heart rate (Fig. 5.4). Greater

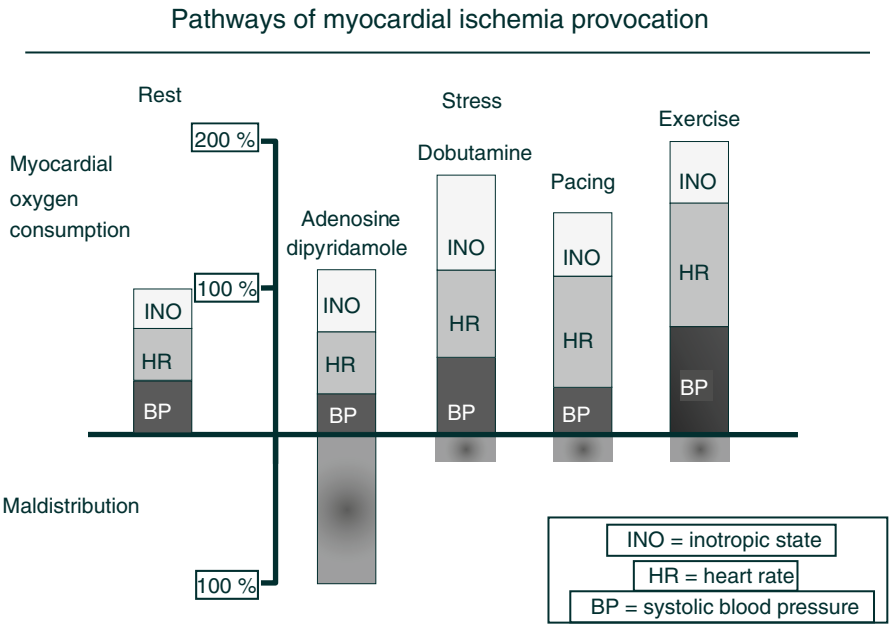

Fig. 5.4 Major determinants of myocardial oxygen consumption in resting conditions (*left*) and during some stresses (*right*) commonly employed with echocardiography. The relative contributions of systolic blood pressure, heart rate, and inotropic state to myocardial oxygen demand are represented. During dipyridamole or adenosine stress, there is a mild increase in oxygen consumption, due to the increase in the heart rate and inotropic state, respectively. The rise in oxygen demand is even more marked during exercise, which causes an increased heart rate as well as increased inotropic state and systolic pressure (Redrawn and modified from Picano [10])

myocardial oxygen consumption due to heart rate increase occurs with the coadministration of atropine with dobutamine [14] and dipyridamole [15, 16].

5.3 Flow Maldistribution

In the presence of coronary atherosclerosis, appropriate arteriolar dilation can paradoxically exert detrimental effects on regional myocardial perfusion, causing overperfusion of myocardial layers or regions already well perfused in resting conditions at the expense of regions or layers with a precarious flow balance in resting conditions [17, 18].

In "vertical steal," the anatomical requisite is the presence of an epicardial coronary artery stenosis, and the subepicardium "steals" blood from the subendocardial layers. The mechanism underlying vertical steal is a fall in poststenotic pressure secondary to the increase in flow across the stenosis [19]. From the hydraulic viewpoint, it is well known that even in the presence of a fixed anatomical stenosis, resistance is not fixed. After administration of dipyridamole, the arterioles dilate,

thereby increasing flow across the stenotic lesion. This increased flow may lead to a greater drop in pressure, the magnitude of which is related to the severity of the stenosis and to the increase in flow. In the presence of a coronary stenosis, the administration of a coronary vasodilator causes a fall in poststenotic pressure and therefore a critical fall in subendocardial perfusion pressure which in turn provokes a fall in absolute subendocardial flow, even with subepicardial overperfusion. In fact, the coronary autoregulation curve can be broken into two different curves, with the subendocardium more vulnerable than the subepicardium to lowering of coronary perfusion pressure. Regional thickening is closely related to subendocardial rather than transmural flow, and this explains the "paradox" of a regional asynergy, with ischemia in spite of regionally increased transmural flow. Because endocardial oxygen demands are greater than epicardial ones, the resistance vessels of the endocardium are more dilated than those of the subepicardium, ultimately resulting in selective subendocardial hypoperfusion.

"Horizontal steal" requires the presence of collateral circulation between two vascular beds (Fig. 5.5); the victim of the steal is the myocardium fed by the more stenotic vessel. The arteriolar vasodilatory reserve must be at least partially preserved in the donor vessel and abolished in the vessel receiving collateral flow [20, 21]. After vasodilation, the flow in the collateral circulation is reduced relative to resting conditions, since the arteriolar bed of the donor vessel "competes" with the arteriolar bed of the receiving vessel, whose vasodilatory reserve was already exhausted in resting conditions (Figs. 5.5 and 5.6).

The stresses provoking this flow maldistribution act through a "reverse Robin Hood effect" [22]; unlike the hero who stole from the rich to give to the poor [23, 24], they steal from the poor (myocardial regions or layers dependent on a critically stenosed coronary artery) and give to the rich (regions or layers already well nourished in resting conditions). The biochemical effector of this hemodynamic mechanism is the inappropriate accumulation of adenosine, which is the main physiological modulator of coronary arteriolar vasodilation. Inappropriate adenosine accumulation can be triggered either by a metabolic stimulus (such as exercise or pacing) or by a pharmacological one (such as exogenous adenosine or dipyridamole, which inhibits the cellular reuptake of endogenously produced adenosine) [25]. It is certainly difficult to quantify the relevance of flow maldistribution in inducing ischemia, but this mechanism is likely to play a key role in adenosine- or dipyridamole-induced ischemia and a relatively minor, although significant, role in exercise- or pacing-induced ischemia [23–26]. Theoretically, dobutamine might also induce a moderate degree of flow maldistribution by stimulating β-adrenergic receptors, which mediate coronary arteriolar vasodilation [27] (Fig. 5.7).

5.4 Exercise-Simulating Agents

Among stresses, a currently used differentiation is between "exercise-simulating agents," such as dobutamine and vasodilator stressors, such as dipyridamole or adenosine. It is important to emphasize that none of the pharmacological stresses are

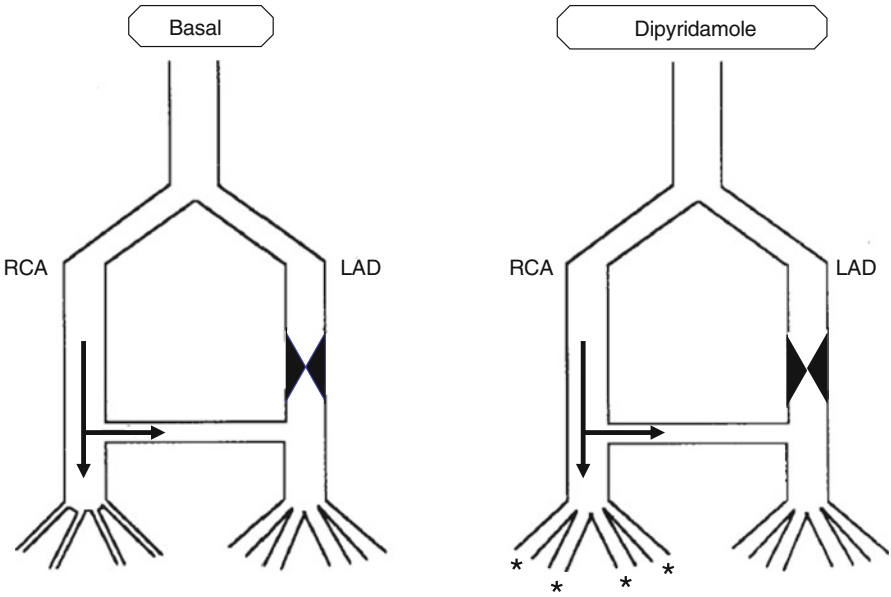

Fig. 5.5 Hydraulic model illustrating coronary horizontal steal. For this example, the right coronary artery (*RCA*) is the supply artery, with the vascular distribution of the severely stenotic left anterior descending (*LAD*) artery supplied by collaterals from the right coronary artery. Coronary steal following coronary arteriolar vasodilation refers to a decrease in absolute forward flow through collateral channels to the collateral-dependent vascular bed. With vasodilation of distal coronary arteriolar beds, there is a flow-related drop in pressure along the supply artery. Therefore, distal perfusion pressure to the collateral vessels falls since collateral flow depends primarily on the driving pressure gradient (between distal perfusion pressure of the supply and collateralized vascular bed) (Redrawn and modified from Picano [17])

"exercise simulating" in a strict sense. Only exercise offers complex information not only on coronary flow reserve but also on cardiac reserve and cardiovascular efficiency (i.e., how the coronary reserve is translated into external work). Coronary reserve and cardiovascular efficiency are codeterminants of exercise tolerance and therefore of the quality of life for the individual patient. No pharmacological stress can mimic the complex hemodynamic, neural, and hormonal adaptations triggered by exercise, nor can they offer information on cardiovascular efficiency. Exercise explores the entire physiological chain supporting external work: the psychological motivation, central and peripheral nervous system, lungs, myocardium, coronary circulation, peripheral blood circulation, and skeletal muscle down to cell respiration and mitochondrial oxygen utilization [28]. Of this chain, pharmacological stresses only test the "coronary" ring. From the echocardiographic viewpoint, the mechanical pattern of stress-induced function increase differs between exercise and pharmacological stresses – including dobutamine [29]. From the clinical viewpoint, changes in rate–pressure product can stratify disease severity with exercise, not with pharmacological stresses. Antianginal therapy affects pharmacological stress results – and especially dobutamine results (as discussed in more detail in Chap. 12)

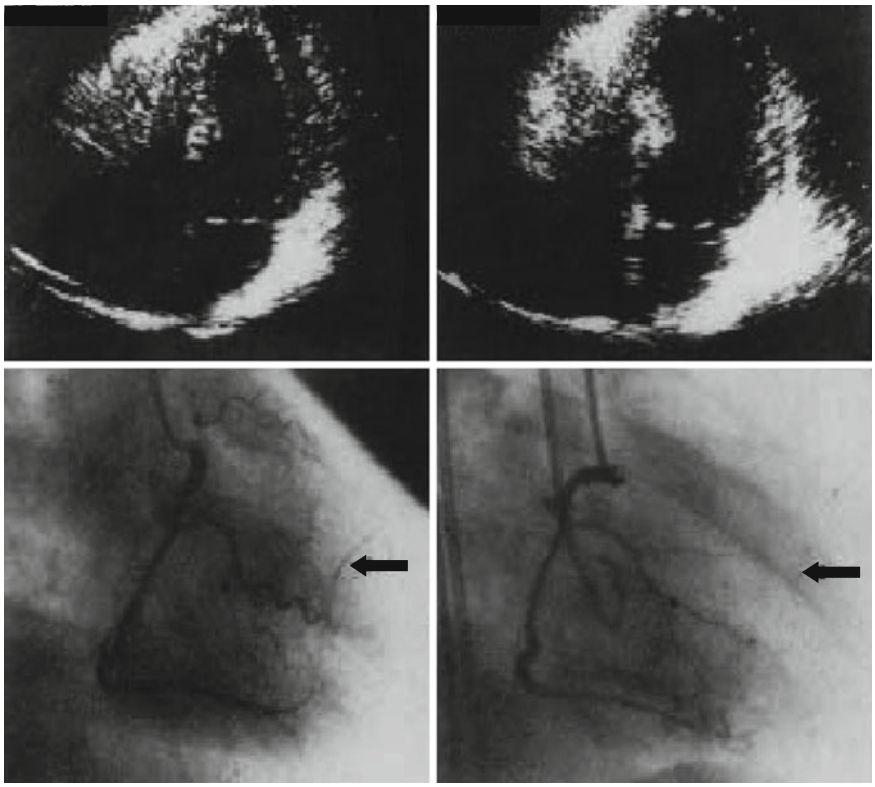

Fig. 5.6 An example in which collaterals were supplied by the right coronary artery to the occluded left anterior descending artery. Two-dimensional echocardiographic frames, taken at end systole (*top*), and coronary angiographic images (*bottom*), obtained in basal conditions and after dipyridamole administration. After dipyridamole, the apex is dyskinetic; the coronary angiography shows almost total disappearance of the collateral vessels (*arrows*) (Modified from Picano [17])

in a manner largely unrelated to the effects of the same therapy on exercise. Finally, arrhythmias, heart rate, and blood pressure response enrich the diagnostic information obtainable with exercise stress testing, not with pharmacological testing. On the other hand, all stresses can be considered "exercise simulating" for the purpose of diagnosing coronary artery disease. Their mechanism of action is the extreme exaggeration of a biochemical and hemodynamic mechanism actually operating during exercise, such as adrenergic stimulation with dobutamine or adenosinergic stimulation with dipyridamole [23–25].

Last but not least, from a less physiological but more pragmatic point of view, all stresses should be considered exercise simulating since they induce ischemia with similar frequency, in the same region, and to a comparable degree as exercise. They also titrate the positive response, but the equivalent of the ischemic workload is the drug dose (the "pharmacological dose load") sufficient to elicit ischemia.

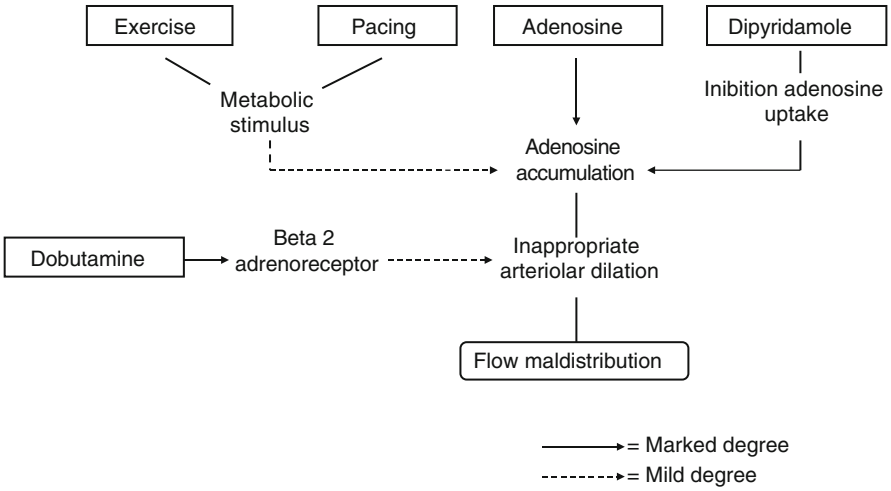

Fig. 5.7 The biochemical pathways leading to inappropriate arteriolar vasodilation under different stresses

5.5 New Pharmacological Stresses

In the family of catecholaminic stresses, there was attempt with arbutamine. It was characterized by a potent β-agonist effect, with a stronger chronotropic and a milder inotropic action than dobutamine. It might be considered conceptually similar to a pacing test, since it stresses the myocardium mainly through an increase in heart rate [30]. It is not now in use anymore. For vasodilator stresses as well, the new A2A agonist (regadenoson) with short half-life (2–3 min vs. up to 15 h for dipyridamole vs. 30 s for adenosine) which may be given in IV bolus (in contrast to dipyridamole and adenosine which have to be administered by IV infusion) was introduced [31–33]. The idea behind its development was to have less side effects with the drug which action is long enough to be administered as IV bolus (see Chap. 14).

5.6 The Atropine Role

Atropine is a naturally occurring antimuscarinic drug consisting of an alkaloid of the belladonna plants. During the time of the Roman Empire, the plant was frequently used to produce poison. This prompted Linnaeus to name the shrub *Atropa belladonna*, after Atropos, the eldest of the Three Fates, who cuts the thread of life. The name belladonna (i.e., "beautiful woman") derives from the alleged use of this preparation by Italian women to dilate their pupils [34]. Atropine is the prototype of antimuscarinic drugs, which inhibit the actions of acetylcholine on anatomical effectors innervated by postganglionic cholinergic nerves. The main effect of atropine on the heart is to induce tachycardia by blocking vagal effects on the M2 receptors on the

sinoatrial nodal pacemaker. Atropine also enhances atrioventricular conduction, and for this reason it is usually given before pacing stress (see Chap. 15). Atropine-induced mydriasis may occasionally raise the intraocular pressure in patients with glaucoma, which is therefore a contraindication to atropine administration. Atropine also decreases the normal amplitude of bladder contraction, and severe prostatic disease is thus another contraindication to atropine administration. Finally, atropine reduces gastrointestinal tract motility and secretion and for this reason can be given before transesophageal stress. Administration of atropine on top of dobutamine [14] vasodilators [15, 16], or exercise [35, 36, 37] improves diagnostic sensitivity. Not surprisingly, however, the risk of resistant ischemia increases with atropine [38, 39], along with nonischemic side effects, including (as described in dobutamine plus atropine) atropine intoxication [40], consisting of restlessness, irritability, disorientation, hallucinations, or delirium, usually disappearing spontaneously over a few hours.

5.7 The Combined Stress Approach

The combined stress can be either dipyridamole–exercise or dipyridamole–dobutamine. There are also attempts and reports on combining mental stress test and exercise [41, 42].

Dipyridamole causes only a trivial increase in myocardial oxygen demand, provoking ischemia mainly through flow maldistribution phenomena triggered by endogenous adenosine accumulation. The flow increase achieved by a high dipyridamole dose lasts for a relatively long time, remaining at plateau for about 30 min and, therefore, representing an ideal "flow maldistribution" background over which another stress can be superimposed. It has previously been shown that dipyridamole does not block the hemodynamic response of exercise [43] or dobutamine [44] and that it potentiates the ischemic potential of both exercise and dobutamine. The underlying hypothesis is that a stepwise increment of myocardial oxygen consumption – unable per se to elicit ischemia in the presence of mild coronary artery disease – might reach the critical threshold when the ischemic ceiling is lowered by concomitant flow maldistribution triggered by dipyridamole infusion [43] (Fig. 5.8). The clinical fact is that the combined stress test can detect anatomically milder forms of coronary disease missed by either test used separately [43–45].

5.8 Vasodilatory Power and the Hierarchy of Testing

Each of the prototype stresses for the detection of coronary artery disease can induce ischemia through either one of the three main pathophysiological pathways: spasm, "steal effect" (also named flow maldistribution), and increased oxygen demand.

No stress is 100 % "pure," since adenosine and dipyridamole also slightly increase heart rate and exercise and dobutamine also induce a certain (mild) degree of flow maldistribution. Both families of stresses are more or less equally effective as ischemic stressors in the presence of significant coronary artery disease (Fig. 5.9).

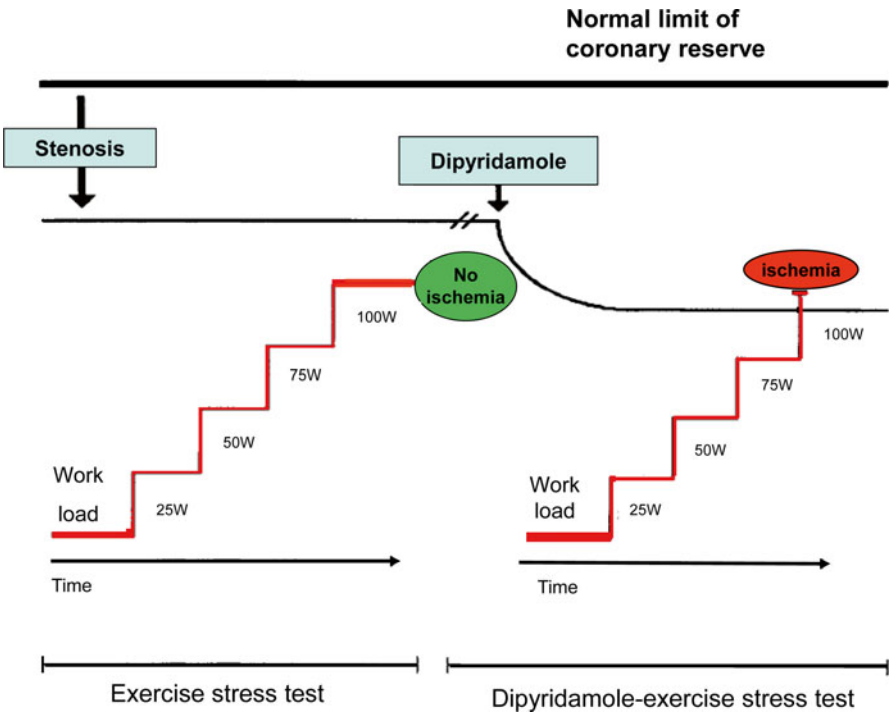

Fig. 5.8 Dipyridamole sensitization of the ischemic potential of exercise. Coronary stenosis (*thick arrow*) may permanently although not severely lower the maximal flow availability (coronary reserve), so that the myocardial ischemic threshold is not reached with an "ordinary" exercise stress test. With dipyridamole premedication (*thin arrow*), the hemodynamic response to exercise is not prevented (normal stepwise increase in workload), but the maximal flow availability is significantly lowered for the occurrence of flow maldistribution phenomena (From Picano et al [43] with permission)

For a given ischemic diagnostic marker (for instance, regional wall motion abnormalities with stress echocardiography), sensitivity is higher for tests combining the two pathways (such as dipyridamole–exercise, dipyridamole–dobutamine, or dipyridamole-atropine) when compared with tests based on one pathway (dipyridamole or dobutamine or exercise) alone. Different stressors are not competitors but allies as there are some comorbidities which are contraindications for particular stressor (regarding atropine mentioned above) [46]. Relative contraindications for dobutamine are hypertension and arrhythmias. Adenosine and dipyridamole are not recommended in bronchial asthma, sinoatrial and atrioventricular blocks, as well as patients taking dipyridamole. Common contraindications for all pharmacological stressors are pregnancy (or attempt to get pregnant) and breastfeeding. Some people due to skeletomuscular problems and/or poor motivation cannot exercise. Therefore in order to diagnose coronary artery disease as well as to conduct efficient follow-up post-myocardial revascularization, each stress-echo lab should be familiar with different stressors. Those stressors may be used like fishermen use nets to catch large-, medium-, or small-sized fish, i.e., to detect mild, moderate, and severe coronary

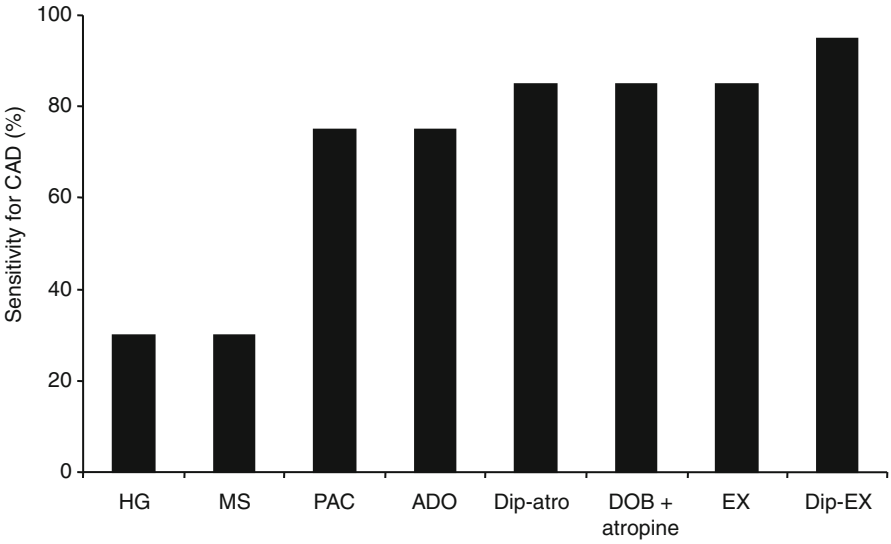

Fig. 5.9 The hierarchy of test sensitivity for the diagnosis of coronary artery disease. The sensitivity is highest for tests combining the two main mechanisms of increased oxygen consumption and steal phenomena. *Dip–Ex* dipyridamole–exercise, *Dip* dipyridamole, *Ado* adenosine, *Dob* dobutamine, *HG* handgrip, *MS* mental stress, *PAC* pacing

heart disease ("the fisherman approach"). As presented in Fig 5.10, dipyridamole or adenosine alone will detect the most severe disease (3 – vessel disease, left main, the sickest of the sick – troublemakers in the relatively short run) and, at the other end of the spectrum, combined dipyridamole with dobutamine or exercise will detect the mild forms (milder single-vessel disease) [47].

The relevance of the steal effect is also directly mirrored by the stress capacity to recruit coronary flow reserve. Adenosinergic stresses are ideally suited for this, since – unlike dobutamine or exercise associated with a threefold flow increase – they determine a fivefold increase in coronary blood flow with a full recruitment of pharmacological flow reserve [48]. The greater the vasodilation, the higher the potential for inappropriate steal phenomena in the presence of coronary artery disease. In recent years, the two different sides of the coin of the stress test, vasodilatory and ischemic stress, merged in the dual imaging of coronary flow reserve and wall motion during vasodilatory stress echocardiography [50, 51, 52]. Triple imaging, i.e., perfusion in addition to wall motion abnormalities and coronary flow reserve with dipyridamole contrast echocardiography, has been described [52].

5.9 Different Pathophysiological Approaches in the Stress-Echo Lab

The use of stress to increase myocardial oxygen demand in order to provoke ischemia is like the classic straddle method in the high jump: it is conceptually familiar to everybody (everyone has tried it at least once) and it is pushed forward by the

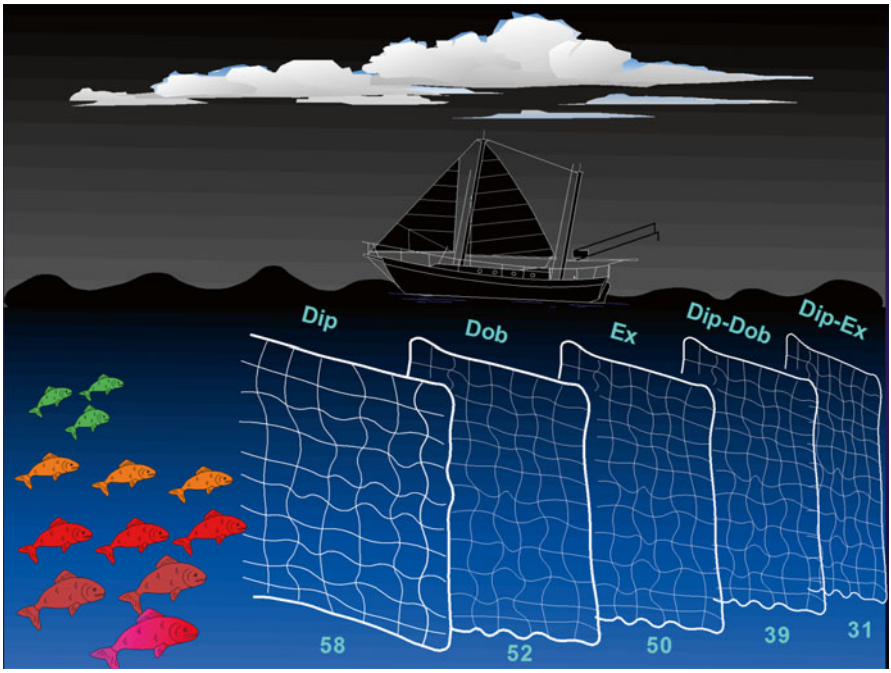

Fig. 5.10 The Fisherman approach: No coronary artery disease (*CAD*) up to very severe CAD are presented as small fish (*green*) up to the biggest ones (*purple*), respectively. The nets with different size holes from the biggest up to the smallest, i.e., dipyridamole (*Dip*), dobutamine (*Dob*), exercise (*Ex*), Dip–Dob, and Dip–Ex are presented. The "size of the holes" for the each stress was determined at the optimal cut-off between sensitivity and specificity where coronary angiography was used as the gold standard for the each particular test in the same set of patients. It may be appreciated that cut-off for Ex was exactly 50 % stenosis (as postulated in animal experiments), for Dip, Dob, Dip–Dob, and Dip–Ex those cut-offs were 58 %, 52 %, 39 %, and 31 %, respectively. Therefore if the interest is just to catch a big fish, Dip will be used

force of tradition. The steal effect is like the "Fosbury flop": it is more recent, may appear counterintuitive, but works at least as well as the straddle method. As a young high jumper in the early 1960s, Dick Fosbury had trouble mastering the standard technique, called the straddle, so he began doing the high jump by approaching the bar with his back to it instead, doing a modified scissor kick and going over the bar backward and horizontal to the ground. As goofy as it looked, it worked. Similarly, as strange as it may look within the supply–demand mismatch framework, the concept of inducing ischemia through a vasodilator instead of by increasing myocardial oxygen demand has worked. Fosbury caused a sensation when he won the gold medal in the 1968 Olympics. The Fosbury flop has since become a standard technique for high jumpers – whether Olympic champions pushing forward the limits of the specialty or kids in gym class at elementary school. Thirty years after the initial proposal in 1985, vasodilatory stress echocardiography is the convenient option for primary care stress echocardiographers, who will benefit from a stress that pollutes the image quality very little, reducing the problems of interpretation. It is also a good option for stress echocardiographers with top-level expertise

and technology, since it allows one to combine wall motion and coronary flow imaging in the same stress [49, 50]. Dual imaging has been recommended by European guidelines as the state-of-the-art approach along with pharmacological stress echocardiography [51]. Recently from the experience of nuclear cardiology imaging in detecting coronary artery disease by using adenosine and synthetic adenosine A2A receptor agonist (regadenoson), serious complications (acute myocardial infarction, cardiac arrest, and death) were observed in patients having signs and symptoms of unstable angina [53]. Although that number is very small having in mind that millions of tests have been done, it prompted FDA to issue a warning on November 20, 2013, advising a special caution in using them and whenever possible switching to dipyridamole or dobutamine. In stress-echo community, it has been very well emphasized from the very beginning by conducting international multicenter registries that provoking myocardial ischemia is like playing with fire, i.e., test is indicated only when the benefit of establishing diagnosis outweighs the risk of test, whatever it is [40, 54].

5.10 Clinical Guidelines

For functional imaging, exercise, dobutamine, and vasodilators have similar diagnostic accuracy, when appropriately high doses of drugs are used. For combined perfusion and functional imaging, vasodilators appear to be more user-friendly. There is no complication free stress-echo test, so it should be used when the benefit of establishing diagnosis outweighs the risk in each individual patient [51, 55–57]. Being an expert not just as stress echocardiographer, but as cardiologist in the field of coronary artery disease is the prerequisite for successful taking care of the patients.

Table of Contents Video Companion

See also in the section Selected presentations: Pharmacologic and myocardial effects of adenosine and dipyridamole

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Echocardiographic Signs of Ischemia

6

Nicola Gaibazzi and Eugenio Picano

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

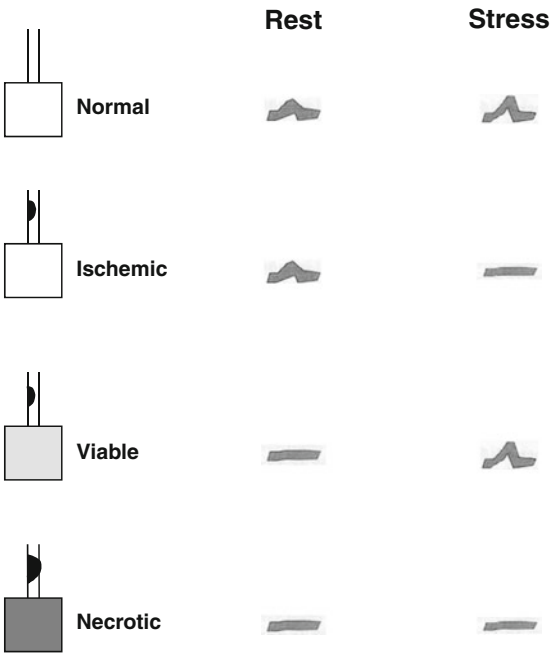

Fig. 6.1 Stress echographic patterns of normal (*upper row*), ischemic (*second row*), viable (*third row*), and necrotic (*fourth row*) responses are schematically represented. On the *left side*, the corresponding schemes of the coronary artery (*parallel lines*) and the myocardium (*box*) are shown. 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

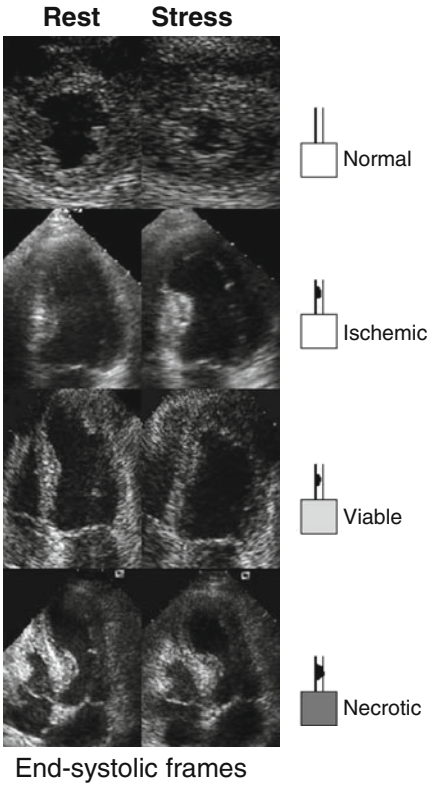

Fig. 6.2 Echocardiographic examples of normal (*upper row*), ischemic (*second row*), viable (*third row*), and necrotic (*fourth row*) responses. On the *left side*, the end-systolic frames of a rest (*left part*) and a stress (*right part*) study are shown. In a viable myocardium with resting dysfunction 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

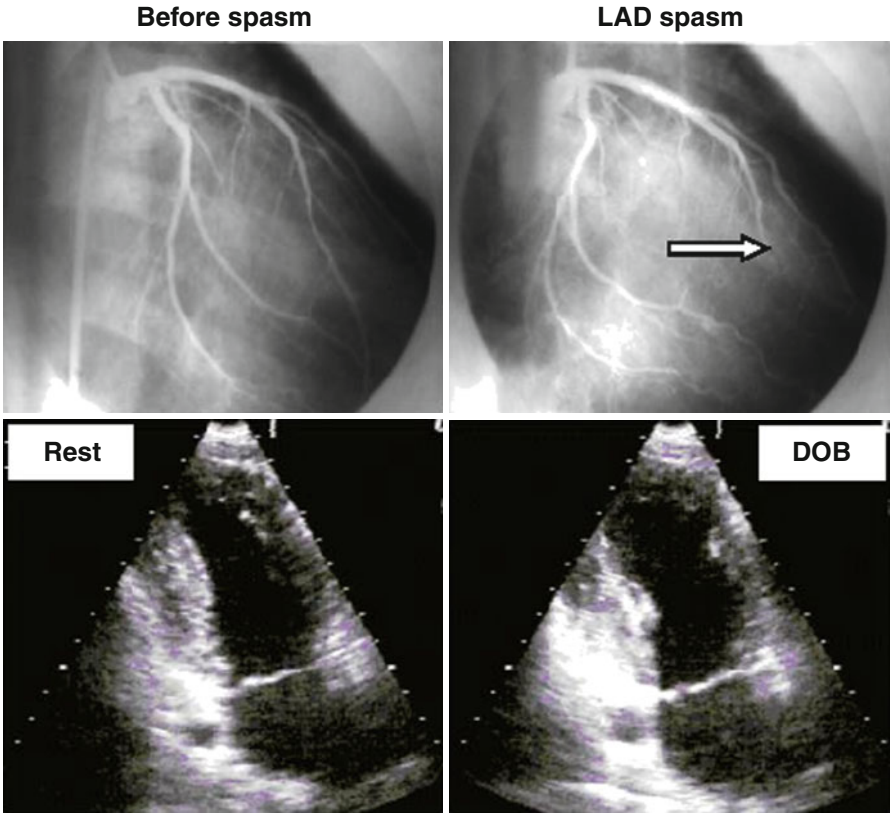

Fig. 6.3 Normal coronary angiogram (*left upper panel*), spontaneous spasm of the left anterior descending coronary artery of the same patient (*right upper panel, indicated by arrow*), and end-systolic frames of the patient in two-chamber view at rest (*left lower panel*) and at peak stress (*right 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.

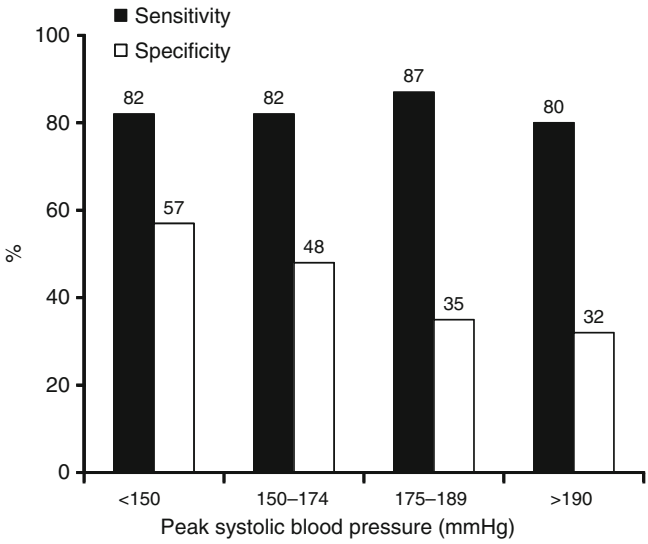

Fig. 6.4 Sensitivity (*empty bars*) and specificity (*full bars*) of exercise echocardiography according to peak systolic blood pressure response during exercise (Modified from Ha et al. [27])

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

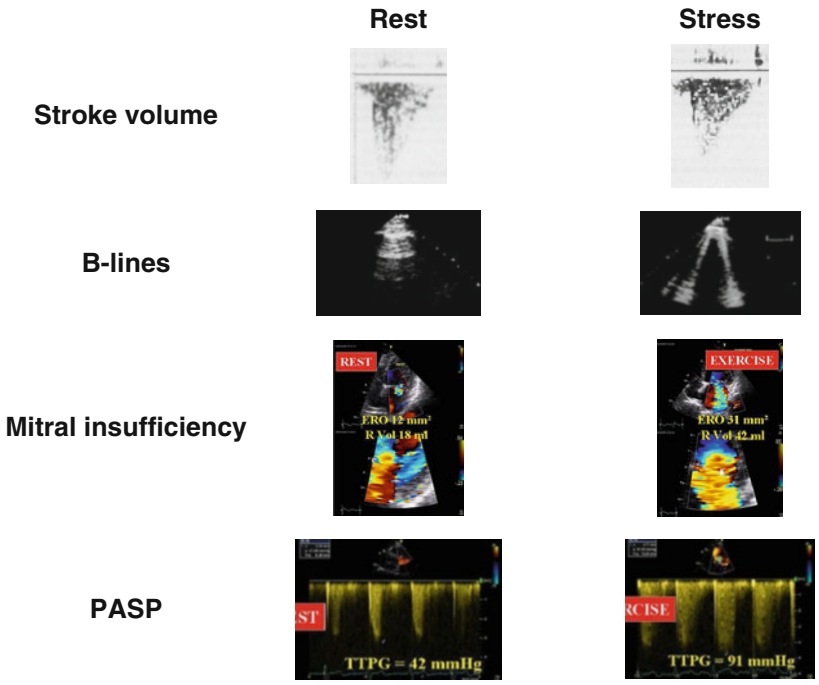

Fig. 6.5 Ancillary signs of ischemia: fall in stroke volume, increase in B-lines, acute severe mitral insufficiency, and rise in pulmonary artery systolic pressure. Each of these signs has an ominous prognostic meaning

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

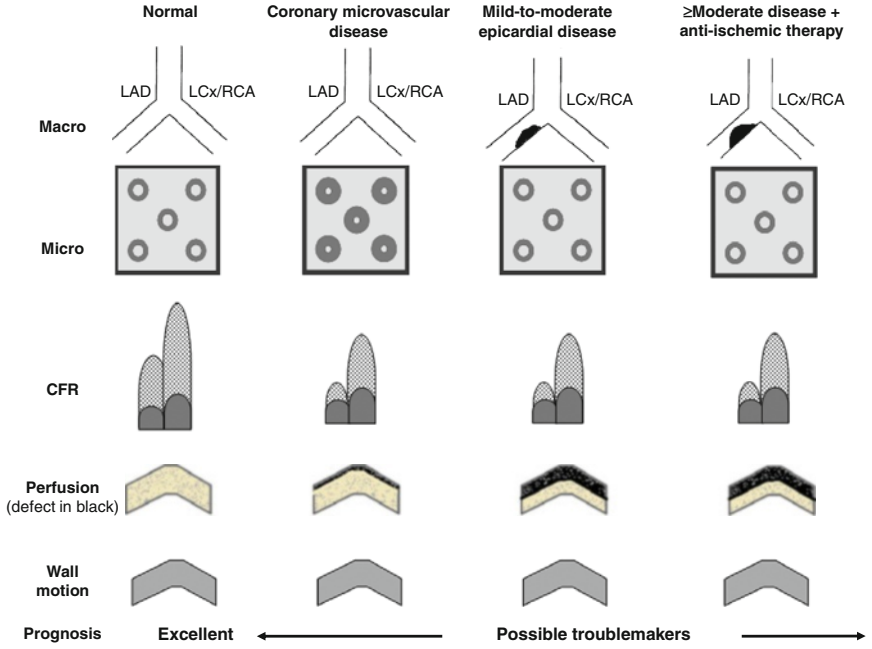

Fig. 6.6 Pathophysiological and prognostic heterogeneity behind normal wall motion response during stress. In the *upper panel*, we show epicardial coronary arteries: normal in the *first two columns*, with moderate disease in the *third column* and moderate-to-severe disease but concomitant, effective 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:

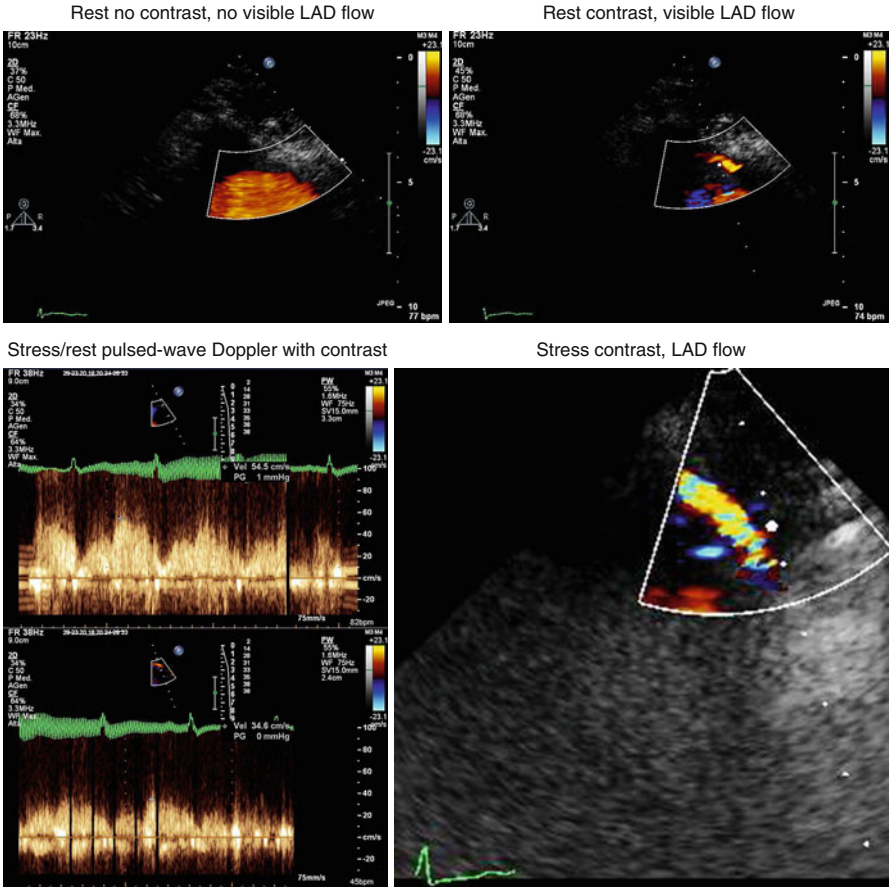

Fig. 6.7 The use of contrast for the enhancement of the LAD color flow in technically difficult cases, in which rest coronary flow is difficult to localize. Figure (lower part) also shows the downside of noisier pulsed-wave Doppler tracings, although quality is usually sufficient for the measurement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

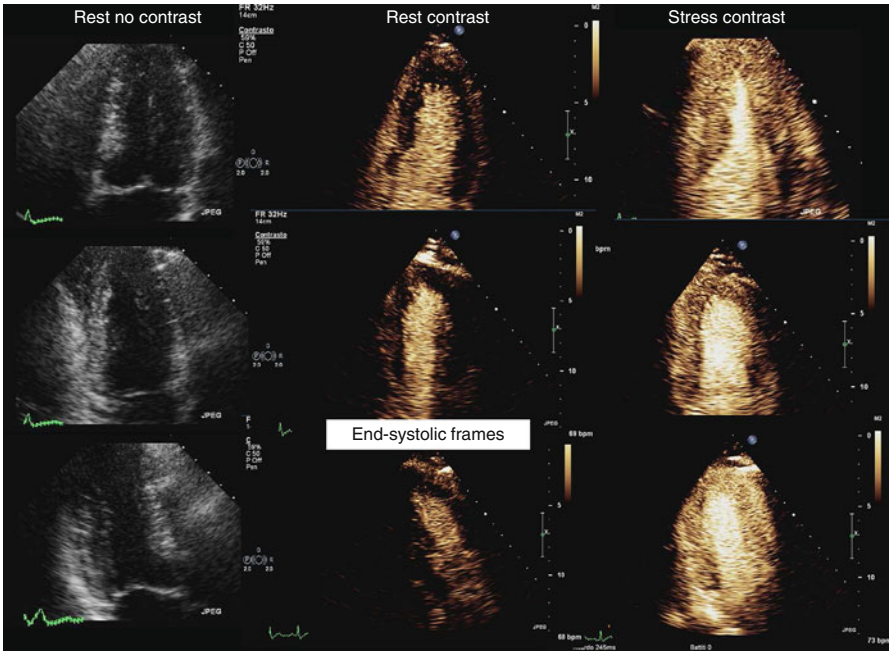

Fig. 6.8 The appearance of four-chamber, two-chamber, and three-chamber end-systolic frames, both at rest (*mid*) and stress (*right*) phases, when using low-mechanical index real-time imaging in conjunction with contrast. The same setting is used for myocardial perfusion imaging, as shown in Fig. 6.9,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

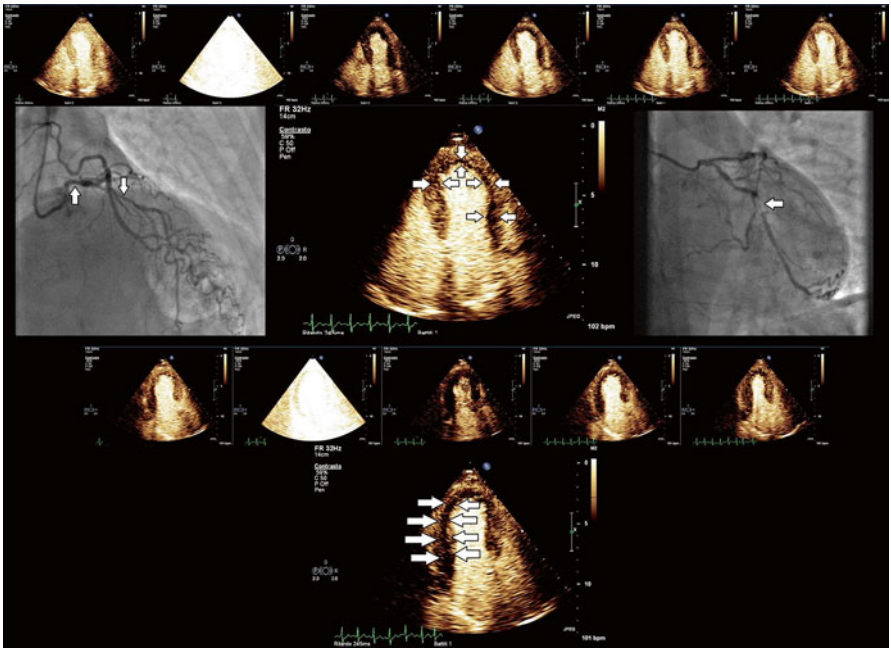

Fig. 6.9 Stress phase in a patient who underwent contrast dipyridamole echocardiography (0.84 mg/kg/6 min). The upper part of figure shows four-chamber contrast flash-replenishment sequence (from left to right), which demonstrates black areas in the subendocardial region of the true apex and apical–septal, 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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Standardized Myocardial Segmentation of the Left Ventricle

7

Luigi P. Badano and Eugenio Picano

As with all cardiac imaging modalities, the assessment of regional left ventricular function with echocardiography is performed by artificially dividing the left ventricular myocardium into a number of segments. The segmentation of the left ventricle reflects coronary perfusion territories, results in segments with comparable myocardial mass, and allows standardized communication within echocardiography and with other imaging modalities [1].

7.1 Left Ventricular Myocardium Segmentation Models

The resolution of the segmental approach is a function of the number of segments; thus, it can range from 20 % (in the 5-segment model) to 5 % (in the 20-segment model). However, increasing the number of segments, and thus reducing their size, leads to an unacceptable complication in the analysis with a greater need for approximation and interpolation. A reasonable trade-off between accuracy and feasibility is represented by the 16-segment model proposed by the American Society of Echocardiography [2]. In this model, the left ventricular myocardium is first divided in three myocardial rings (basal, mid-cavity, and apical) whose height is 1/3 of the left ventricular length. Both the basal and the mid-cavity rings account for about 35 % of left ventricular myocardium mass, while the apical ring accounts for the remaining 30 % [3]. The basal and mid-cavity (papillary muscle) rings are then divided into six segments (each segment accounts for 60° of left ventricular circumference) and the apical level into four segments (e.g., 90° of left ventricular circumference at that level). The segmentation starts at the anterior junction of the interventricular septum and the right ventricular free wall and continues counterclockwise. Basal and mid-ventricular segments are labeled as anterior, anteroseptal, infero-septal, inferior, inferolateral, and anterolateral. The corresponding apical segments will be septal, inferior, lateral, and anterior [1] (Fig. 7.1).

The 16-segment model has been modified to obtain a segmentation standard applicable to all imaging modalities by adding a 17th segment (the “apical cap”),

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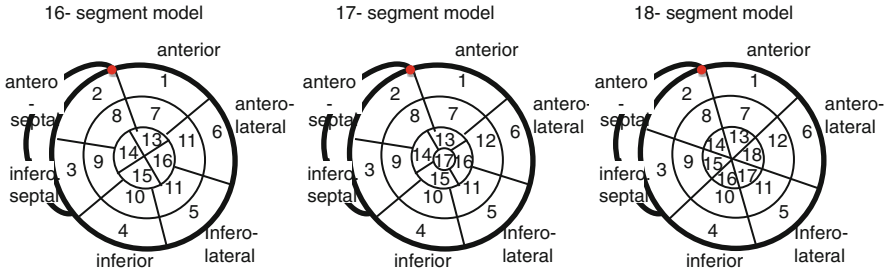

All models
1. basal anterior
2. basal antero-septal
3. basal infero-septal
4. basal inferior
5. basal infero-lateral
6. basal antero-lateral

7. mid anterior
8. mid antero-septal
9. mid infero-septal
10. mid inferior
11. mid infero-lateral
12. mid antero-lateral

16- and 17-models
13. apical lateral
14. apical septal
15. apical inferior
16. apical anterior

17-segment model only
17. apex

18-segment only
13. apical anterior
14. apical antero-septal
15. apical infero-septal
16. apical inferior
17. apical infero-lateral
18. apical antero-lateral

Fig. 7.1 Schematic diagrams comparing the different left ventricular myocardium segmentation models. *Left diagram*: 16-segment model. *Central diagram*: 17-segment model. *Right diagram*: 18-segment model. In all diagrams the outer ring represents the basal segments, the mid ring the segments at mid-cavity (papillary muscle) level, and the inner ring at the apical level. In the 17-segment model, an additional segment (apical cap) is added in the center of the bull's-eye diagram. The anterior insertion of the right ventricular free wall into the left ventricle (*red dot*) defines the border between the anterior and anteroseptal segments (see text for details)

which is defined as the myocardium beyond the length of the left ventricular cavity [4] (Fig. 7.1). Some authors suggested to divide the apex into six segments, similar to the segmentation of the basal and mid-ventricular levels. This will create an 18-segment model which is intuitive but will result in over-representation of the apical myocardium in scoring (Fig. 7.1). Since the endocardial excursion and myocardial thickening of the "apical cap" are imperceptible by the observer, the 17-segment model should be used for myocardial perfusion studies or when comparing echocardiographic findings with different imaging modalities, specifically single-photon emission computed tomography, positron emission tomography, and cardiac magnetic resonance. The 16- and the 18-segment models are more suitable for the assessment of wall motion abnormalities.

The myocardial segments are identified according to internal anatomical landmarks of the left ventricle, in the standard parasternal (Fig. 7.2), apical (Fig. 7.3), and subcostal views. Each segment can usually be visualized in more than one echocardiographic view and from different approaches for a more reliable and complete evaluation of wall motion.

As a rule, segmental wall motion can be reliably assessed when the endocardial contour is clearly visualized for at least 50 % of the segment length. With echocardiography, segmental myocardial function is usually assessed subjectively by examining endocardial excursion and myocardial thickening. There are some limitations

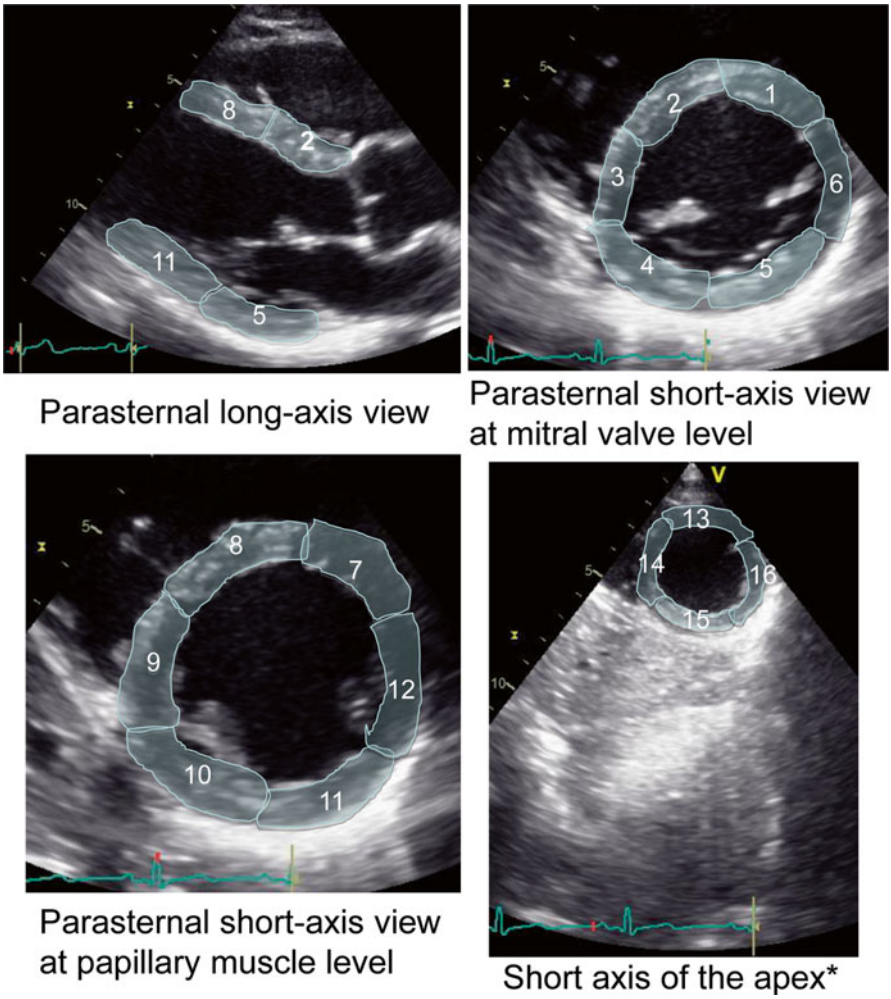

Fig. 7.2 Localization of left ventricular myocardial segments on standard two-dimensional echocardiographic views. Numbers of the segments correspond to the diagrams in Fig. 7.1. *apical short-axis view is usually obtained from the apical approach, moving the probe one intercostal space higher than the one used for the conventional 4-chamber view and tilting the probe toward the right shoulder in order to obtain a circular view at the level where the right ventricular apex disappears

to using endocardial excursion as the sole criterion to assess segmental wall motion. The motion of any given segment of the left ventricle is influenced by the adjacent muscle to which it is attached. For example, in a chamber with a dyskinetic ischemic segment, some of the adjacent normal myocardium may appear hypokinetic because its motion is restricted by the attached dyskinetic muscle. The reverse phenomenon can also occur. If a vigorously contracting normal muscle is next to an

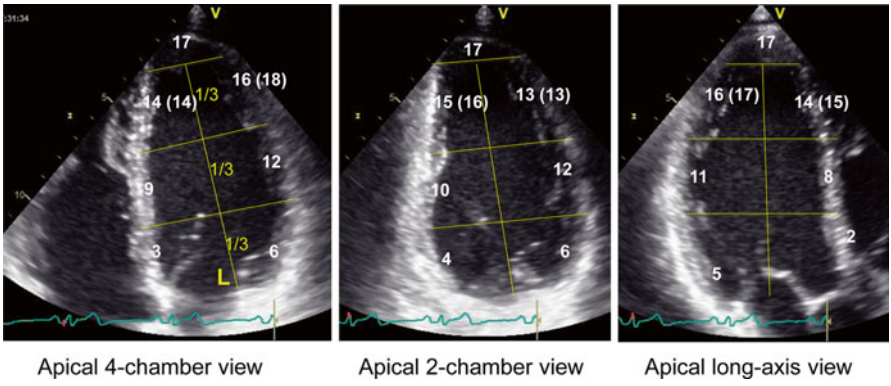

Fig. 7.3 Localization of left ventricular myocardial segments on standard two-dimensional echocardiographic apical views. To identify the segments the length of the left ventricular cavity (L) is divided by 3. The 17th segment (the "apical cap") is defined as the myocardium beyond the length of the left ventricular cavity. Numbers of the segments correspond to the diagrams in Fig. 7.1. Number in parenthesis at the apical level indicates the segments in the 18-segment model

ischemic area, the hyperdynamic segment may pull the ischemic muscle toward the cavity, which may mask the abnormally perfused area. In general, endocardial excursion alone overestimates the degree of ischemia seen in the myocardium. A more specific finding to detect ischemic myocardium is the reduction of systolic wall thickening. Normal myocardium muscle increases in thickness during systole (see Chap. 6). Ischemia causes a reduction or absence of systolic wall thickening. Indeed, acute ischemia may also cause systolic thinning (i.e., wall thickness is greater in diastole than in systole). It has been shown that the predictive power of the extent and severity of wall thickening abnormality is superior to that of endocardial excursion abnormality evaluation for predicting outcome after myocardial infarction [5].

Clinical situations in which endocardial excursion may be abnormal with preserved wall thickening include left bundle branch block, Wolff–Parkinson–White syndrome, and paced rhythm. The presence of preserved systolic wall thickening in these conditions confirms that the wall motion abnormalities are not due to intercurrent myocardial ischemia.

7.2 Assignment of Segments to Coronary Arterial Territories

There is tremendous variability in the individual coronary artery blood supply to left ventricular myocardial segments. Nevertheless, it has been agreed to assign individual segments to specific coronary artery territories. The assignment of the 17 segments to one of the three major coronary arteries is shown in Fig. 7.4 and (with bull's-eye format) in Fig. 7.5.

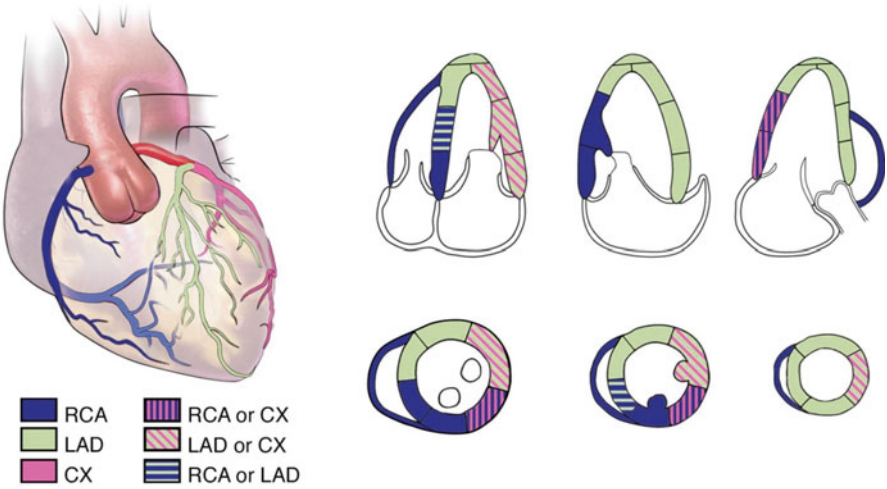

Fig. 7.4 Assignment of the 17 myocardial segments to the territories of the left anterior descending (*LAD*), right coronary artery (*RCA*), and left circumflex coronary artery (*LCX*) (Modified from [1], by courtesy of Roberto Lang et al.)

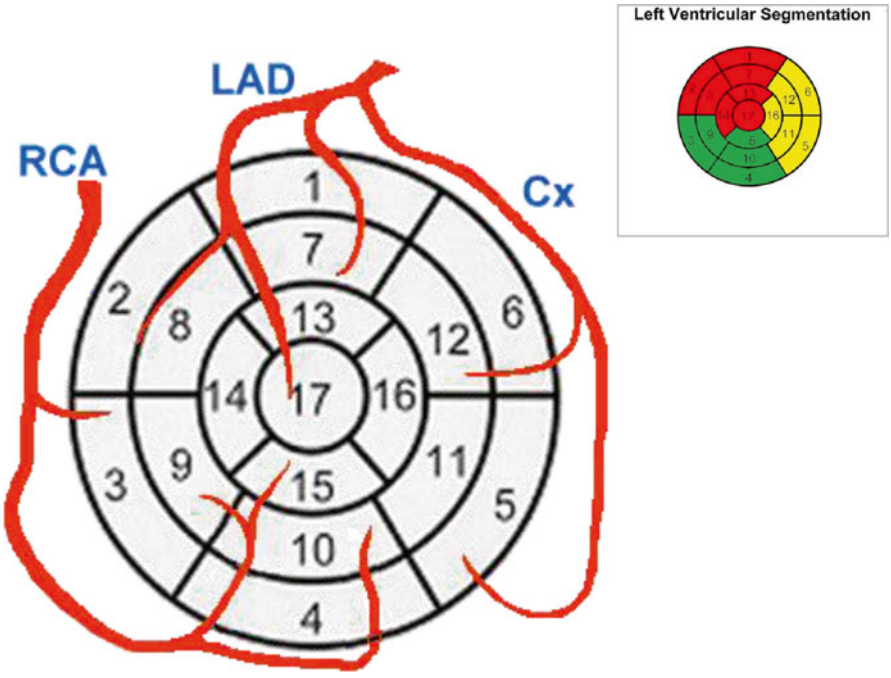

Fig. 7.5 Assignment of the 17 myocardial segments to the territories of the left anterior descending (*LAD*), right coronary artery (*RCA*), and left circumflex coronary artery (*LCX*) (Modified from Feigenbaum [6])

The greatest variability in myocardial blood supply occurs at the apical cap (segment 17) which can be supplied by any of the three arteries. Segments 1, 2, 7, 8, 13, 14, and 17 are assigned to the left anterior descending coronary artery distribution. Segments 3, 4, 9, 10, and 15 are assigned to the right coronary artery when it is dominant. Segments 5, 6, 11, 12, and 16 are generally assigned to the left circumflex artery. Individual myocardial segments can be assigned to the three major coronary arteries with the recognition that there is anatomic variability. In the parasternal long-axis view, the inferolateral wall may be supplied by either the left circumflex or right coronary artery, depending on the dominance of the system. The most proximal portion of the interventricular septum (segment number 2) is perfused by the first septal perforator, and with a high-grade proximal obstruction of the left anterior descending artery, the basal segment of the interventricular septum may be involved. The parasternal short-axis view of the left ventricle is the most suitable for assessing the distribution of the three main coronary arteries. The posterior descending branch of the right coronary artery supplies the infero-septal as well as the inferior segments. If the basal segment of the anterior wall (segment number 1) is affected, a high-grade proximal stenosis of the left anterior descending artery before the origin of the first septal perforator can be suspected. The anatomical relationships described above, although frequent, are by no means uniform: different anatomical patterns may be found in different patients [6]. In particular, the assignment of myocardial regions to coronary artery territories may change substantially with a dominant right coronary artery or with a less frequent dominant left circumflex artery. The apex is a heterogeneous territory for coronary perfusion, and its infero-apical segment quite often is supplied by the right coronary artery. However, as a rule of thumb, the presence of a clearly visualized stress-induced dyssynergy reliably predicts the presence and location of a coronary stenosis, especially when the segments supplied by the left anterior descending artery are affected.

The 4-chamber subxiphoidal view closely parallels the image obtained with the apical 4-chamber view, and subcostal short-axis views are similar to the short-axis parasternal ones. The main advantage is that this acoustic window remains “open” in patients in whom the ultrasonic study would otherwise be difficult, such as those who are obese or bronchopneumopathic. This view is certainly useful for assessing a right ventricular ischemia, which is usually accompanied by acute dilation of the right ventricle.

Multiple views from different acoustic windows can, and should, be obtained during stress echocardiography in order to guarantee a high feasibility of the technique with interpretable images in over 95 % of patients studied and a complete, integrated assessment of all left ventricular segments.

7.3 Left Ventricular Function in a Number

The segmentation of the left ventricle also represents the anatomical background for rapid (real-time) semiquantitative assessment of wall motion. Numerical values can be assigned to any segment corresponding to the degree of wall motion abnormality. According to the recommendations of the American Society of

Table 7.1 The segmental scoring system

Score:
1 = Normal/hyperkinetic: normal/increased systolic endocardial excursion and myocardial thickening
2 = Hypokinetic: decreased systolic endocardial excursion (<5 mm) and myocardial thickening (<30 %)
3 = Akinetic: absent systolic endocardial excursion (< 2 mm) and myocardial thickening
4 = Dyskinetic: outward systolic wall motion and absent myocardial thickening

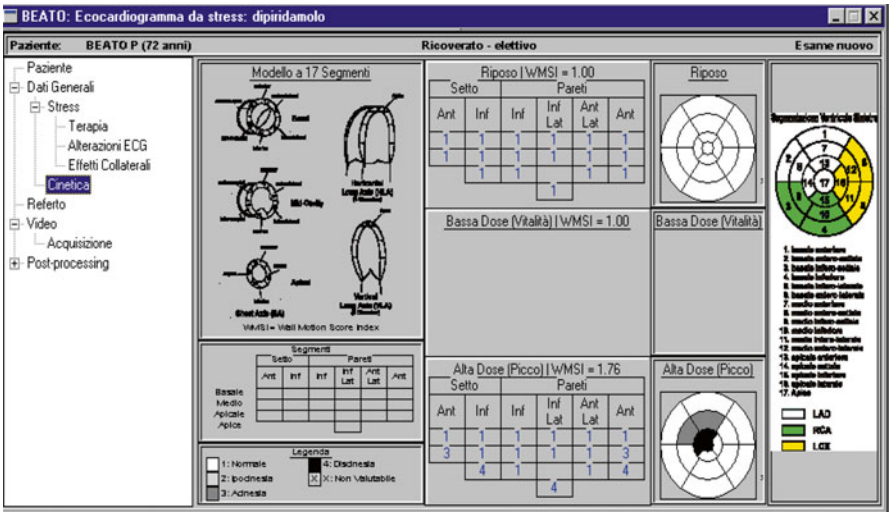

Fig. 7.6 Typical report from a positive stress echocardiography response. The bull's-eye representation of the left ventricle at baseline and during stress allows one to transfer the integrated view of baseline (*upper panel,* normal function, resting wall motion score index = 1) and stress function (*lower panel*, extensive ischemia, peak wall motion score index = 1.56)

Echocardiography and European Association of Cardiovascular Imaging [1], 1 is given for normokinesis or hyperkinesis, 2 for hypokinesis, 3 for akinesis, and 4 for dyskinesis or aneurysm (Table 7.1).

The scores of all segments are summed to obtain the left ventricular wall motion score which is divided by the number of scored segments to obtain a wall motion score index. For instance, in the 17-segment model, a normal left ventricle has an index of 1 (17 points/17 segments); hypokinesia of two segments will give an index of 1.12 (19 points/17 segments); dyskinesia of three segments will correspond to an index of 1.53 (26 points/17 segments). The wall motion score index can be calculated both in resting conditions and during stress and represents an integrated – although simple and easy to obtain – measurement of the extent and severity of ischemia. The wall motion score index is computer independent and obtainable within a few seconds. An example of a stress echocardiography report is shown in Fig. 7.6.

Table 7.2 Indices of global left ventricular function

	Wall motion score index	Ejection fraction
Nature of parameter	Semiquantitative	Quantitative
Time required	Seconds	Minutes
Geometric assumptions	No	Yes
Analysis	Visual	Post-processing
Computer facilities required	No	Yes
Audience	Echocardiographers	Cardiologists

The assessment of ejection fraction – different from wall motion score index – requires the manual tracing of endocardial border and geometric assumptions about the left ventricular shape (Table 7.2).

However, the ejection fraction has unquestionable advantages over the wall motion score index. The ejection fraction – as an index of global function – is a term unrelated to the jargon (known by echocardiographers only); rather, it belongs to the common language of the cardiological community at large, being a parameter common to all imaging methods and one that is used in angiographic, nuclear, and echocardiographic techniques. It has a very wide range of values, from below 10 % to above 80 %, and its prognostic value has been extensively validated.

However, the use of ejection fraction entails limitations, too. It is a global index which does not discriminate between the segmental and diffuse nature of the myocardial dysfunction; in addition to myocardial function, it is also affected by ventricular preload and afterload and heart rate, and it remains insensitive to mild or limited regional myocardial dysfunctions. Echocardiographic ejection fraction may be calculated using the same views recorded to assess regional wall motion and to integrate the information on regional function, with no need for dedicated imaging during the echocardiographic study, as in the case with Doppler ultrasound.

Conversely, wall motion score index is sensitive to even the slightest abnormality in regional function. The hypokinesis of one segment does not significantly affect the ejection fraction, but it does generate an abnormal wall motion score index. Estimation of wall motion score index does not require that all segments of a certain view are visible but only that each left ventricular segment be visualized in at least one view. This is a great advantage for clinical studies, when the full visualization of the entire ventricular silhouette in a given view can be problematic in resting conditions and even more during stress.

The major limitations to the widespread use of the wall motion score index are its subjectivity (interobserver variability is particularly high for hypokinetic segments) and its unfamiliarity to many cardiologists who do not practice echocardiography.

7.4 Artifactual Pseudoasynergies

Usually, the assessment of the regional wall motion abnormalities is performed examining several echocardiographic views of the left ventricle, each view having its own merits and limitations.

The spatial resolution of two-dimensional echocardiography is optimal in the axial direction of the ultrasonic beam. A regional dyssynergy can be artifactually "created" by incorrect positioning of the transducer. Therefore, the presence of a regional dyssynergy should be assessed visualizing the same left ventricular segment from different acoustic windows using different echocardiographic views.

The long-axis parasternal view allows optimal visualization of the anterior septum and of the inferolateral wall, since the endocardium is perpendicular to the ultrasonic beam. However, this view can be limited by the susceptibility to translational motion of the heart due to respiratory interference induced by the hyperventilation associated with some stressors. A foreshortened long-axis view may create a false hyperkinesis (masking a true hypokinesia) of apical segments and create a false hypokinesis of the basal septal and inferolateral segments.

The parasternal short-axis view at the papillary muscle level allows a simultaneous assessment of the left ventricular segments belonging to the distribution territories of all the three coronary arteries. This view is particularly suited for quantitative wall motion analysis, although it may be challenging to obtain in patients with relatively advanced age, such as those with coronary artery disease. Even less frequently utilized is the parasternal short-axis view at the mitral level, where a spurious transient dyssynergy of the inferobasal segment is commonly seen. The cause of this pseudoasynergy is the physiological systolic shortening of the left ventricle in a base-to-apex direction, so that in diastole the left ventricular wall is imaged, whereas, in systole, it is the left atrium which enters the image plane. A further drawback is that with many stressors the extent of the base-to-apex shortening of the left ventricle is increased compared to resting conditions. Accordingly, if a wall motion abnormality in the inferolateral basal segment is visualized in the parasternal short-axis view at the mitral level, it should be reported with caution unless the inferolateral basal segment can be visualized asynergic in another apical view.

The perfect short-axis view must be round. An elliptic shape of the short-axis view can mask a wall motion abnormality of the anterior segments and mimic a hypokinesis of inferolateral ones (Fig. 7.7). The apical (4- and 2-chamber) views are the most frequently used and most useful views in stress echocardiography. Inducible ischemia affects the subendocardial layer of the left ventricular wall first. Since myocardial fibers in the subendocardial layer are oriented longitudinally, the first function lost by the ischemic myocardium is the ability to shorten longitudinally (in the base-to-apex direction), and this abnormality can be visually appreciated using the apical views.

To properly acquire the apical views of the left ventricle, particular care should be taken to properly orient the view and to avoid the foreshortening of the cavity [7, 8]. A properly oriented 4-chamber view will maximize the right ventricular cavity area and will not show the aortic root. A foreshortened 4-chamber view can mask a hypokinesia of the apex (which will appear falsely hyperkinetic) and can mimic a hypokinesia of the basal lateral and basal infero-septal segments.

The apical 2-chamber view, if properly acquired, should not show either the aortic root or the right ventricular cavity. It is analogous to the right anterior oblique projection employed in ventriculography and clearly shows the inferior and anterior walls. A foreshortened 2-chamber view can mask a hypokinesia of the apex and mimic a hypokinesia of the basal inferior wall.

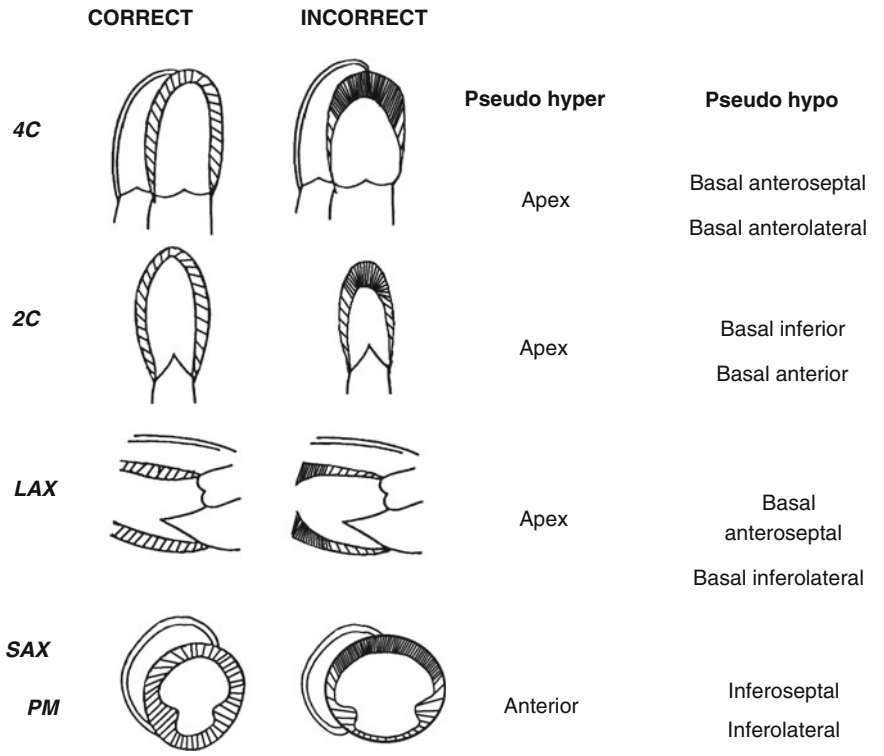

Fig. 7.7 Stress echocardiographic iatrogenesis. The *left panel* shows the correct imaging for each of the main views; the *right panel* shows the incorrect imaging which may mask or mimic regional dysfunction during stress

A properly acquired apical long-axis view will show the aortic root. It is analogous to the left anterior oblique projection employed in ventriculography and clearly shows the inferolateral wall and anterior septum. A foreshortened apical long-axis view can mask a hypokinesia of the apex and mimic a hypokinesia of the basal inferolateral wall.

7.5 Matching Between Transthoracic and Transesophageal Segments

Transesophageal stress echocardiography can be performed in patients with limited transthoracic echocardiography image quality. The semi-invasive nature of the technique makes it more unpleasant for the patient [9, 10], as stated by conventional wisdom that "transesophageal echocardiography can be considered a noninvasive examination if you do it and an invasive examination if others do it on you."

Excellent results have been obtained with pharmacologic transesophageal stress echocardiography for the assessment of myocardial ischemia (with dobutamine or dipyridamole) [11–13], myocardial viability (with dobutamine) [14], coronary flow reserve (with dipyridamole or adenosine) [15–19], and prognostic

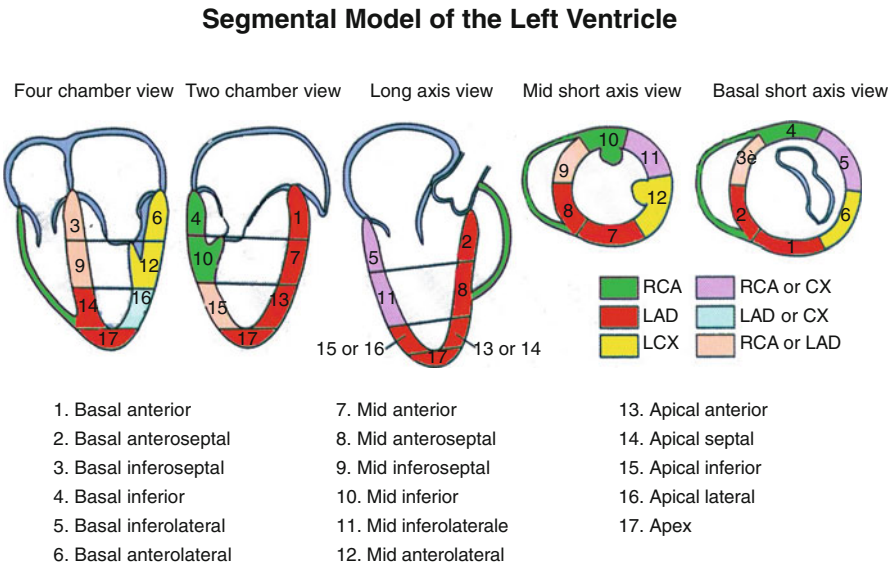

Fig. 7.8 Model of left ventricular segmentation using transesophageal echocardiographic images. The short-axis view is obtained from the transgastric approach, and 4-chamber and 2-chamber views are recorded from the mid-esophageal position. *Ant* anterior, *ao* aortic root, *inf* inferior, *LA* left atrium, *lat* lateral, *inf-lat* inferior–lateral, *RV* right ventricle, *sept* septum (Modified from Panza et al. [20], with permission)

stratification on the basis of inducible wall motion abnormalities [20, 21]. Segmental analysis is generally performed using the 17-segment model modified for transesophageal echocardiography (Fig. 7.8) [9, 10]. However, intraoperative monitoring of the left ventricular regional function is generally restricted to the six segments of the transgastric papillary view. In this view, the areas of myocardium supplied by the three major coronary arteries are visible. Despite its undisputed accuracy, the clinical role of transesophageal stress echocardiography is decreasing because of the emerging use of cardiac stress magnetic resonance imaging in patients with difficult acoustic windows which do not improve either after using native second harmonic imaging or contrast-enhanced echocardiography. Transesophageal stress echocardiography remains the first choice stress test modality in patients in the operating room (for early assessment of functional results of revascularization) or in the intensive care unit (for instance, for recruitment of heart donors).

7.6 Left Ventricular Segments: Matching Between 2D and 3D Imaging

Three-dimensional echocardiography is an attractive technique to overcome most of the limitations of the two-dimensional technique during stress echocardiography like limited visualization of the myocardial mass by conventional parasternal and apical views (less than 10 % of the actual myocardium is visualized, Fig. 7.9), poor

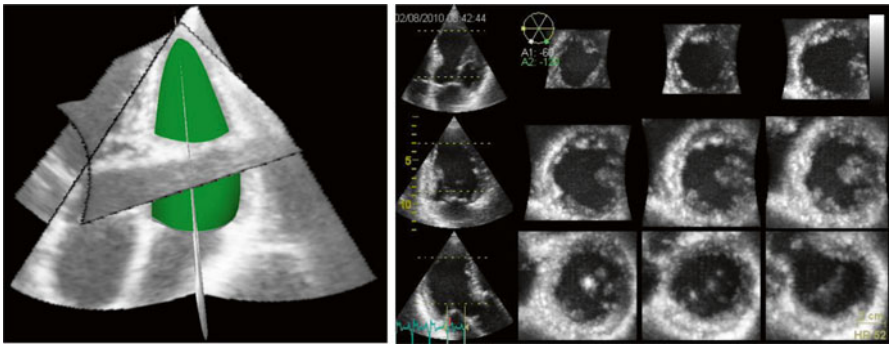

Fig. 7.9 Different visualization of the left ventricular segments by two (*left panel*)- and three (*right panel*)-dimensional echocardiography. Two-dimensional echocardiography obtains a number of tomographic planes which encompass a limited surface of the endocardium (and of the myocardial mass). Most of the endocardial (myocardium) surface (*green surface* in the figure) is not actually visualized by two-dimensional technique. Conversely, three-dimensional data sets can be sliced in a number of slices (12 in the figure) covering the whole circumference and length of the endocardium offering a more comprehensive visualization of the endocardium

acoustic windows with incomplete visualization of all left ventricular segments, incorrect orientation (foreshortening of the views), difficulties in perfectly matching the orientation of corresponding view at the different steps of the stress protocol, and time-consuming serial acquisition of several views with the risk of missing short-lasting ischemia.

Full-volume three-dimensional echocardiography allows the operator to rapidly acquire images and to visualize the entire left ventricle in an unlimited number of planes simply by rotating and slicing the acquired volumetric data set. Besides the extraction of conventional two-, three-, and four-chamber views, multiple parallel short-axis cut planes (usually six to nine, equally spaced, from base to apex, Fig. 7.9) of the left ventricle can be used for a comprehensive analysis of regional wall motion. In addition, once a volumetric data set is acquired, proper and clear matching views for baseline and peak stress can easily be aligned for the comparison of the same left ventricular segments [22, 23, 24]. Finally, 3DE has been reported to shorten significantly the time required to perform stress echocardiography, making 3D stress echocardiography more cost-effective [25–31].

Studies using first- and second-generation three-dimensional echocardiographic scanners and related software have shown similar sensitivity of pharmacologic stress testing performed using 2-D echocardiography [25, 28, 32, 33]. However, all these studies reported three major limitations that may reduce the use of three-dimensional echocardiography for stress testing in routine clinical practice: (1) limited temporal resolution of three-dimensional echocardiographic data sets, (2) long analysis time required to obtain the desired views by cropping the data set, and (3) impossibility to display cropped images side by side both at baseline and during peak stress. All these technical limitations have been overcome with the last generation of three-dimensional scanners.

Table 7.3 Ejection fraction: from 2D to 3D in the echocardiography laboratory

	2D	3D
Foreshortening artifacts	Yes	No
Geometric assumption	Yes	No
Accuracy	Good	Excellent
Reproducibility	Good	Excellent
Imaging time	Minutes	Seconds
Analysis time	Minutes	Minutes

The ability to obtain unlimited views of the left ventricle with three-dimensional echocardiography gives this technology the potential to improve the sensitivity of stress echocardiography for the detection of ischemia, particularly in those patients with single-vessel disease and limited wall motion abnormalities. This holds true especially if ischemia is located at the LV apex [26, 31, 34] increasing the sensitivity of the technique for the detection of left anterior descending coronary artery disease.

There is little doubt that RT3D has great potential to make stress echocardiography more quantitative and less technically demanding and is now already the gold standard for assessment of cardiac volumes, left ventricular mass, and ejection fraction at baseline and during stress [1], with accuracy and reproducibility comparable to cardiovascular magnetic resonance (Table 7.3). By using three-dimensional echocardiography, ancillary information can be derived during stress that may be clinically important: the stroke volume (relevant, for instance, during dobutamine stress echocardiography in low-flow, low-gradient aortic stenosis), the end-systolic volume (relevant, for instance, to measure the pressure–volume relationship during stress as an index of contractile reserve in heart failure), the mean diastolic filling rate (potentially important for the characterization of the diastolic function and which can be derived from stroke volume and duration of cardiological diastole), and the vascular impedance (expressed as the ratio of stroke volume/arterial systolic pressure).

The reduction of transducer size and the development of fully automated volumetric analysis have allowed three-dimensional echocardiography to evolve from complex, time-consuming, and research-oriented method into a routine clinical tool increasingly used in the stress echo lab [24].

Table of Contents Video Companion

See stress echo primer, coronary arteries, and myocardial segments.

See also, in the section illustrative cases, case number 10 (by Prof. Bogdan Popescu, MD, Romania), number 21(by Jorge Lowenstein, MD, Argentina), and 42 (by Prof Edyta Plonska, MD, Poland).

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Right Heart Stress Echocardiography

8

Ekkehard Grunig and Eugenio Picano

The behavior of the right side of the heart during stress has been underemphasized and sparsely investigated by cardiologists and pneumologists. Reasons vary, but the right ventricle has traditionally been considered a passive conduit between the venous system and the lungs largely because of early animal experiments showing no increase of central venous pressure after the free wall of the right ventricle had been destroyed [1–3]. In addition, echocardiography of the right heart is less well standardized [4] as imaging of the left ventricle. Recent pathophysiological, clinical, and prognostic data have defined an important role for the right ventricle in many conditions, including ischemic heart disease and heart failure. Given that the right ventricle and the left ventricle share a common septum, have an overlapping blood supply, and are bound together by the pericardium, changes induced by myocardial ischemia and/or heart failure are reflected in pulmonary hemodynamics and right ventricular function [5]. Modern Doppler echocardiography allows a systematic evaluation of five key aspects of cardiopulmonary pathophysiology during stress: segmental right ventricular function; global right ventricular longitudinal function; coronary flow reserve in the posterior descending of the right coronary artery; indices of pulmonary hemodynamics, namely, pulmonary artery systolic pressure, pulmonary velocity time integrals, and pulmonary vascular resistances; and extravascular lung water in the lung, mirroring the distress of the alveolar–capillary membrane. Technical improvements were also matched by a greater understanding of the complexity and the clinical relevance of the adaptation of the right heart (functionally including pulmonary circulation and lung alveolar–capillary membrane) in several pathological conditions, from coronary artery disease to heart failure [5]. In many situations, it is not possible to fully understand heart disease if we do not look at the right heart and pulmonary stress hemodynamics.

E. Picano, *Stress Echocardiography*, DOI 10.1007/978-3-319-20958-6_8

8.1 Regional Right Ventricular Function in Coronary Artery Disease

The right ventricle is less vulnerable to ischemia than the left ventricle for several anatomic and functional factors, including the rich system of Thebesian veins in the right ventricle (allowing perfusion of the papillary muscles of the right ventricle), the dual anatomic supply system (in which the left coronary branches perfuse almost one-third of the right ventricle), the rapid development of collateral vessels to the right ventricle given the lower resistance that favors a left-to-right transcoronary pressure gradient, and the relatively thin walls and lower stroke work and wall tension (with lower oxygen demand and less vulnerability to transmural perfusion heterogeneity during stress) [5]. Blood supply of the right ventricle is characterized by a rich collateral system and a perfusion during diastole and systole. The perfusion rate of the right ventricle at rest is 50 ml min^{-1} 100 g^{-1}, much lower than that of the left ventricle (120 ml min^{-1} 100 g^{-1}). However, right ventricular ischemia may occur during stress and is difficult to recognize, if not specifically looked for. It requires additional projections (subcostal view) to image RV ischemia and more experience to recognize it.

The evaluation of right ventricular size and function is made difficult by the retrosternal position, complex geometry, and heavy trabeculation of the right ventricle, which also partially overlaps with the silhouettes of the left ventricle. There is not one single echocardiographic view in which the complete right ventricle can be seen. For purposes of echocardiographic analysis, the right ventricle can be divided into four segments [6]: anterior wall, lateral wall, inferior wall, and wall of the outflow tract (Fig. 8.1).

Schematically, the right ventricle is composed of an inflow and an outflow tract. The former has an anterior and an inferior (also named diaphragmatic) wall. The inferior wall lies over the diaphragm. The acute margin of the heart is formed by the external edge of the right ventricle. From an echocardiographic perspective, it is called the lateral wall and it borders anteriorly with the anterior wall and posteriorly with the inferior wall. The outflow portion of the right ventricle is limited upward by the pulmonary valve and downward by the crista supraventricularis, the septal papillary muscle (Luschka's muscle), the anterior leaflet of the tricuspid valve, and the septal band. The outflow tract has an anterior wall (echocardiographically named wall of the outflow tract) and a posterior wall that is part of the interventricular septum. The inferior wall is irrigated by the marginal branches and the posterior descending artery, the lateral wall by the marginal branches, and the outflow tract and the anterior wall by the posterior and anterior descending artery. Although the interventricular septum is part of the right ventricle, the evaluation of its function is usually included in the analysis of the left ventricle. In right-dominant hearts (85 % of cases), the right ventricle is nourished by the right coronary artery. The development of contraction abnormalities of the right ventricle (more often lateral and inferior segments) is a hallmark of coronary artery involvement by coronary vasospasm in ergonovine-induced [7] or tight stenosis in dobutamine-induced ischemia [8, 9] (Table 8.1). These alterations appear later than in the left ventricle [10], are best

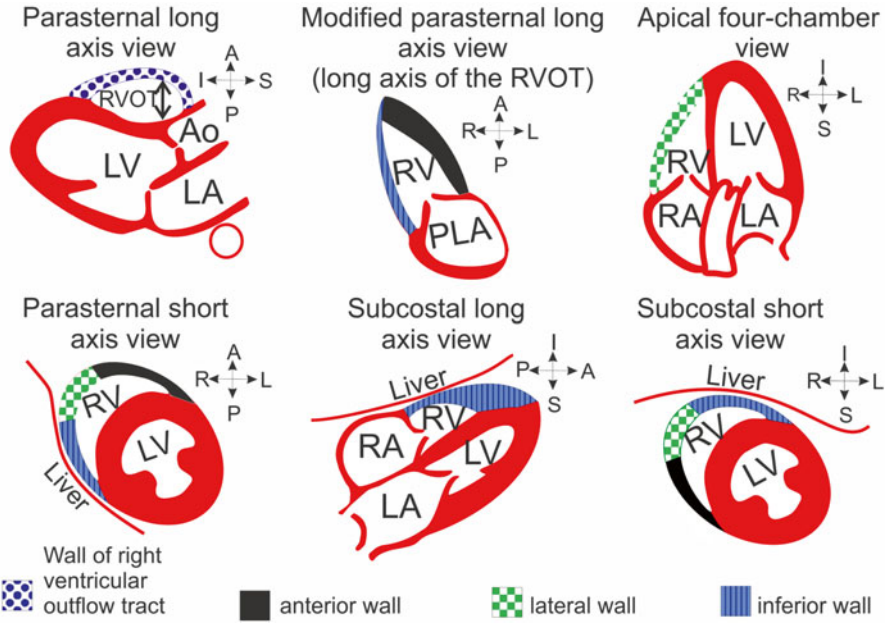

Fig. 8.1 Systematic approach to the right ventricular function during stress echocardiography. *A* anterior, *AO* aorta, *I* inferior, *L* left, *LA* left atrium, *LV* left ventricle, *P* posterior, *R* right, *RA* right atrium, *RV* right ventricle, *RVOT* right ventricular outflow tract, *S* superior

Table 8.1 Differences between right and left ventricular ischemia during stress echocardiography

	Right	Left
Prevalence in RCA disease	40–60 %	70–90 %
Prevalence in LCA disease	0–20 %	70–90 %
ECG abnormalities	Right precordial leads	Standard leads
Isolated presentation	Rare	Frequent
Feasibility to be detected	60–80 %	90–98 %
Prognostic value	Additive to left	Established

recognized from a modified parasternal and subcostal long-axis view (Fig. 8.2), and can be accompanied by severe right ventricular and right atrial enlargement [8, 11], sometimes with reduction of the tricuspid annular plane systolic excursion (TAPSE) with *M*-mode, which is an index of global longitudinal right ventricular function.

Rest or stress-induced right ventricular enlargement is not necessarily due to coronary artery disease but can be due to other conditions such as stress-induced pulmonary hypertension which may nevertheless be of prognostic significance. Isolated right ventricular ischemia occurs in 2 % of patients with right coronary artery stenosis when assessed by wall motion abnormalities [11] but increases to 5–10 % if assessed by failure of TAPSE to increase >2 mm [12] or other indices of

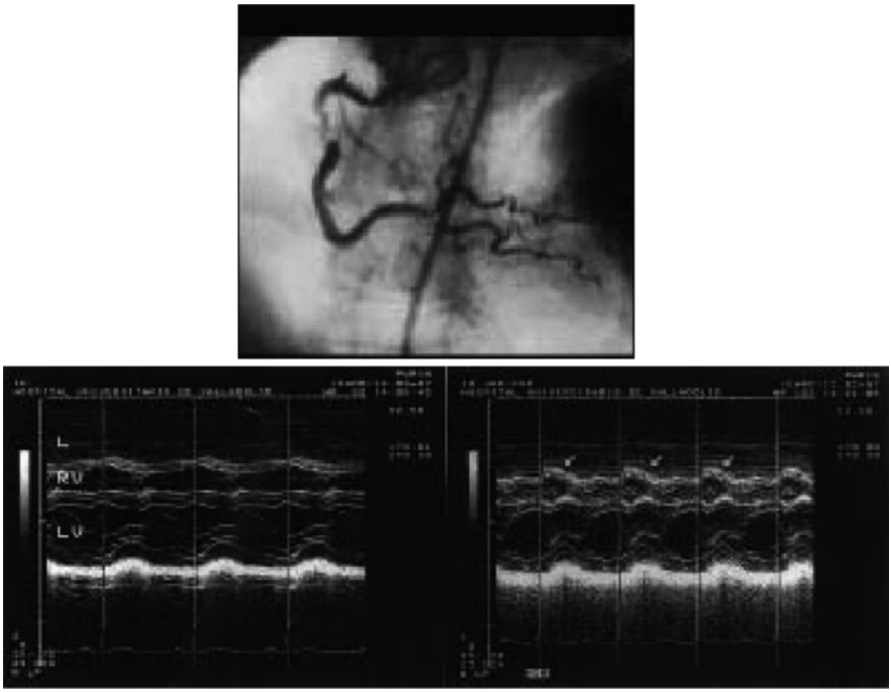

Fig. 8.2 *M*-mode study from the subcostal window. Resting exam (*left*) shows normal right ventricular wall motion. During dobutamine infusion (*right*), dyskinesis of the inferior wall of the right ventricle is clearly seen (*arrows*). *Vertical lines* correspond to ventricular systole. *L* liver, *LV* left ventricle, *RV* right ventricle (By courtesy of Alberto San Roman et al., Ref. [10])

RV longitudinal function [11]. Right ventricular dysfunction is found in 20 % of patients with concomitant inferior wall ischemia, in whom it contributes to a negative prognostic outlook [11].

8.2 Global Right Ventricular Function

The global inotropic reserve of the right ventricle can be measured as the increase in ejection fraction, or in fractional area change, or in a simpler and at least equally accurate way as augmented descent of the right ventricular base or TAPSE. The latter index of global right ventricular function can be calculated from the apical 4-chamber view and 2D-targeted *M*-mode tracings (Fig. 8.2) by recording the free wall long-axis amplitude of movement (normally 15–20 mm). A good relationship has been reported between TAPSE and the right ventricular ejection function measured by radionuclide ventriculography in a manner independent of geometric assumptions [13, 14]. Conceptually, TAPSE (or, if available, peak systolic S wave velocity of Doppler tissue imaging of the lateral tricuspid annular motion) assesses longitudinal function of the right ventricle in the same way as MAPSE (mitral

annular plane systolic excursion) by simple *M*-mode or myocardial velocity imaging does of the left ventricle [15]. The assessment of TAPSE avoids the approximation, mistakes, and computational burden inherent to the calculation of ejection fraction in the right ventricle, whose crescentic and irregular shape eludes any geometric modeling [16], although real-time 3D echocardiography has potential to solve or at least limit this problem. Moreover, its simplicity makes it easy to calculate and translates into a very low-intra- and interobserver variability even when measured by untrained readers during stress [17], an important issue when searching for end points in clinical trials. The indices of right ventricular function all increase significantly during exercise stress in healthy subjects, but their increase is blunted in pulmonary hypertension [18] or severe dilated cardiomyopathy with RV involvement [19, 20]. Interestingly, the right ventricular contractile reserve is preserved in chronic mountain sickness in spite of reduced resting RV function, suggesting that the lower resting values may represent a physiologic adaptation to chronic hypoxic conditions rather than impaired RV function [21].

8.3 Coronary Flow Reserve of the Right Coronary Artery

Stress testing of coronary flow reserve has now become a clinical reality with last-generation, fast, high-dose vasodilatory stress echocardiography coupled with second harmonic imaging technology and pulsed Doppler of the middistal left anterior descending coronary artery [22, 23]. Under normal conditions, in the absence of stenosis, coronary blood flow can increase at least threefold over resting values when hyperemia is induced pharmacologically, for instance, with administration of exogenous adenosine or dipyridamole, which accumulates endogenous adenosine. Coronary flow reserve is the capacity of the coronary circulation to dilate and can be expressed by the difference between the hyperemic flow and the resting flow curve. This pathophysiological concept recently entered the stress echocardiography laboratory, and the combined assessment of regional wall motion by 2D echocardiography and pulsed Doppler imaging of the left anterior descending coronary artery is the recommended state-of-the-art stress echocardiography protocol in the latest recommendations (2008) of the European Association of Echocardiography [24]. More recently, the posterior descending artery of the right coronary artery has been consistently imaged, with a success rate around 75 % [25, 26], usually from a modified apical 2-chamber view with counterclockwise rotation and anterior angulations of the probe [27] (Fig. 8.3). The information of right coronary artery flow reserve is derived as the ratio of peak diastolic flow velocity during stress over rest. A concordant reduction in both left anterior descending and posterior descending arteries is associated with a worse prognosis than a reduction in either one coronary artery – both in coronary artery disease [28] and in dilated cardiomyopathy patients [29]. In addition, a reduction in right coronary artery reserve is associated with conditions of right ventricular pressure overload and may help in the functional characterization, for instance, of congenital heart disease patients [30].

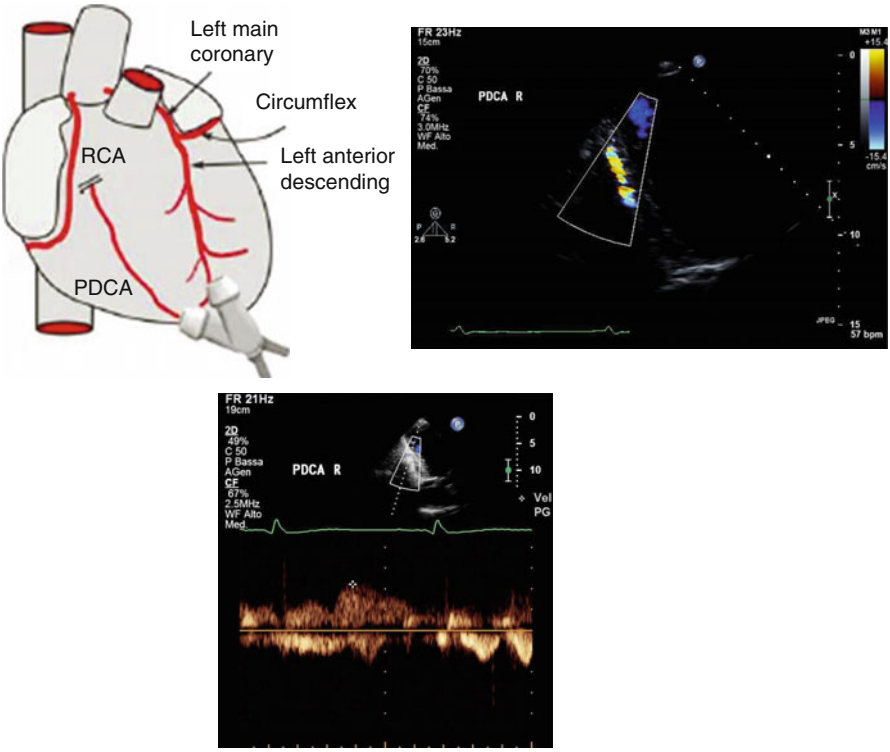

Fig. 8.3 *Upper left panel*: artist's drawing illustrating transducer beam orientation to the posterior descending coronary artery. The middistal tract is imaged from a modified apical 2-chamber view with counterclockwise rotation and anterior angulations of the probe. *Upper right panel*: the corresponding echocardiographic image of posterior descending color flow. *Lower panel*: the corresponding pulsed Doppler flow signal at rest, on which the peak diastolic flow velocity is measured. The variation in diastolic flow velocity between rest and peak vasodilation (following adenosine or dipyridamole infusion) gives an index of coronary flow reserve

8.4 Pulmonary Hemodynamics

Pulmonary artery systolic pressure can be estimated from peak tricuspid regurgitation (TR) jet velocities according to the well-validated modified Bernoulli's equation [31]: pulmonary artery systolic pressure = $4(V)^2$ + right atrial pressure, where V is the peak velocity (in m/s) of the tricuspid valve regurgitant jet (Table 8.2), and right atrial pressure is estimated from inferior vena cava diameter and respiratory changes, yielding a value from 5 (inferior vena cava diameter <17 mm, >50 % reduction with inspiration) to 20 mmHg (inferior vena cava diameter >17 mm, no reduction with inspiration) [16] (Table 8.3). Technically adequate signals have complete envelopes with well-defined borders, a sweep velocity of at least 100–200 mm s^{-1}, and can be obtained (often without need of contrast) at baseline and at peak exercise stress in the majority of patients (Fig. 8.4). The assessment of

Table 8.2 Noninvasive assessment of pulmonary pressure by Doppler echocardiography

		Normal values (rest)
PASP	4×TR peak velocity^2+RAP	<35
PAP m	79–0.45 (RVOT AT) 4×peak pulmonary regurgitation velocity	<25
PEDP	4×(pulmonary regurgitation end-diastolic velocity)+RAP	<15
PVR	10×TR velocity/$RVOT_{TVI}$	<2.0

PASP pulmonary artery systolic pressures, *PVR* pulmonary vascular resistances, *PEDP* pulmonary end-diastolic pressure, *PAP* pulmonary artery pressure, *TR* tricuspid regurgitation

Table 8.3 Echocardiographic estimation of the right atrial pressure (*RAP*) by measuring the diameter of the inferior vena cava and the respiratory motion of the inferior vena cava

Inferior vena cava diameter (cm)	Respiratory collapse (%)	RAP (mmHg)
<1.7	≥50 %	5
>1.7	≥50 %	10
>1.7	≤50 %	15
>1.7	0	20

From Lang et al. [16]

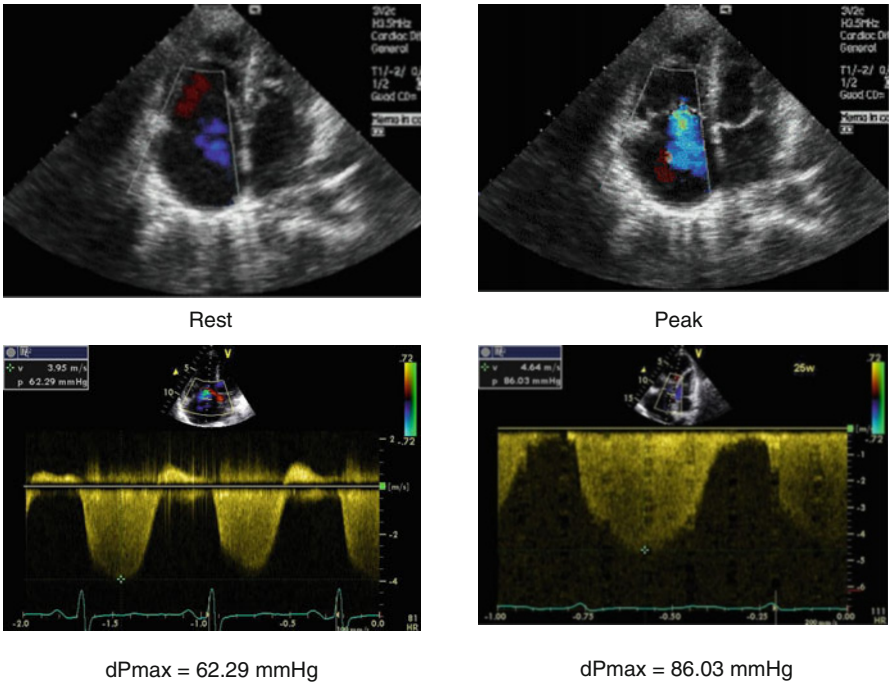

Fig. 8.4 Patients with resting pulmonary artery systolic pressure (estimated from jet velocity of tricuspid regurgitation) of 64 mmHg. During mild exercise, the patient experiences severe dyspnea and dramatic rise in pulmonary artery systolic pressure

pulmonary artery systolic pressure (PASP) depends on the presence of an at least trivial TR, which is found in about 40–85 % of normal subjects [32] and 80–90 % of patients with pulmonary hypertension [33, 34]. Furthermore, training is required to be able to assess TR velocity during exercise correctly. Over- and underestimation of TR velocity is a frequent problem. In the case of missing TR, subjects can be asked to drink 500–1000 ml before assessment which increases the preload and the size of the right atrial area and usually helps for the test to be successful. The quality of the TR velocity recording may be enhanced with contrast echocardiography by injecting agitated saline solution or other contrast echocardiographic agents intravenously [35]. However, an estimate of PASP can be obtained in the absence of TR from the blood pool and – more simply – with pulsed-wave Doppler tissue imaging, the isovolumic relaxation time of the tricuspid annulus of the right ventricle can be derived [36–38]. Pulmonary hypertension causes a significant delay in the onset of right ventricular filling. A third approach is based on the assessment of pulmonary forward flow [38]. Generally, the shorter the acceleration time (measured from the onset of Q wave on ECG to the onset of pulmonary flow velocity), the higher the pulmonary vascular resistance and hence the pulmonary arterial pressure. However, assessment of acceleration time especially during exercise has a high inter- and intraobserver variability.

Notably, the pulmonary artery diastolic pressure (PADP) can be estimated at rest from the velocity of the end-diastolic pulmonary regurgitant jet (Vedpr), using the modified Bernoulli's equation [PADP = 4 * (Vedpr)^2 + right atrial pressure [39] (Table 8.2). When used with the tricuspid regurgitant jet to estimate pulmonary artery systolic pressure, the yield for direct information on pulmonary artery pressures increases to 90 % [40].

The simple ratio of peak TR velocity (in m/s) to RVOT VTI (in cm) multiplied by 10 allows for the evaluation of pulmonary artery pressures in hemodynamic terms, namely, the basic relationship of Δpressure = flow * resistance [41, 42] (Table 8.2). A ratio greater than 1.8 resistance units is predictive of an abnormal pulmonary vascular resistance by cardiac catheterization and may predict which pre-liver transplant patients, who often have elevated pulmonary artery pressures due to increased cardiac output with or without pulmonary vascular changes that results in portopulmonary hypertension, need catheter-based evaluation [43]. The method is easy to incorporate into a standard echocardiography exam and helps to identify a group of patients with apparently increased PASP (which may be influenced by right ventricular stroke volume) as normal [41]. This method does have an inability to replicate higher values of Wood's units and may be further limited in patients with very dilated pulmonary arteries or RVOTs and with severe pulmonic regurgitation. Overall, the most reliable method to measure PASP or mean pulmonary artery pressure during exercise is to use continuous-wave Doppler echocardiography.

Pulmonary arterial hypertension is defined as a group of diseases characterized by a progressive increase of pulmonary vascular resistances leading to right ventricular failure and death [44]. Pulmonary hypertension is defined by a mean pulmonary arterial pressure over 25 mmHg at rest [44]. Transthoracic echocardiography is a key screening tool in the diagnostic algorithm [45–48]. It not only provides an estimate of pulmonary artery pressure at rest and during exercise, but it may also

help to exclude any secondary causes of pulmonary hypertension, predict the prognosis, monitor the efficacy of specific therapeutic interventions, and detect the preclinical stage of disease [47, 49]. By transthoracic echocardiography, normal values are defined by pulmonary artery systolic pressure of less than 35 mmHg at rest [45, 50]. The reliability of tricuspid regurgitation velocity (TRV) cut-off values, using right heart catheterization (RHC) as reference, has previously been assessed in SSc patients [51, 52]. A TRV of ≥3.4 m/s with an assumed right atrial pressure of 5 mmHg (thus corresponding to a PASP of 50 mmHg) has been recommended as cut-off value for performing RHC to diagnose or exclude PH in the ESC/ERS guidelines [44]. However, transthoracic Doppler echocardiography (TDE) at rest using these cut-off-values was not reliable enough to detect early forms of associated pulmonary arterial hypertension in systemic sclerosis [53]. The DETECT Study performed RHC in each systemic sclerosis patient and showed that of 85 patients with manifest associated pulmonary arterial hypertension in systemic sclerosis only 29.8 % had a TRV >3.4 m/s at rest. More than 40 % of patients would have been overseen using TDE only [53].

Up to now, there is no firm consensus on which PASP threshold is diagnostic for exercise-induced pulmonary hypertension, particularly if stress echocardiography is applied. There are only few invasive and noninvasive studies analyzing the normal values for pulmonary artery pressures during exercise [45, 50]. Usually, in healthy subjects the systolic pressures do not exceed 40 mmHg even during heavy exercise [42, 54]. However, in well-trained athletes [45, 46] and those older than 55 years, systolic pressures as high as 55–60 mmHg are encountered [34]. Pulmonary hypertensive response during exercise (as shown in Fig. 8.6) can be clinically important in several conditions [4], including pulmonary hypertension due to mitral valve disease (regurgitation or stenosis) [55], heart failure [56, 57], congenital heart disease, connective tissue diseases, autoimmune diseases (e.g., lupus or systemic sclerosis) [46, 58, 59], after lung transplantation [60] and, possibly, healthy subjects with susceptibility to high-altitude pulmonary edema [61].

The assessment of PASP or mean pulmonary artery pressure during exercise by exercise Doppler echocardiography may help to identify asymptomatic gene carriers in families with pulmonary arterial hypertension who may be at risk of developing clinically overt disease over the years [33, 62]. Also in patients with systemic sclerosis, the abnormal pulmonary pressure response to exercise has been identified as a risk factor for the development of a manifest pulmonary hypertension [59]. Only out of the group of systemic sclerosis patients with elevated pressures during exercise did some (10 %) develop manifest pulmonary hypertension within a 3-year period. Unfortunately, at present using echocardiography and right heart catheterization at rest, more than 80 % of patients with pulmonary hypertension will not be diagnosed until right heart failure has occurred with the consequence of a markedly impaired life span. Thus, the assessment of PASP during stress echocardiography may be a promising method for detecting pulmonary hypertension at an early stage.

Furthermore, stress echocardiography may also be useful in detecting subjects susceptible to pulmonary hypertension in special environmental and physical conditions [63]. Subjects susceptible to high-altitude pulmonary edema showed similar abnormal PASP response to exercise in normoxia and during prolonged hypoxia

(12 % volumes of oxygen corresponding to a 4.500-m altitude) [63]. Although echocardiography during exercise may be a promising approach for detecting early stages of pulmonary hypertension, most guidelines recommend echocardiography at rest only [44, 48]. The accuracy of stress Doppler echocardiography for this indication has not been assessed in a larger group of patients and/or susceptible subjects.

From our point of view, PASP of >40 mmHg at rest and of >45 mmHg during low-dose exercise (25–50 W over 2 min) seem to be reasonable cut-off values for the noninvasive detection of manifest pulmonary hypertension, as they are in line with exercise pathophysiological mechanisms [64] and methodological prediction formulas of mean pulmonary arterial pressure [65–67]. The thresholds are based on publications, stating that healthy subjects do not exceed these values at rest [33] or during low-dose exercise [68] defined as CO below 10 l/min. Furthermore, using the Chemla formula (PAPm = 0.61*PASP + 2 mmHg) [67] or the Syyed formula (PAPm = 0.65*PASP + 0.55 mmHg) [65] which both revealed a high accuracy and precision [66], PAPm of 25 mmHg at rest is equal to a PASP of 38 mmHg; PAPm of 30 mmHg during exercise would reflect a PASP of 45.9 mmHg. These PASP-cut-off values are also within the recommended values mentioned in the ERS/ESC guidelines for pulmonary hypertension [33].

The technique has pitfalls. From the pathophysiological viewpoint, on the basis of the fundamental equation of flow ($F = \Delta/R$), the abnormal exercise-induced increase in pressure can be linked to a supernormal increase in flow (e.g., in athletes) or to a normal increase in flow but with a subnormal fall in resistances due to a limited capability of pulmonary vessel recruitment and vasodilation (e.g., in chronic obstruction pulmonary disease with parenchymal pulmonary hypertension or congenital heart disease).

Furthermore PASP values during exercise have been shown to be directly linked to left atrial pressure [69] and left ventricular diastolic function and the presence of interstitial lung disease [70]. The current European Respiratory Society/ESC guidelines for the diagnosis of pulmonary arterial hypertension do not specify an indication for performing SE, because of limited information regarding standard values for PASP during exercise and the lack of prospective prognostic data [44], in spite of the acknowledged great potential for detecting the preclinical stages of disease via the exercise-induced increase in PASP disproportionate to the increase in cardiac output [4, 71].

The Doppler assessment of PASP has imperfect agreement with the gold standard of right heart catheterization, remains unfeasible in 15 % of patients with inadequate tricuspid regurgitation jet, and is unreliable in massive tricuspid regurgitation. During stress, we still lack accepted cut-off values of normal and abnormal responses. PASP values are linearly dependent on cardiac output, and multipoint pulmonary artery pressure-flow relationship should also be integrated with the evaluation of pulmonary vascular resistances. Post-exercise measurements are unreliable because of rapid return to baseline of pulmonary hemodynamics.

The prognostic meaning of exercise-induced increase in PASP varies radically depending on the clinical context. In patients with left heart failure or significant

Table 8.4 The clinical applications of PASP stress test

Disease	Level of evidence		
	Appropriate	Uncertain	Inappropriate
Symptomatic, mild mitral stenosis	√		
Asymptomatic, severe mitral insufficiency	√		
Heart failure		√	
Suspected PAH in normal resting TTE		√	
Reevaluation of exercise-induced PH on therapy		√	
Proven resting PH			√

PASP pulmonary artery systolic pressure, *HAPE* high-altitude pulmonary edema, *PAH* pulmonary arterial hypertension

mitral valve disease, PASP increase reflects an increase in left atrial pressure and impaired LV diastolic reserve and is a predictor of poorer prognosis. Instead, in patients with severe pulmonary hypertension and right heart failure, it indicates a preserved right ventricular contractile reserve and indicates a better prognosis [72].

At present, the only application endorsed by general cardiology guidelines [73] is the exercise Doppler study in symptomatic individuals with mild mitral stenosis and asymptomatic severe aortic insufficiency and mitral regurgitation [73] (Table 8.4). In these patients, valve surgery is considered reasonable (class II a, level of evidence C) for asymptomatic patients with preserved left ventricular function and pulmonary artery systolic pressure greater than 60 mmHg during exercise [73].

Thus, the European Society of Cardiology's updated guidelines strongly recommend exercise echocardiography in patients with valvular heart disease [73]. Exercise stress echocardiography may provide prognostic information in asymptomatic severe aortic stenosis by assessing the increase in mean pressure gradient and change in left ventricular function with exercise. In asymptomatic patients with moderate or severe mitral regurgitation without left ventricular dysfunction/dilatation, exercise echocardiography may identify a subset of patients who are at a higher risk of developing symptoms. In patients with mitral stenosis who are asymptomatic, the development of symptoms during exercise is strongly associated with the changes in the systolic pulmonary arterial pressure [74].

The indication to perform the study on patients with suspected pulmonary hypertension and normal or indeterminate findings after resting echocardiography study [75] remains uncertain. Other promising indications remain investigational at present.

8.5 B-Lines

B-lines detected by lung ultrasound (LUS), also called ultrasound lung comets, represent a useful, practical, appealingly simple way to image directly the extravascular lung water [76, 77]. Because the current technology for measuring pulmonary edema can be inaccurate (chest X-rays), cumbersome (nuclear medicine or

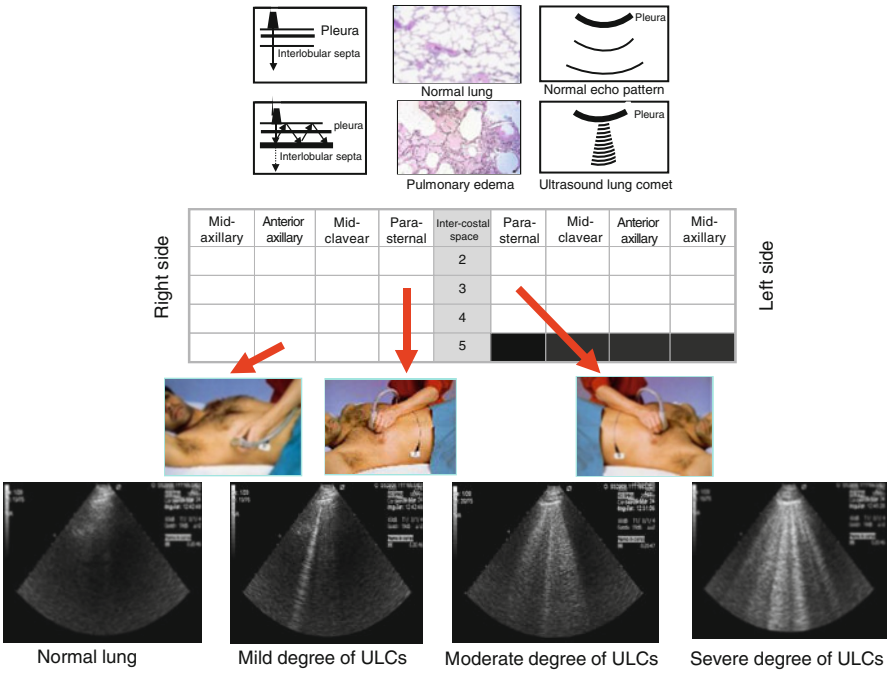

Fig. 8.5 How B-lines are generated (*upper panel*), counted (*middle panel*), and displayed (*lower panel*). The normal lung is "black" (no signal); the abnormal wet lung is "*black and white*" (with *white rockets* departing from the pleural line); and the lung with overt pulmonary edema is "*white*" (increase of coalescing comets on chest sonography)

radiology techniques), or invasive (indicator dilution), there is a great potential for technology that could quantify lung edema noninvasively in real time with a simple, semiquantitative, user-friendly, radiation-free direct imaging of extravascular lung water (Fig. 8.5). The cardiac transducer is employed to scan the anterior chest, and the number of B-lines in each intercostal space is summed up to generate a simple score. This can be extremely important in intensive care, for instance, in detecting acute respiratory distress syndrome, or in cardiology departments for identifying a cardiogenic cause of dyspnea but also in the stress testing laboratory [78]. In fact, membrane alveolar–capillary distress is a recognized adverse prognostic determinant in patients with heart failure. Indeed, a non-physiologic abrupt increase in pulmonary capillary wedge pressure can cause ultrastructural changes in the wall of pulmonary capillaries resulting in interstitial and alveolar edema. Particularly in patients with heart failure, a marked increase in pulmonary artery pressure and pulmonary capillary wedge pressure is observed during exercise even at very low levels creating an alveolar–capillary membrane dysfunction that contributes to symptom exacerbations and exercise intolerance (Fig. 8.6). Exercise may in fact determine the sudden appearance of B-lines on the chest in heart failure patients, in whom an increase in capillary wedge pressure may occur with absence of inducible ischemia,

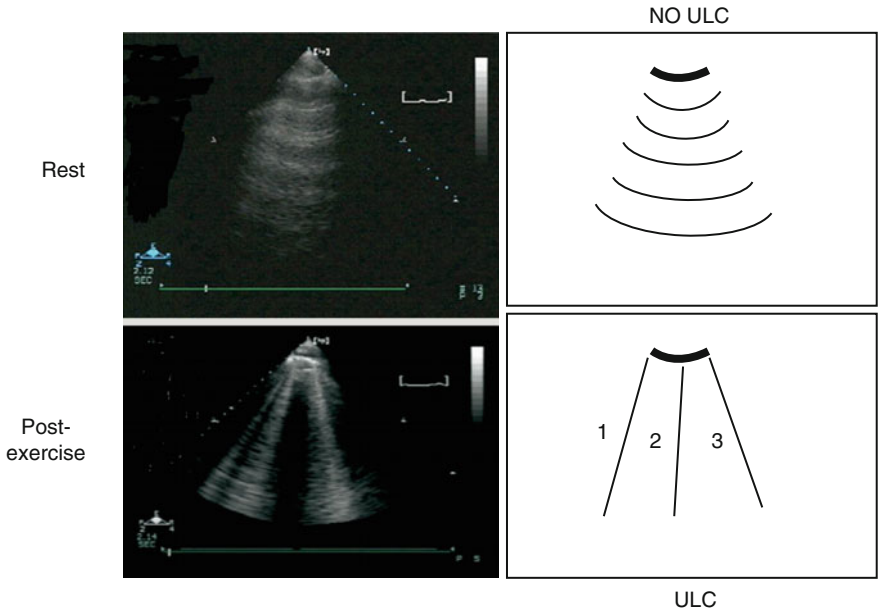

Fig. 8.6 Lung ultrasound (third right intercostal space) at rest (*left upper panel*) and immediately after exercise (*left lower panel*). On the right panels, the schematic drawing showing at rest normal, parallel, horizontal A-lines (*right upper panel*) and three vertical B-lines departing from the pleural line after exercise (*right lower panel*). The exercise-induced appearance of B-lines (also called ultrasound lung comets, ULC) reflects the acute increase of extravascular lung water. (Modified from Agricola et al., [78])

or in patients with extensive induced ischemia, in whom B-lines increase has the same conceptual meaning of the increased lung-to-heart ratio observed during sestamibi or thallium stress scan [78]. B-lines are usually accompanied by a marked stress-induced rise in E/e', which is a marker of raised left ventricular filling pressures and/or of PASP [79]. Another interesting model is an environmental stress-induced pulmonary edema. In high-altitude trekkers, healthy elite apnea and scuba divers or underwater fishermen [80–82], and extreme athletes involved in sports such as triathlon or marathon [83], B-lines can be detected in the presence of and, more often, in the absence of symptoms of pulmonary edema.

Therefore, stress lung ultrasound is useful in two separate settings, heart failure and extreme physiology (Table 8.5). In heart failure, B-lines may be helpful to titrate diuretic therapy or dialysis session, which should be increased in the presence of subclinical pulmonary edema present at rest or induced by exercise. LUS is performed in the stress echo lab with the standard high-end echocardiographic instruments and add as ancillary information to the standard evaluation of regional and global wall motion obtained during stress testing. In extreme physiology settings, B-lines can be obtained with portable pocket-size instruments, which are usable even in hostile environments. With batteries, power source, image storage (USB or laptop), and ultrasound gel, the total weight does not exceed 15 Kg. The technique can be easily learned by absolute beginners after an intensive 1-day training and

Table 8.5 Main applications of stress lung ultrasound

Setting	Heart failure	Extreme physiology
Environment	Stress laboratory	Ecological
Instrument	High cost, high weight	Low cost, pocket size
Subjects	HF patients	Divers, trekkers, runners
Technique	Stress echo + LUS	LUS
Location	Indoor	Outdoor
Target	Pulmonary edema	Non-cardiogenic pulmonary edema

also performed with e-learning interactive infrastructure. LUS can be performed within few minutes and hence reduces the time of patient exposure, which is especially important in cold mountain environments [79]. LUS in extreme physiology setting is therefore the best example of a new paradigm of "ecological" stress, under real-life conditions. This is especially important in extreme physiology setting, where changing levels of exercise, temperature, humidity, and distress are virtually impossible to reproduce in the stress testing lab. LUS stress echo is the paradigm of "next-generation" stress echo, leaving the controlled, artificial conditions of the laboratory to enter the universe of ecological, real-life world of stress.

B-lines may arise not only from water-thickened but also from fibrous-thickened subpleural septa, which are an important sign of alveolar–interstitial syndrome, for instance, in interstitial lung disease of systemic sclerosis [84]. Fibrotic B-lines are diuretic resistant, whereas watery B-lines of pulmonary edema are reduced by diuretics or dialysis [76].

Conclusion

It is now time to remember, also in the stress echocardiography laboratory, the "forgotten" right heart, which can be extensively studied in its regional and global, segmental, and longitudinal function, as well as in the novel dimension of coronary flow reserve of the right coronary artery and pulmonary hemodynamic and alveolar–capillary membrane response. The versatility of this information can help to better characterize a variety of patients, from coronary artery disease to dilated cardiomyopathy, from valvular heart disease to pulmonary hypertension, and from systemic sclerosis to healthy subjects susceptible to high-altitude pulmonary edema [85, 86]. From a practical viewpoint, it is certainly not feasible to do everything to all patients, since there are so little time during stress and so many things to see. Therefore, the variable of potential diagnostic interest should be strategically tailored to the individual patient (Table 8.6). The integration of right heart evaluation (including right ventricle, right coronary artery, pulmonary hemodynamics, and alveolar–capillary membrane) will allow the characterization of an exciting new target to be included in stress echocardiography. It was said several years ago in 1994 that "*the pulmonary circulation in patients with chronic pulmonary disease is often considered a no-man's land, falling between the domains of the respirologist and the cardiologist and understood only by the physiologist*!" [87]. It can be said today that a functional dynamic evaluation of

Table 8.6 Right heart stress echocardiography: targets and tools

	Method	Disease	Stress
Segmental function	2D	CAD	Any
Global function	*M*-mode	DCM	Dob (ex)
RCA coronary flow reserve	Color (PW) Doppler	CAD/DCM	Dip (ado)
PASP	CW Doppler (TR)	Primary or secondary pulmonary hypertension	Ex
B-lines	Lung ultrasound	Heart failure, HAPE	Hypoxia (ex)

CAD coronary artery disease, *CW* continuous wave, *DCM* dilated cardiomyopathy, *Dip* dipyridamole, *Dob* dobutamine, *Ex* exercise, *HAPE* high-altitude pulmonary edema, *PASP* pulmonary artery systolic pressure, *PW* pulsed wave, *TR* tricuspid regurgitation

right ventricular function, right coronary artery flow reserve, pulmonary hemodynamics, and extravascular lung water can offer a unique opportunity to the cardiologist and the pneumologist to better understand the cardiovascular physiology in a variety of cardiovascular and lung diseases.

Table of Contents Video Companion

See in the section illustrative cases: case number 29 (diastolic dysfunction by Maria Joao Andrade MD, Carnaxide–Lisbon, Portugal), case number 31 (comets during exercise stress in heart failure patient), and case numbers 32–35 (pulmonary pressure in aortic stenosis).

See also in the section selected presentations: B-lines, in and out the stress echo lab.

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Coronary Flow Reserve

9

Fausto Rigo and Eugenio Picano

9.1 Historical Background and Physiological Basis

The seminal concept of coronary flow reserve (CFR) was proposed experimentally by Lance K. Gould in 1974 [1]. Under normal conditions, in the absence of stenosis, coronary blood flow can increase approximately four- to sixfold to meet increasing myocardial oxygen demands. This effect is mediated by vasodilation at the arteriolar bed, which reduces vascular resistance, thereby augmenting flow. Coronary reserve is the capacity of the coronary circulation to dilate following an increase in myocardial metabolic demand and can be expressed by the difference between the hyperemic flow and the resting flow curve. In most clinical applications, hyperemia is induced pharmacologically, not via an increase in oxygen demand. A combined anatomical and physiological classification can ideally identify four separate segments in the hyperemic curve (Fig. 9.1): (1) the hemodynamically silent range of 0–40 % stenosis, which does not affect CFR (>2.5) to any detectable extent; (2) the clinically silent zone, where stenosis ranging from 40 to 70 % may marginally reduce the CFR without reaching the critical threshold required to provoke ischemia with the usual stresses; (3) the severe stenosis range (70–90 %), where critical stenosis reduces CFR less than 2.0 and myocardial ischemia is usually elicited when a stress is applied; and (4) the very severe stenosis range (>90 %), producing a marked transstenotic pressure drop at rest, with a reduction of baseline myocardial blood flow and a CFR close to 1, or even less; in these patients, the administration of a coronary vasodilator actually decreases the poststenotic flow for steal phenomena. This experimental paradigm can be accurately reproduced clinically in highly selected series of patients with single-vessel disease, no myocardial infarction, no coronary collateral circulation, normal baseline function, no left ventricular hypertrophy, and no evidence of coronary vasospasm and who are off therapy at the time of testing. In these patients, the more severe the stenosis, the more profound the impairment in CFR. The correction of the stenosis improves CFR, and perfect dilation normalizes the CFR. The perfect, predictable relationship found in the experimental animal and in a very selected patient population [2] falls apart in the clinical

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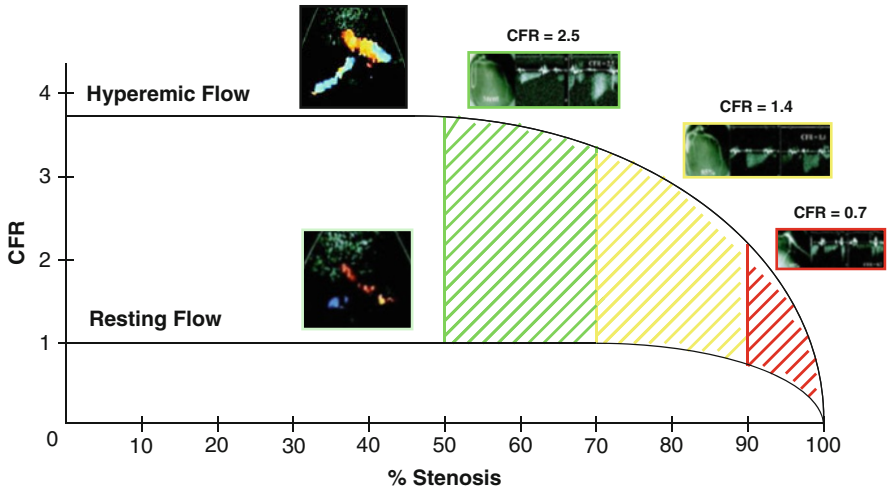

Fig. 9.1 The curve of CFR with the four segments: hemodynamically silent (0–40 % stenosis), clinically silent (40–70 % stenosis), hemodynamically significant (70–90 % with CFR <2.0), and very severe stenosis (>90 %, with CFR <1.0) (Redrawn and adapted from Gould and Lipscomb [1] and Pizzuto et al. [17])

arena [3], where many variables can modulate the imperfect match between epicardial coronary artery stenosis and CFR. Among others, these variables include:

1. The geometric characteristics of the stenosis
2. The presence of coronary collateral circulation
3. The microvascular component of coronary resistance
4. Left ventricular hypertrophy modulating the myocardial extravascular component of coronary resistance
5. The viable or necrotic state of the myocardium distal to the stenosis
6. The presence of coronary macrovascular or microvascular spasm
7. The presence of concomitant anti-ischemic therapy

In fact, this impressive scatter of data leads to the need to reconsider our original view of ischemic heart disease focused on coronary stenosis [4]. According to that view, each level of stenosis precisely predicts the level of impairment in coronary blood flow. This concept has some corollaries: stenosis is the disease, and dilating the stenosis means curing the disease; the probability of subsequent occlusion depends on the severity of the stenosis; the stress test accurately maps the area at risk for subsequent infarction. Although reasonable, all these corollaries are at least partially wrong; the stenosis is only the fruit of the atherosclerotic plant, which has deep genetic, metabolic, and hemodynamic roots that must be identified and treated in order to better cure this disease. Critical stenosis may occlude, but the majority of clinically catastrophic occlusions occur in previously noncritical stenosis; the stress test accurately identifies the area at risk of subsequent infarction in only a minority

Table 9.1 Methods of assessing CFR

	Measurements of flow	Radiation exposure	Cost	Availability	Accuracy	Interest
PET	Absolute	2–5 mSv	Very high	–	+++	Research
SPECT	Relative	10–20 mSv	High	++	++	Clinical cardiology
CMR	Relative	0	High	±	++	Clinical cardiology
Intracoronary Doppler	Relative	5 mSv	High	±	+++	Cath lab
Transesophageal Doppler	Relative	0	Low	+	++(+)	Echo lab
Transthoracic echocardiography	Relative	0	Very low	+++	++(+)	Clinical cardiology

CXR chest radiograph, *mSv* millisievert, *PET* positron emission tomography, *SPECT* single-photon emission computed tomography, *CMR* cardiovascular magnetic resonance

(four out of ten) of patients. In two out of ten patients, the stress test is right for the wrong reason (the test results are positive, and the patient develops infarction, but in an area different from the induced ischemia), and in four out of ten, the test is wrong (normal findings in a patient who subsequently develops infarction) [5]. The appeal of coronary flow reserve is to gain insight into a key physiological variable that integrates functional assessment during a stress [6]. This assessment can be obtained clinically, with six different basic approaches (Table 9.1): positron emission tomography (PET), myocardial scintigraphy, magnetic resonance perfusion imaging, intracoronary Doppler flow wire, transesophageal echocardiography, and transthoracic echocardiography. PET is highly accurate and allows a quantitative assessment of absolute myocardial blood flow but is exorbitantly expensive, technically demanding, and available in very few centers and exposes the patient to radiation biohazards. Single-photon emission computed tomography (SPECT) is less expensive and is also less accurate than PET, with a high radiation burden of 500–1500 chest X-rays for a sestamibi or thallium scan, respectively. Intracoronary Doppler flow wire is invasive, risky, and expensive, requiring intracoronary catheterization; radiation exposure is required for intracoronary catheter placement, although not directly for CFR measurement. Instead, transesophageal echocardiography has the limitation of being semi-invasive, while transthoracic echocardiography has the merit of being noninvasive, nonionizing, and compatible with other forms of functional testing for induction of wall motion abnormalities in the echocardiography laboratory. All these approaches are based on the theoretical prerequisite that the imaging technique combined with hyperemic stress will generate a signal whose intensity is correlated (possibly in a linear, direct fashion) with coronary flow, especially in the high-flow range that is the most important one for diagnostic purposes. Unfortunately, none of the available techniques for noninvasive assessment of CFR allows a truly accurate quantitative assessment [7] (Fig. 9.2). For instance, a 40 %

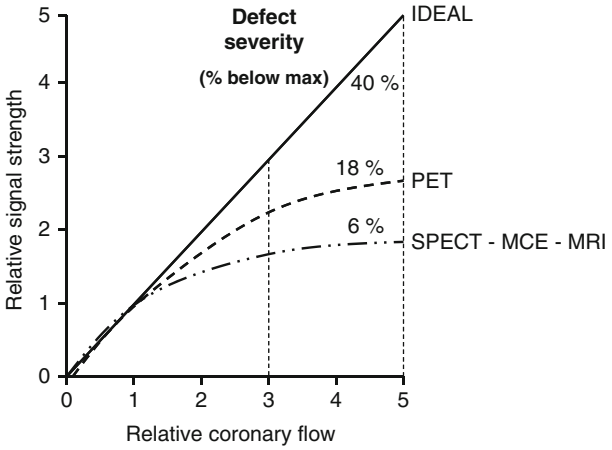

Fig. 9.2 Relationship between the true increments of coronary flow and the flow signal strength obtained with the currently available imaging techniques. All techniques, including the most sophisticated and expensive ones, are considerably far from the ideal, in which the signal increases in a linear and direct fashion with flow. In the high-flow range – the most important one following a vasodilatory stimulus – the relationship between flow and signal tends toward a plateau, implying only minimal (if any) signal differences. For instance, if the flow is fivefold higher in the normal coronary vessel and only threefold in the stenotic vessel, the recorded flow difference will be 18 % by positron emission tomography (*PET*) and around 10 % by SPECT, myocardial contrast echocardiography (*MCE*), transthoracic echo Doppler flowmetry, and magnetic resonance imaging (*MRI*) (Adapted and modified from Gould [7])

reduction in CFR compared with normal values (i.e., a flow reserve of 3 in diseased myocardium compared to a flow reserve of 5 in the normal myocardium) will yield a difference in signal intensity of only 6 % with SPECT (comparable to myocardial contrast echocardiography) and of 18 % with PET, whose results correlate well with intracoronary, transesophageal, and transthoracic echocardiography Doppler techniques [8]. We are still far from the ideal test of CFR. Nevertheless, the possibility of a reasonably accurate estimation of CFR during a stress targeted on functional testing for wall motion analysis opens new, exciting clinical and research opportunities.

9.2 Coronary Flow Reserve in the Echocardiography Lab

With either transesophageal (sampling the proximal tract) or transthoracic echocardiography (exploring the mid-distal tract), the left anterior descending coronary blood flow velocity profile recorded with pulsed-wave Doppler is consistent with the pathophysiological premises. Coronary flow velocity by Doppler assessment appears to be biphasic, with a lower peak during systole and a higher peak during diastole. Myocardial extravascular resistance in fact is higher in systole and lower in diastole due to the effect of myocardial contraction (Fig. 9.3) [9]. The flow

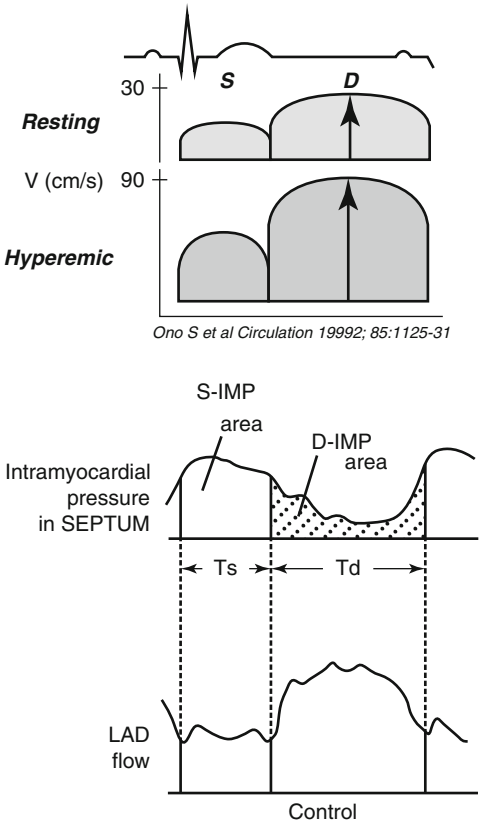

Fig. 9.3 Schematic representation of coronary flow velocity profile obtained with transthoracic Doppler of the mid-distal left anterior descending coronary artery and measurement of the CFR through peak diastolic flow velocity. The coronary blood flow velocity is higher in diastole. The *lower panel* shows the experimental data obtained with intramyocardial pressure monitoring and left anterior descending flowmetry in the dog (From Ono et al. [9], with permission)

velocity variations are proportional to the total blood flow if the diameter of the vessel lumen is kept constant. In reality, the diameter of epicardial coronary arteries increases by an average of 30 % in healthy subjects following adenosine infusion [10]. Therefore, failure to take into account epicardial coronary artery vasodilation during hyperemia may cause a nonsystematic underestimation of CFR, which can be more accurately calculated as velocity time integral cross-sectional area [10]. In practice, and with an unavoidable approximation, the coronary flow velocity reserve (CFVR) between baseline and peak effect of a coronary vasodilator makes it possible to derive an index of CFR in the left anterior descending artery territory. Several parameters might be measured from Doppler tracings of left anterior descending artery flow, including systolic flows, time–velocity integrals, and mean flows [8]. However, the best parameter is peak diastolic flow; it is not only the simplest parameter to be measured and the easiest to obtain but also the most reproducible and the one with the closest correlation with coronary perfusion reserve measured with Doppler flow wire [11] and PET [12]. The signal of coronary flow on the left anterior descending coronary artery was first made possible by transesophageal echocardiography, with excellent diagnostic results [11,

12], but only recently has there been increased clinical interest in the development of the transthoracic method [13–17]. There were technological factors that allowed the totally noninvasive transthoracic imaging of the mid-distal left anterior descending coronary artery: second-harmonic imaging, which provides better definition of smaller structures such as the left anterior descending coronary artery, and high-frequency transducers (up to 8 MHz), which provide improved resolution imaging of near-field structures (Fig. 9.4). The availability of contrast agents also improved the signal-to-noise ratio, increasing the feasibility of transthoracic imaging of the left anterior descending coronary artery above the threshold of potential clinical impact.

The Doppler assessment of CFVR has some limitations. The assessment of absolute blood velocity can be limited in some patients by the large incident angle between the Doppler beam and blood flow. However, calculation of the flow reserve allows assessment of flow patterns without the need for absolute values. More importantly, the velocity ratio is used as a surrogate of flow reserve; flow within the coronary artery is not calculated because cross-sectional visualization of the vessel does not accurately measure the diameter of the vessel. The estimated flow reserve can be accurate if the coronary artery functions only as a conduit, with no change in its diameter during drug infusion. The variability and heterogeneity in coronary artery diameter response following administration of adenosine [10] or dobutamine [18] introduce a remarkable source of error, which is amenable to correction only through direct measurement of epicardial vessel diameter changes with

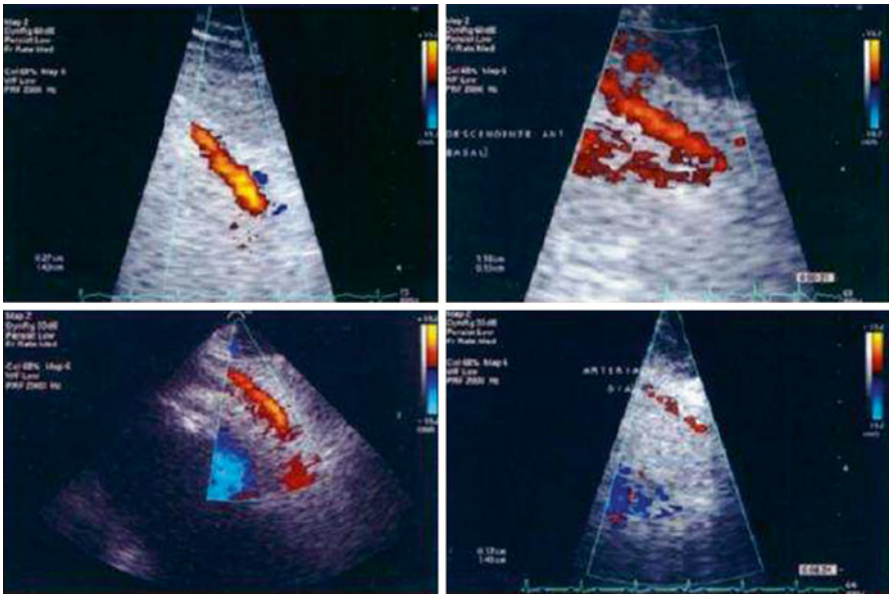

Fig. 9.4 Color Doppler flow imaging of the left anterior descending artery, visualized in its middle-to-distal portion to a variable extent in four different patients (Courtesy of Dr. Jorge Lowenstein)

high-resolution imaging [10]. However, the positive correlation between true CFR and CFVR, together with the lower method variability of the latter, makes it suitable for a robust assessment of CFR in most experimental and clinical settings [19].

9.3 Methodology

Stress testing of CFVR introduces a change in the choice of the stress, the use of transducers, and the methodology of testing.

After stress, the balance between exercise, dobutamine, and vasodilators clearly goes in the direction of vasodilators (Fig. 9.5), which fully recruit CFR [20] (Fig. 9.6) and minimize the factors polluting image quality [21]. Among vasodilators, dipyridamole is better tolerated subjectively than adenosine [22]; it induces less hyperventilation (which may pollute the echocardiography images), costs much less in most countries, and has a longer-lasting vasodilatory effect [23] (Fig. 9.7), which is more convenient for dual flow and function imaging (Table 9.2).

A broadband transducer (2–7 MHz) or two transducers (with low-frequency imaging of wall motion and high-frequency imaging of left anterior descending coronary artery flow) must be used, allowing alternative opening of imaging windows on coronary flow and left ventricular function [24, 25]. Besides the classic projections for stress echocardiography testing, specific projection for left anterior descending coronary artery imaging should be integrated into the cardiac imaging sequence (Fig. 9.8). The posterior descending artery (Fig. 9.9) and the left circumflex artery (Fig. 9.10) can be imaged with dedicated imaging projections but with greater difficulty and a lower success rate. The imaging protocol methodology also changes, with a shift from left anterior descending coronary artery flow to left ventricular function. This is more technically demanding but also more thrilling for the skilled stress echocardiographer, as it combines the two different aspects of flow and functional imaging into a single test [24–26]; the split brain of imaging formally finds its conceptual corpus callosum in the echocardiography laboratory (Figs. 9.11 and 9.12). The normal values are quite similar for all three coronary arteries and are clearly normal when above 2.5, borderline between 2.0 and 2.5, and clearly

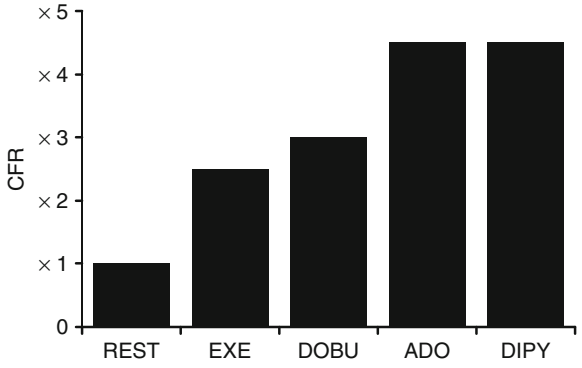

Fig. 9.5 CFVR and stresses: vasodilators [adenosine (*ADO*) or dipyridamole (*DIPY*)] evoke a greater recruitment of CFR, substantially higher than dobutamine (*DOB*) and exercise (*EXE*). They are more appropriate stressors for testing CFR (Modified from Iskandrian et al. [20], with permission)

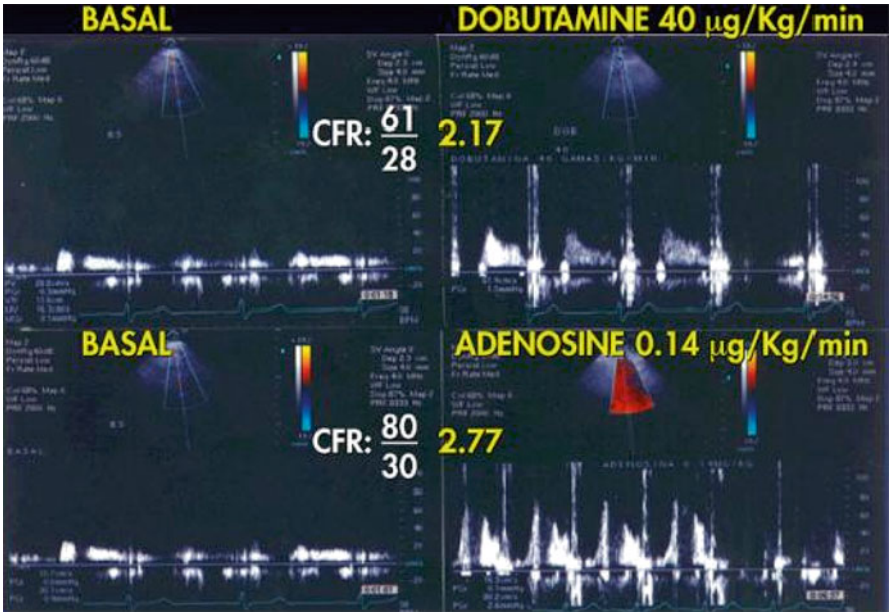

Fig. 9.6 CFVR assessed in the same patient with transthoracic echocardiography by dobutamine (*upper panels*) and adenosine (*lower panels*). *Left panels*, baseline signal. *Right panels*, peak stress signals. The increase in CFVR is substantially higher with adenosine than with dobutamine (Courtesy of Dr. Jorge Lowenstein)

abnormal below 2.0. Athletes show supernormal values (above 4.0). A reduction in CFVR can be linked to a significant epicardial coronary artery stenosis but also to microvascular disease or to factors increasing extravascular resistance and endoluminal compressive forces with normal coronary arteries, as happens in syndrome X, dilated or hypertrophic cardiomyopathy, and aortic stenosis [27].

9.4 Coronary Flow Velocity Reserve: The Diagnostic Results

Good results have been reported with CFVR evaluation during transesophageal [11, 12] or transthoracic echocardiography [13–17] for noninvasive diagnosis of coronary artery disease (Fig. 9.13). Nevertheless, the use of CFVR as a stand-alone diagnostic criterion suffers from major pitfalls, since only the left anterior descending coronary artery is easily sampled in different tracts, and CFVR cannot distinguish between microvascular and macrovascular coronary disease [27]. Therefore, it is much more interesting (and clinically realistic) to evaluate the additive value over conventional wall motion for left anterior descending coronary artery detection. The assessment of CFVR adds sensitivity for left anterior descending coronary artery disease, with a modest loss of specificity [28–32]. In some ways, CFVR and wall

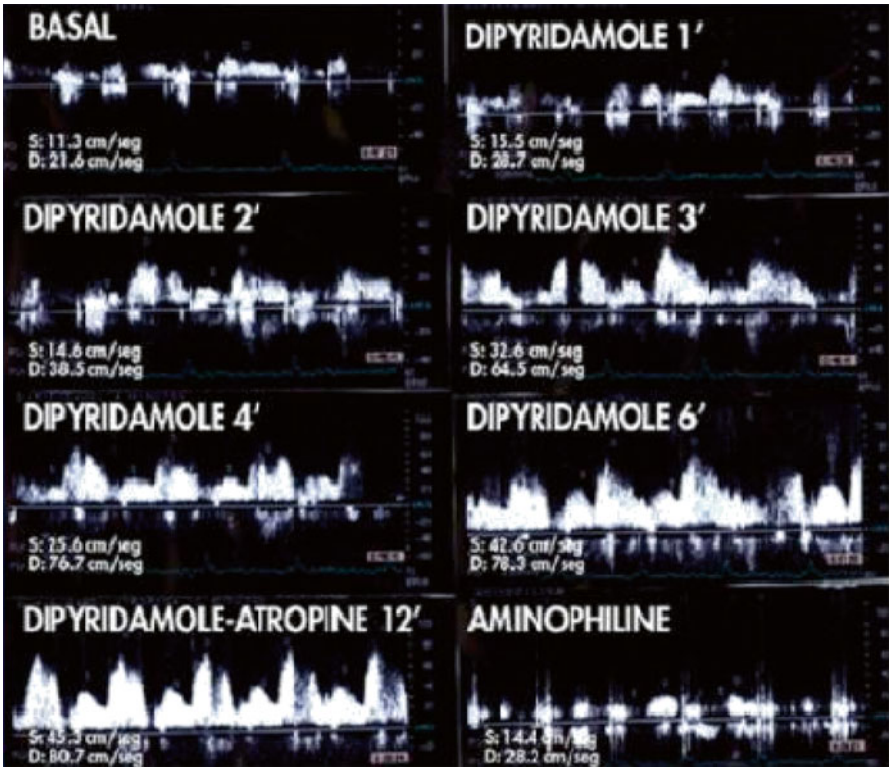

Fig. 9.7 The temporal sampling of CFVR by transthoracic echocardiography. There is a progressive, stepwise increase in CFVR peaking after the high dose and immediately reversed upon administration of aminophylline

Table 9.2 Vasodilator stress imaging

Drug	Adenosine	Dipyridamole
Patient tolerance	Lower	Higher
Vasodilator effect onset	Seconds	Minutes
Multiple coronary imaging	Difficult	Possible
Combined wall motion and CFVR	Difficult	Possible

CFVR coronary flow velocity reserve

motion analysis offer complementary information during stress echocardiography (Table 9.3). From the pathophysiological viewpoint, wall motion positivity requires ischemia as a necessary prerequisite, whereas CFR can be impaired in the absence of induced ischemia. Wall motion is easy to acquire but can be difficult to analyze. CFVR can be difficult to acquire, but it is usually straightforward in its quantitative interpretation of a Doppler signal. In the interpretation phase, a regional wall motion abnormality has higher positive predictive value for predicting the presence

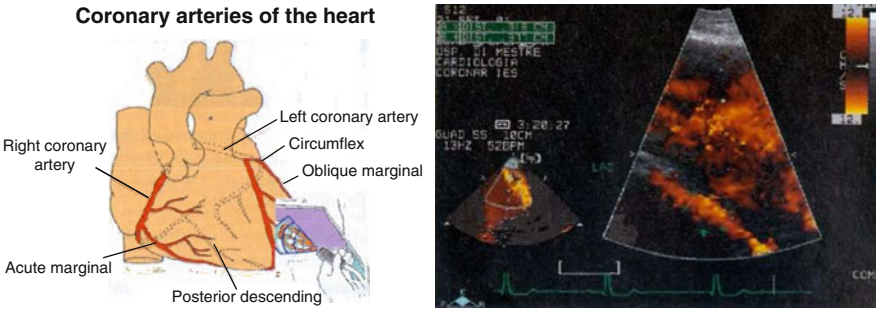

Fig. 9.8 *Left panel*: Artist's drawing illustrating transducer beam orientation to the left anterior descending coronary artery. The mid-distal tract is imaged from a modified apical 2-chamber view. *Right panel*: The corresponding echocardiographic image of left anterior descending color flow

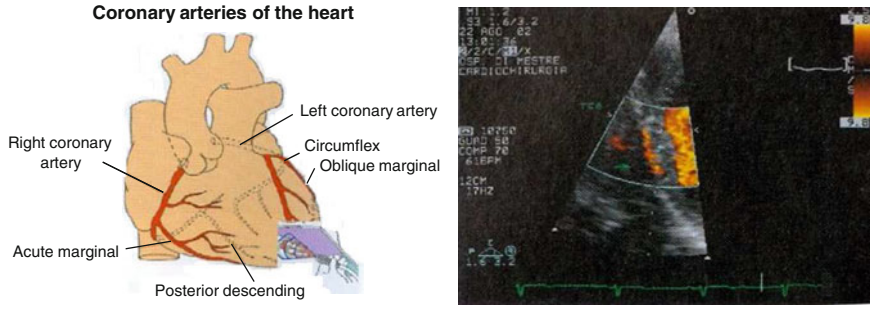

Fig. 9.9 *Left panel*: Artist's drawing illustrating transducer beam orientation to the posterior descending coronary artery. The mid-distal tract is imaged from a modified apical 2-chamber view with counterclockwise rotation and anterior angulation of the probe. *Right panel*: The corresponding echocardiographic image of posterior descending color flow

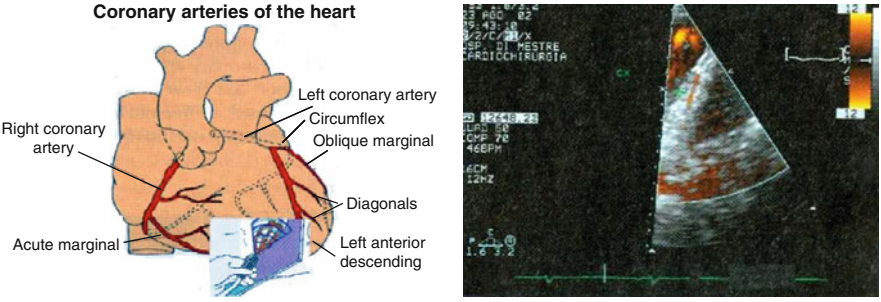

Fig. 9.10 *Left panel*: Artist's drawing illustrating transducer beam orientation to the left circumflex coronary artery. The mid-proximal tract of the left circumflex artery is imaged from a modified apical 4-chamber view with 50–80° clockwise rotation and posterior angulation of the probe. *Right panel*: The corresponding echocardiographic image of left circumflex color flow

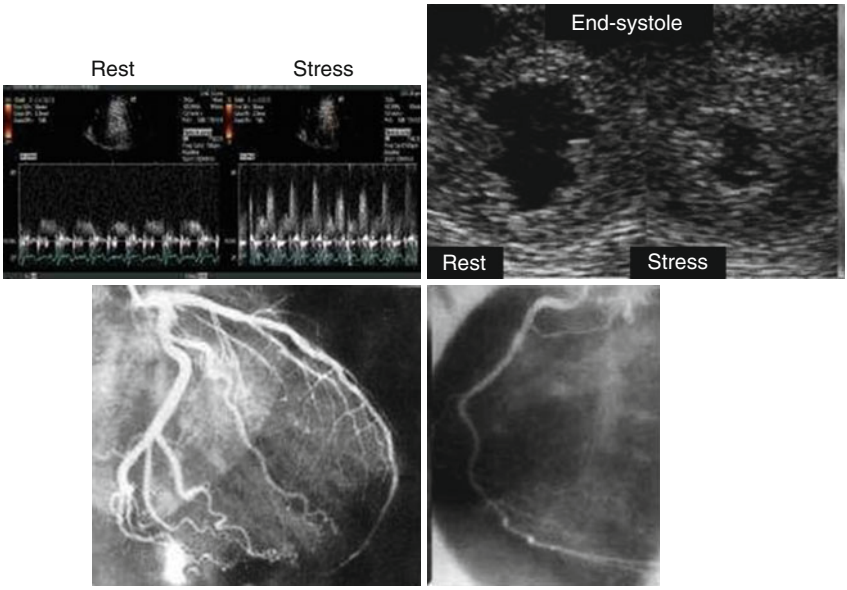

Fig. 9.11 A typical example of a normal regional wall motion and CFVR pattern from a patient with normal coronary arteries. The end-systolic frames from parasternal short-axis view show a normal thickening at rest (*left upper panel*) and during stress (*right upper panel*). On the *left*, pulsed Doppler shows a threefold increase in Doppler peak diastolic flow velocity from baseline (*left lower panel*) to peak dipyridamole (*right lower panel*)

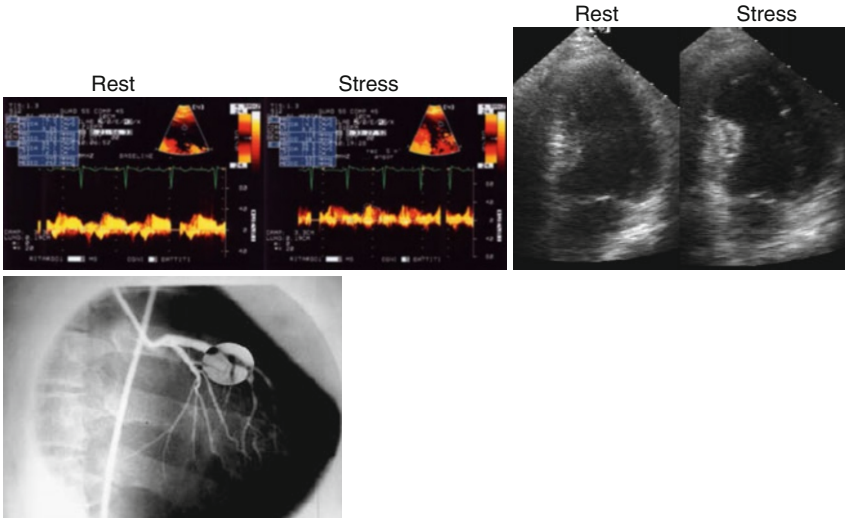

Fig. 9.12 A typical example of a regional wall motion (*right upper panel*) and CFVR (*left upper panel*) pattern from a patient with a tight proximal stenosis of the left anterior descending artery (*lower panel*). On the *right*, the end-systolic frames from the apical 4-chamber view show a normal thickening at rest and akinesia of the apex during stress. On the *left*, pulsed Doppler shows no significant increase in Doppler peak diastolic flow velocity from baseline (*left*) to peak dipyridamole (*right*)

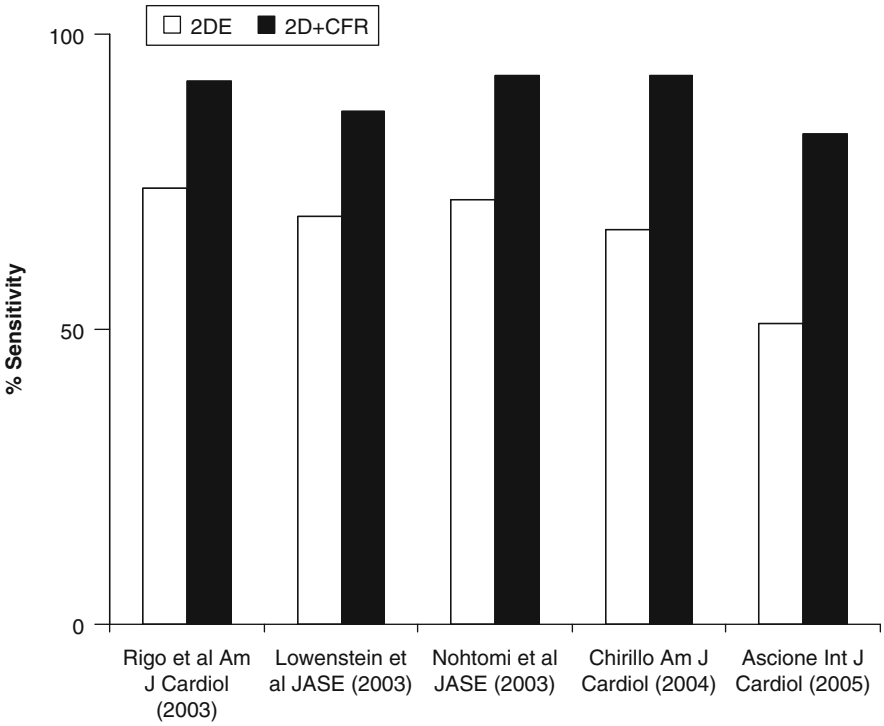

Fig. 9.13 The sensitivity for noninvasive detection of anatomic disease of the left anterior descending coronary artery on the basis of wall motion (2D echocardiography) and CFVR criteria in five different studies, all consistently showing the higher sensitivity achieved with the contribution of 2D echocardiography and CFR criterion versus 2D echocardiography alone (Redrawn and adapted from original data of [28–32])

Table 9.3 The two faces of stress echocardiography testing

	Wall motion	Coronary flow reserve
Specificity	Higher	Lower
Sensitivity	Lower	Higher
Technical difficulty	Lower	Higher
Interpretation	Difficult	Easier
Prognostic value	High	Unknown
Segmental positivity response	All or one	Continuous
Coronary arteries explored	All territories	Mostly LAD

LAD left anterior descending artery

of epicardial coronary artery stenosis. A normal CFVR has a higher negative predictive value. Therefore, the two pieces of information on flow and function can complement each other since a wall motion abnormality is highly specific and a normal CFVR is highly sensitive for coronary artery disease [28–32]. In addition, the flow information is relatively unaffected by concomitant antianginal therapy, which

markedly reduces sensitivity of ischemia-dependent regional wall motion abnormality [33] and does not influence CFVR except to a limited extent, if at all [34]. In this way, the CFR can already help in the difficult task of identifying patients with coronary artery disease. Obviously, such help will be greater with the potential of imaging all three major coronary arteries, with segments of the posterior descending and left circumflex coronary artery [35, 36] being more difficult for ultrasonic imaging at present.

9.5 The Prognostic Value of Coronary Flow Velocity Reserve

In patients with idiopathic dilated cardiomyopathy [37] or hypertrophic cardiomyopathy [38] and in patients with normal to nonsignificant coronary artery disease [39, 40], a severely depressed CFR is a predictor of poor prognosis. These studies were performed on small patient series, with a limited number of events, and employed complex and demanding techniques such as PET [37, 38] or the intracoronary Doppler flow wire technique [39, 40]. With the advent of CFVR in the stress echocardiography laboratory, in a few years a striking amount of information became available through large-scale multicenter studies, showing the impressive prognostic value of CFVR. This value has been proven in patients with stable angina [41, 42], in patients with intermediate stenosis of single-vessel disease [43, 44], and in several other challenging subsets characterized by negative wall motion response during stress echocardiography, such as patients with diabetes [45, 46] or hypertension [47], under antianginal therapy at the time of testing [48], with left bundle branch block [49], dilated cardiomyopathy [50], hypertrophic cardiomyopathy [51], or heart transplant [52]. The prognostic value has also been shown

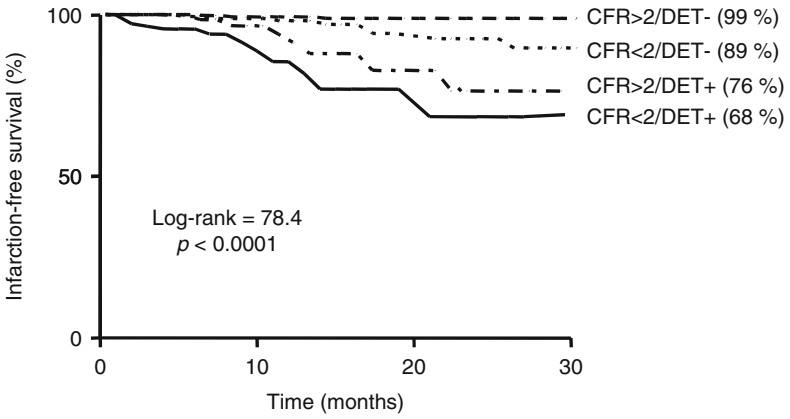

Fig. 9.14 Kaplan–Meier survival curves (considering only death and myocardial infarction as end points) in patients stratified according to normal (>2.0) or abnormal (<2.0) CFVR at Doppler echocardiography and the presence or absence of wall motion abnormalities by 2D echocardiography

for hard end points only [53] and adds incremental information over the value of inducible wall motion abnormalities (Fig. 9.14). The prognostic information provided by CFVR can be further expanded if the response is titrated according to a continuous spectrum rather than artificially dichotomized, with lowest quartiles (<1.8) identifying higher risk than higher quartiles with progressively more benign prognosis [54]. At this point, an evidence-based use of CFVR in clinically driven decision-making is possible and fully justified. Similar diagnostic and prognostic results can be obtained in the assessment of left ventricular wall motion and CFVR in left internal mammary artery and right internal mammary artery grafts [55–58].

9.6 Targets, Tips, and Traps in Coronary Flow Reserve Assessment

At present, different segments of native or grafted coronary arteries can be imaged transthoracically in the echocardiography laboratory. Each of the segments has different transducer frequency windows, different initial velocity range, different projections, and different technical difficulties (Table 9.4). There are biological and technical problems with CFR assessment. The CFR depends on a coronary as well as a myocardial component. Patent native arteries or graft with a low flow reserve supply myocardium that is partially scarred from previous infarction. Under these conditions, the vasodilating capacity of the recipient myocardium is probably reduced independently of any stenosis. In diagnostic terms, this may account for a reduced specificity of CFR (abnormal with patent arteries). Poststenotic CFR accurately reflects the residual vasodilatory capacity of that vascular bed which is specifically affected by the stenosis [24–27]. Prestenotic CFR can be diagnostically

Table 9.4 CFVR in the echocardiography laboratory: technicalities and targets

Vein graft	LAD	LCx	PD	LIMA	RIMA	Saphenous
Success rate	90 %	50 %	60 %	90–100 %	90–100 %	80–90 %
Transducer	Modified	Modified	Modified	Left supra	Right	Modified
Position	Apical	Apical 4-chamber	Apical 2-chamber	Clavicular area	Supraclavicular area	Parasternal
Transducer frequency (MHz)	5–7	3.5	3.5	5–7	5–7	3–5
Best CFR cutoff for stenosis detection	<2.0	<2.0	<2.0	<1.9	<1.9	<1.6

CFR coronary flow reserve, *LAD* left anterior descending artery, *LCx* left circumflex artery, *PD* posterior descending artery, *LIMA* left internal mammary artery, *RIMA* right internal mammary artery

unreliable, since the abnormal response in the poststenotic territory can be pseudonormalized by the normal vasodilatory response in the territories supplied by the branching vessels stemming off the main trunk between the sampling zone and the stenosis. CFR will yield the greatest information when combined with wall motion imaging. Contrast agent injection is sometimes – although not often – needed, and this will impact favorably on the cost-effectiveness profile of the method.

9.7 Stress Echo Response Patterns

Assessment of CFVR integrates and complements classic stress echocardiography founded on regional wall motion analysis. With the addition of CFVR to wall motion, the stress echocardiography response can be stratified into a severity code mirroring the ischemic cascade. On one end of the spectrum, there is the totally normal pattern, with hyperdynamic left ventricular function and preserved CFR, which is highly predictive of normal coronary anatomy and normal physiological response of coronary micro- and macrocirculation. At the opposite end of the spectrum, there is the totally abnormal pattern with regional wall motion abnormalities and abnormal coronary flow response, which is highly predictive of diseased epicardial coronary anatomy and impaired flow reserve. In between these extreme "black and white" responses, a gray zone can be found, more often with prognostically meaningful mild to moderate abnormal CFR and normal function (Fig. 9.15). At present, CFVR in coronary artery disease is a feasible, useful, and prognostically validated tool to be considered with standard wall motion analysis for the "two birds with one stone" approach of dual imaging in stress echocardiography. Its noninvasive, radiation-free nature also make it ideally suited for ethically immaculate, radiation-free research-oriented studies, especially when each subject or patient acts as his/her own control, allowing establishment of acute or chronic changes in CFR, induced, for instance, by acute food or beverage intake (such as alcohol or chocolate) or ingestion of medication in chronic therapeutic interventions, for instance, statins or antihypertensive drugs [59–61]. Although substantial technological and conceptual refinements are expected in the near future, for instance, with 3D imaging and the possibility of accurately assessing CFR with simultaneous evaluation of coronary flow velocity profiles and stress-induced changes in coronary diameter, there is little doubt that the technique is here to stay.

9.8 Pitfalls

The feasibility and clinical impact are highest for the mid-distal native left anterior descending coronary artery and the left internal mammary artery graft, while it is lowest (albeit still feasible) for posterior descending and left circumflex arteries. CFVR can be altered by changes in resting and hyperemic flows, which are

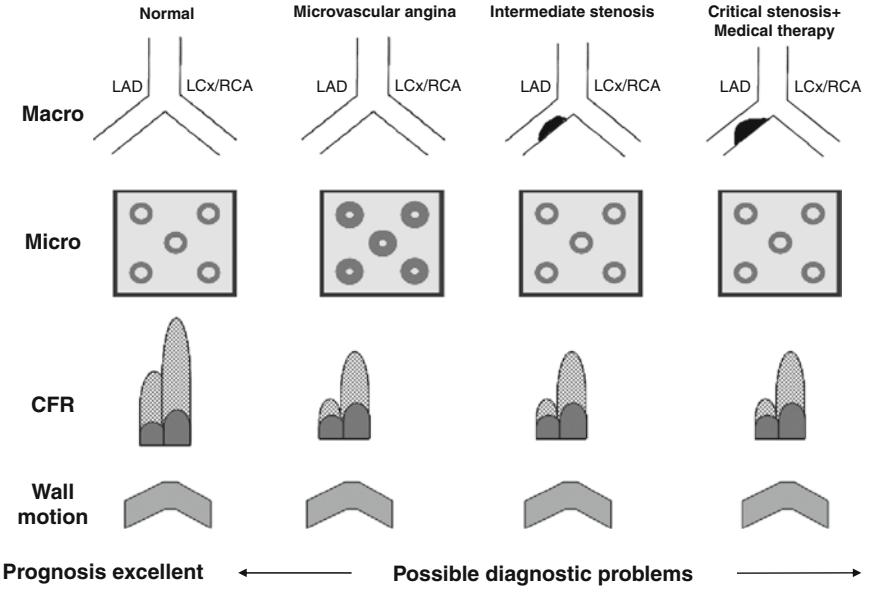

Fig. 9.15 Pathophysiological and prognostic heterogeneity behind normal wall motion response during stress. In the *upper panel*, we show epicardial coronary arteries: normal in the *first two columns*, with moderate disease in the *third column*, and moderate-to-severe disease but concomitant, effective 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 columns*) as *bold circles* (structural or functional impairment). All four very different pathophysiological conditions show the negativity of wall motion response. The abnormal CFVR response is present in the *last three columns*, with abnormality of micro- or macrocirculation. *Panel B*: Pathophysiological and prognostic heterogeneity behind abnormal wall motion response during stress. Symbols as in *panel A*. The CFVR can be normal in spite of wall motion abnormality when the left anterior descending artery is not significantly involved and the microcirculatory level is not impaired (*left panel*)

influenced by hemodynamics, loading conditions, and contractility. For example, tachycardia increases basal flow and decreases hyperemic flow, thus reducing CFVR by 10 % for each 15-beat increase in heart rate. The main problem with CFR in clinical practice resides in its lack of specificity for the epicardial vessel: an abnormal CFR value does not determine whether this abnormal flow velocity relates to the epicardial stenosis, to microvascular disease, or both [62].

9.9 Clinical Guidelines

ESC guidelines 2013 recognize that invasive measurements of CFR using a Doppler wire are complex and time-consuming and carry a small risk. Therefore, in angina with normal coronary arteries, objective evidence of ischemia of microvascular disease may be alternatively be obtained by measuring diastolic coronary blood flow in the LAD at peak vasodilation and at rest using transthoracic echocardiography

Doppler recordings [63]. A CFVR <2.0 strongly suggests coronary microvascular disease. Specialist guidelines endorse a more extensive application of CFR in the stress echo lab, suggesting that "whenever possible, it is recommended to perform dual imaging (flow and function) vasodilator stress echo" [64].

9.10 Future Directions

The possibility of mapping coronary flow velocity going from proximal to distal tract (Fig. 9.16) of LAD can highlight an abnormal coronary flow velocity due to an atherosclerotic plaque. More precisely, a recording on LAD of a higher velocity,

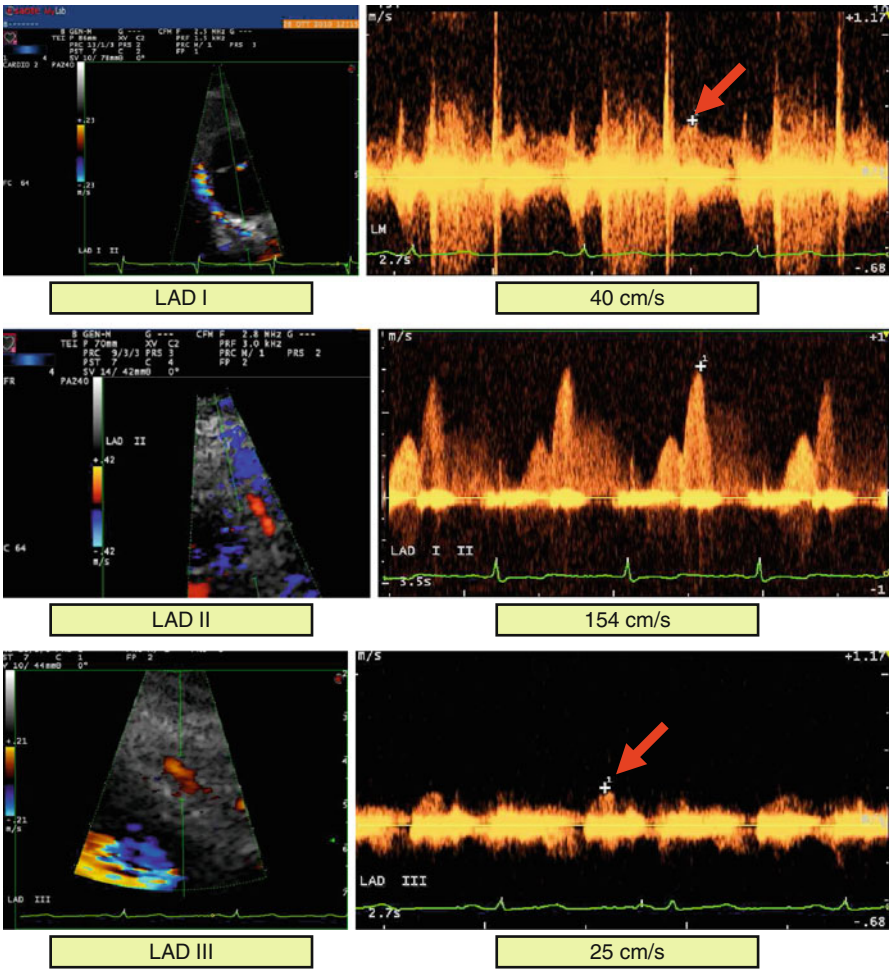

Fig. 9.16 Coronary flow velocity mapping, with color and pulsed Doppler, of proximal tract mid-distal tract of left anterior descending coronary artery in an abnormal case

more than 80 cm/s, especially in mid-distal tract of LAD, means a critical narrowing of coronary artery [65, 66].

Recently, some authors have proposed a new technique by applying Doppler flow wire, an innovative parameter labeled wave intensity analysis [67] that enables to highlight the different forces that drive coronary filling: proximal aortic pushing effect and distal suction effect. At present, matching coronary flow velocity information obtained by transthoracic echo Doppler recorded simultaneously with non-invasive arterial brachial pressure, both integrated electronically with a dedicated software, it is possible to define accurately the coronary filling. In so doing, we could better identify different coronary wave filling patterns that characterized different coronary artery diseases and therefore improve and tailor better our therapeutic strategy.

Table of Contents Video Companion

See in the section illustrative cases: cases number 13–18
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Technology and Training Requirements

10

Eugenio Picano and Bogdan Alexandru Popescu

Stress echocardiography is relatively simple and widely available [1]. However, skill in interpretation cannot be acquired in a few days or weeks. With a handheld echocardiographic machine and an inexpensive drug or an ergometer, any sonographer can become a stress echocardiographer [2]. Ordering patterns might be distorted by financial incentives because the test can be performed in a physician's office. In the absence of a strict system of credentialing and quality control, any lab may soon experience a backlash of distrust regarding the technique [2]. Interpretation of stress echocardiography requires extensive experience in echocardiography and should be performed only by physicians with specific training in the technique [3, 4].

10.1 General Test Protocol

The patient lies in a decubitus position, the position required to achieve an optimal echocardiographic view. Electrocardiographic leads are placed at standard limb and precordial sites, slightly displacing (upward and downward) any leads that may interfere with the chosen acoustic window. A 12-lead electrocardiogram (ECG) is recorded in resting conditions and at each minute throughout the examination. An ECG lead is also continuously displayed on the echocardiography monitor to provide the operator with a reference for ST segment changes and arrhythmias (Fig. 10.1). Cuff blood pressure is measured in resting conditions and at each minute thereafter with an automatic device. Echocardiographic monitoring is usually performed from the apical (both 4- and 2-chamber view) and parasternal (both long and short axes) approaches. In some cases, the subxiphoidal view is employed. Images are recorded in resting condition from all views. The echocardiogram is continuously monitored and intermittently recorded. In the presence of obvious or suspected dyssynergy, a complete echocardiography examination is performed and recorded from all approaches employed to allow optimal documentation of the presence and extent of

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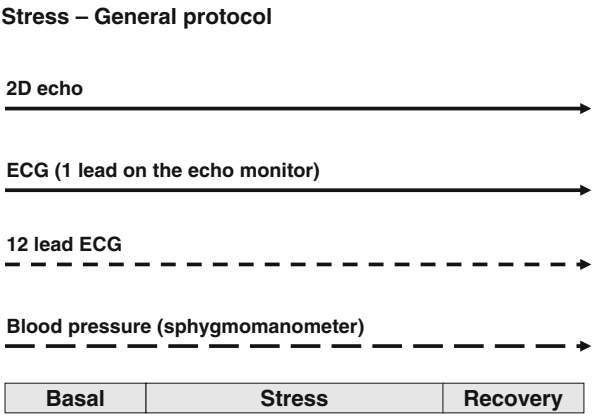

Fig. 10.1 General protocol of stress echocardiography test

Table 10.1 Diagnostic end points of stress echocardiographic testing

Maximal dose/workload
Target heart rate
Obvious echocardiographic positivity
Severe chest pain
Obvious ECG changes (>2 mm ST segment shift)

myocardial ischemia. The same projections are obtained and recorded in the recovery phase, after cessation of the stress (exercise or pacing) or administration of the antidote (aminophylline for dipyridamole, beta-blockers for dobutamine). The segmental function can be evaluated by means of a triple comparison: stress vs resting state; stress vs recovery phase; and at peak stress, with the neighboring normally contracting segments. A clear standardization of the procedures allows the work plan to be optimized, thus improving the overall quality of diagnostic performance in the stress echocardiography laboratory. The nurse explains the procedure and the aims of testing to the patient, marks the acoustic approaches, and, in the case of pharmacological stresses, prepares the doses of drugs, including the antidote. A 12-lead ECG is recorded, and blood pressure is measured. After placement of the intravenous line (in the case of pharmacological stress or contrast administration), the sonographer records the resting echocardiogram, and the stress begins. Throughout the study, the nurse keeps a written protocol of the study (clinical events, drugs injected, ECG, and echocardiographic changes noted by the physician), infuses drugs or varies the workload, measures blood pressure, and evaluates the 12-lead ECG each minute. A well-trained nurse with sonographer skills is essential in increasing the workflow and expanding the imaging service in a stress echo lab [5]. Diagnostic and nondiagnostic end points of stress echocardiography testing are reported in Tables 10.1 and 10.2, respectively.

Table 10.2 Submaximal nondiagnostic end points of stress echocardiography testing

Intolerance symptoms
Limiting asymptomatic side effects
Hypertension: SAP >220 mmHg; DAP >120 mmHg
Hypotension (relative or absolute): >30 mmHg drop in blood pressure
Supraventricular arrhythmias: supraventricular tachycardia, atrial fibrillation
Ventricular arrhythmias: ventricular tachycardia, frequent and polymorphic premature ventricular beats

SAP systolic arterial pressure, *DAP* diastolic arterial pressure

10.2 Imaging Equipment and Techniques

Digital acquisition of images has evolved from the days of stand-alone computers that digitized analog video signals to the current era in which ultrasound systems have direct digital output. By digitizing two-dimensional echocardiographic images, it is possible to put a single cardiac cycle into a continuous loop so that the cycle can be viewed whenever necessary for an indefinite period of time. This technique offers valuable advantages. Even in an exercising individual who is breathing rapidly and deeply, one can still see a technically good cardiac cycle between inspirations; therefore, it reduces the respiratory artifact. Another advantage of using the computer to record the two-dimensional echocardiogram digitally is that it is possible to place the resting and stress cardiac cycles side-by-side in a split-screen or quad-screen format. This reduces the time and difficulty of analyzing the examination and may also simplify the recognition of subtle changes in wall motion. Although there is no evidence that it improves diagnostic accuracy when compared with videotape reading [6, 7], digital acquisition certainly makes storage, retrieval, analysis, and communication of stress echocardiography data faster and easier. Videotape recordings are recommended as a backup.

Tissue harmonic imaging improves image quality over conventional imaging. This is obtained mainly through the elimination of ultrasound artifacts (namely, the side-lobe, near-field, and reverberation artifacts) with consequent increase in lateral resolution and signal-to-noise ratio. The increased image quality is mirrored in a better visualization of the left ventricular endocardium and epicardium, and this has a favorable impact on the evaluation of both global and regional left ventricular function at rest.

In the setting of stress echocardiography, tissue harmonic imaging reduces the number of uninterpretable segments, deflates observer variability, and increases diagnostic accuracy [8, 9]. The increase in interpretable myocardium is particularly valuable for the apical, lateral, and anterior wall segments (Fig. 10.2) imaged in the apical views at higher heart rates. Tissue harmonic imaging should be used for stress echocardiography imaging [3, 4]. When used in conjunction with harmonic imaging, contrast agents increase the number of interpretable left ventricular wall

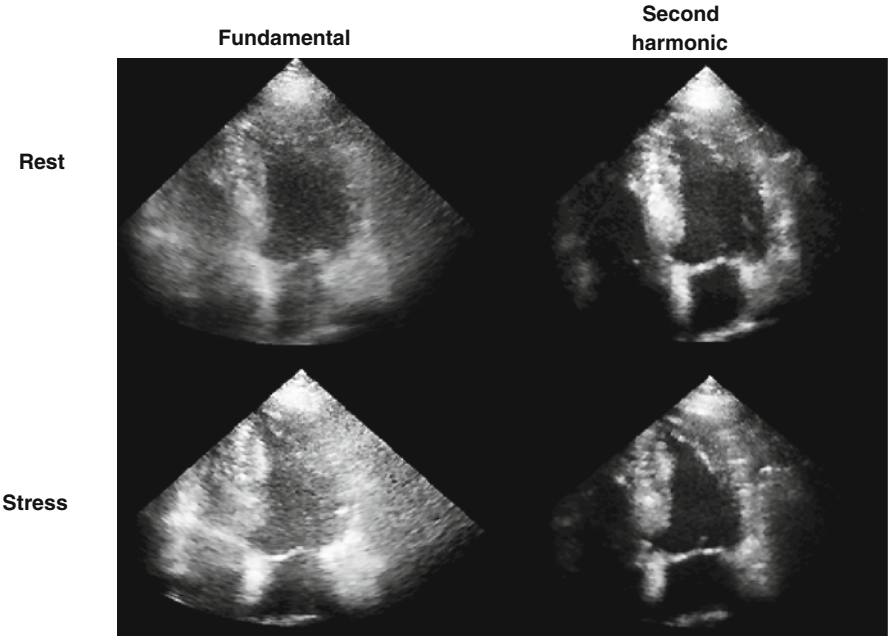

Fig. 10.2 Fundamental (*left*) and tissue harmonic imaging (*right*) of rest (*upper panels*) and stress (*lower panels*) end-systolic still frames of an apical four-chamber view. Basal and apical segments of the lateral wall are more sharply delineated with tissue harmonic imaging mode (From Rodriguez et al. [8])

segments, enhance diagnostic confidence, and reduce the need for additional noninvasive tests due to equivocal non-contrast stress examination [10]. Enhancement of Doppler signals and myocardial contrast echocardiography for perfusion remains off-label uses. Previous concerns regarding the safety of contrast agents have been addressed by recent data supporting the excellent safety profile of contrast agents, which should be used when two or more segments are not well visualized [11].

10.3 Training Requirements

For proper and safe performance of stress echocardiography, accreditation of both the individual performing the study and the laboratory where the study is performed should be mandatory. Establishing clear standards for the requirements of personnel training, staffing level, and equipment available in a stress echo laboratory is an important measure with the ultimate goal of safeguarding patients undergoing stress echocardiograms.

It is not reasonable to begin using stress echocardiography without thorough training in transthoracic echocardiography (level 2, American Society of Echocardiography). The basic skills required for imaging the heart under resting

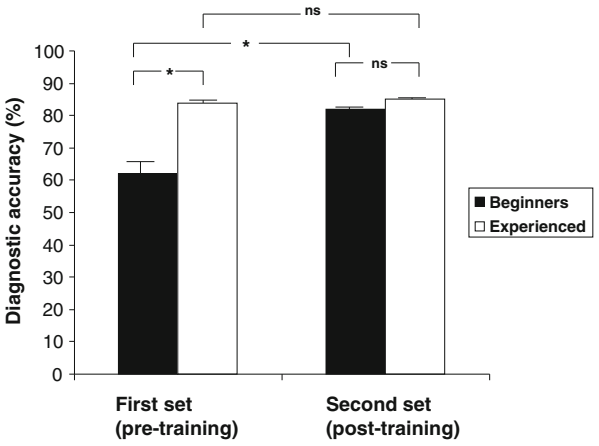

Fig. 10.3 Histograms showing the diagnostic accuracy of the five beginners (*white bars*) and five experts (*black bars*) who reviewed two sets of 50 videotapes before and after a 6-month training period (100 stress echocardiography studies with a supervisor); *$p<0.001$ (From Picano et al. [13])

conditions are not substantially different from those required for imaging the same heart from the same projections during stress. Furthermore, the echocardiographic signs of ischemia are basically the same as those during myocardial infarction. In both cases, the assessment is based on a comparison between the "suspected" zone and the neighboring normal regions; in induced ischemia, however, the operator can use the suspected region as its own control, considering both resting conditions and the recovery phase. The use of stresses is associated with the possibility of life-threatening complications, both ischemia related and ischemia independent. Therefore, as happens with a simple exercise test, the cardiologist-sonographer (and the attendant nurse) should be certified in basic and advanced life support, as also required by the American Heart Association guidelines for stress testing [12].

The diagnostic accuracy of an experienced echocardiographer who is an absolute beginner in stress echocardiography is more or less equivalent to that achieved by tossing a coin (Fig. 10.3). However, 100 stress echocardiography studies are sufficient to build the individual learning curve and reach the plateau of diagnostic accuracy [13]. With Doppler, it is wise to assess one's own learning curve in cases where a recent catheterization provides a standard against which the presence and severity of regurgitation and gradients can be estimated; instead, with stress echocardiography, it is wise to test one's initial performance in patients who have recently undergone coronary angiography and possibly with other imaging techniques using the same stress.

After 15–30 days of exposure to a high-volume stress echocardiography laboratory, the physician should begin to accumulate his or her own experience with a stepwise approach, starting from more innocuous and simple stresses such as low-level supine exercise echocardiography and moving up to more technically demanding ones.

The interpretation of stress echocardiography is necessarily qualitative and subjective. The cardiologist-echocardiographer performing the test evaluates the study online. Rarely is a "blind" reading by two independent observers made for

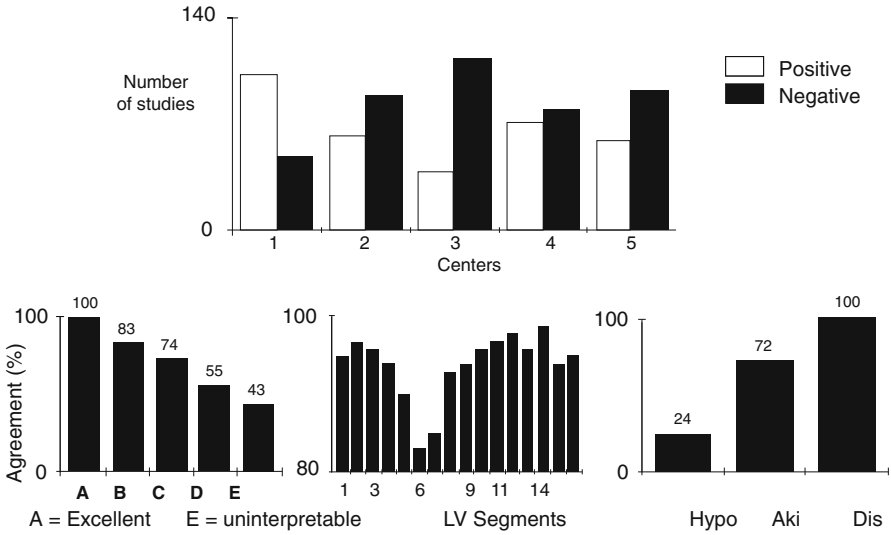

Fig. 10.4 Histogram showing inter-institutional variability in the reading of 150 dobutamine stress echocardiograms from five different centers with long-standing experience in stress echocardiography (Aachen, Cleveland, Essen, Pisa, Rotterdam). Positivity reading ranges from 102 of 150 (center 1) to 32 of 150 (center 3). Obviously, center 1 will have an outstanding sensitivity and poor specificity, whereas center 3, on the very same images, will have a low sensitivity and an outstanding specificity. Probably, both are right. Diagnostic accuracy compared with angiographically assessed coronary artery disease will be higher for center 1 in a population with a high prevalence of disease and higher for center 3 in a population with a low prevalence of disease. This stunning inter-institutional reading variability is not without method, however. In the *bottom panel*, the factors modulating variability are shown: image quality (*left*), location of the wall motion abnormality (*middle*), and severity of dysfunction (*right*). Variability is substantially higher for poor-quality images (*left*); for tricky segments such as the posterobasal segment or basal inferior septum (numbers *6* and *7* in *middle panel*), which may be "physiologically hypokinetic" even at baseline; and for a mild degree of dysfunction such as hypokinesia (*right*) (From Hoffmann et al. [14])

diagnostic or clinical purposes. Quantitative analysis of regional wall motion is never performed for purely diagnostic reasons; quantitative methods are time-consuming and require extra equipment and images of better quality than those interpretable with a qualitative assessment, and they certainly do not clarify uncertain readings; they simply measure and make the obvious "certain" without reducing the number of questionable studies. Diagnostic accuracy is not increased by quantitative methods, since the human eye naturally integrates space and time, and its discriminatory power is very difficult to equal and virtually impossible to surpass. However, it is also true that different individuals have different eyes, and the degree of inter-institutional variability tested on identical images can be substantial, even among laboratories of unquestionable reputation (Fig. 10.4) [14]. Diagnostic accuracy is not only a function of experience; for a given diagnostic accuracy, every observer has his/her own sensitivity-specificity curve: there are "over-readers" (high sensitivity, low specificity) and "under-readers" (low sensitivity, high specificity),

Table 10.3 Stress echocardiography and the human factor

	Increases variability	Reduces variability
Physician related		
1. Previous training in stress echocardiography	No	Yes
2. Exposure to joint reading	No	Yes
3. Development of "a priori" reading criteria	No	Yes
4. Basal inferior septum	Yes	No
5. Positivity for "lack of hyperkinesis"	Yes	No
6. Positivity for "severe hypokinesis"	No	Yes
Technology related		
7. Videotape instead of digital	Yes	No
8. Native tissue harmonic	No	Yes
Stress related		
9. Use of stressor polluting image quality	Yes	No
Patient related		
10. Resting images of borderline quality	Yes	No

depending on whether images are aggressively or conservatively interpreted as abnormal. Many studies yield unquestionably negative or positive findings; still, there is a "gray zone" of interpretable tests in which the visualization of some regions can be suboptimal and the cardiologist's level of experience in interpreting the test is critical for a correct reading.

Interobserver variability is certainly a common problem in medicine, and in cardiology variability can be substantial with almost all diagnostic methods, including resting electrocardiography [15], exercise electrocardiography [16], perfusion scintigraphy [17], and coronary angiography [18]. For thallium perfusion images, the interobserver agreement for a majority of observers was found to be 75 % for an abnormal and 68 % for a normal interpretation [19]. In only 65 % of coronary angiograms did all four experienced coronary angiographers (from the same institution) agree on the significance of a stenosis, defined as 50 % narrowing of lumen diameter [18]. However, a perception of the diffuse nature of the problem does not reduce interobserver variability in stress echocardiography. There are several ways to minimize this variability, representing the key factor which may ultimately determine the real impact of stress echocardiography in modern cardiology. Again, experience with nuclear medicine has taught us that agreement can be doubled by moving from an interpretation without standardization to an interpretation with standardization of display and quantification [19]. Similarly, there are many precautions that may minimize variability, providing not only high accuracy but also better reproducibility.

These parameters are related to the physician interpreting the study, the technology used, the stress employed, and the patient under study (Table 10.3). Variability will be substantially reduced if one agrees in advance not to consider minor degrees of hypokinesia, since mild hypokinesia is a normal variant under most stresses and

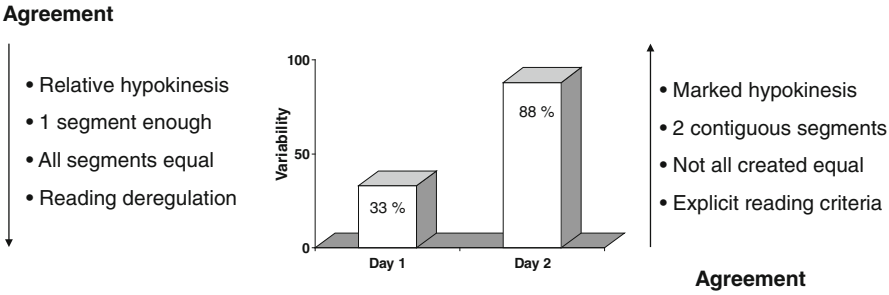

Fig. 10.5 The greater variability of reading occurs when there is no a priori agreement in reading criteria. With strict characterization of conservative reading criteria (ignore mild hypokinesia, ignore relative hypokinesia, ignore isolated infero-basal hypokinesia, etc.) and a limited experience in joint reading, interobserver agreement rises spectacularly (*right panel*) (Modified from Varga et al. [22])

there is a wide overlap between normal and diseased populations [20, 21]. Also, the inclusion of isolated asynergy of posterobasal or basal inferoseptal segments among positivity criteria will inflate variability. Obviously, the inclusion of patients with resting images of borderline quality, or the use of stresses degrading image quality, will also dilate variability, which is closely linked to the quality of the images. The single most important factor deflating variability is dedicated training in a large-volume stress echocardiography laboratory with exposure to joint reading [22] and "a priori" development of standardized [23] and conservative [24] reading criteria (Fig. 10.5).

10.4 Pitfalls

Regardless of the number of stress echocardiography studies performed and intensity of training, some readers still do not reach a satisfactory degree of accuracy and can be considered "nonresponders" to stress echo, which can be done by many but not all sonographers [24]. This is true with all activities involving development of cognitive skills. The five most frequent mistakes in stress echocardiography training can be summarized as follows:

1. *Self-made stress echocardiography:* it is far better to perform and/or review 100 stress echocardiography studies with an expert supervisor than 1000 stress echocardiography studies done all by oneself without a diagnostic reference standard.
2. *Starting one's learning curve at university level:* post-treadmill exercise is the most familiar stress for the cardiologist and the patient but by far the most technically demanding. The best way to improve image quality, diagnostic accuracy, and interobserver reproducibility is to use semisupine exercise as a physical stress and a vasodilator as a pharmacological stress.

3. *Underestimating ischemic risk:* the technicalities of pharmacological stress echocardiography can be surprisingly simple, but one has to know how to treat ischemia and its unforeseeable and potentially catastrophic complications. A stress echocardiography laboratory run by technicians and sonographers without an attending experienced cardiologist can be a real danger for the patient. For instance, the early stop of a pharmacological stress for an obvious regional dysfunction developed after very low dose of a drug (dipyridamole or dobutamine) can make the difference between an uneventful and a catastrophic stress. Not all patients were created equal during stress, and a fixed, inflexible approach with maximal dose administration in all can be dangerous.
4. *Skills in resting echocardiography are not enough:* pediatric, transesophageal, transthoracic, and vascular echocardiography speaks a different ultrasound idiom than does stress echocardiography. You have to learn stress echocardiography during dedicated training, or your experience will be disappointing and your results inconsistent.
5. *Technology without cardiology:* it is better to have the best eyes with a suboptimal technology than the worst eyes with the best technology. Usually, there is economic interest in selling technology, not in improving culture. Unfortunately, to date, no method for quantitative analysis has increased the clinical impact of stress echocardiography [25]. In the future, quantitative methods may serve as an adjunct to expert visual assessment of wall motion. The widespread use of quantitative methods will require further validation and simplification of analysis techniques [3, 4]. Stress echocardiography – and in particular pharmacological stress echocardiography – requires a tight integration of echocardiographic knowledge and cardiological experience. If this happens, clinical rewards will be outstanding, and stress echocardiography is now an integral part of the core curriculum of the clinical cardiologist according to the European Society of Cardiology.

10.5 Clinical Guidelines

The checklist for starting and keeping alive a stress echocardiography activity is reported in Table 10.4 (training requirements recommended by the American Society of Echocardiography), Table 10.5 (equally important cultural requirements suggested by the Task Force of the American College of Cardiology/American Heart Association), and Table 10.6 (staff and organization/equipment requirements as proposed by the European Association of Cardiovascular Imaging) [26–28]. As an additional requirement, the American Society of Cardiovascular Imaging recommends for cardiac sonographers a dedicated training course in radiation safety, since echocardiography (and more frequently stress echocardiography) is often performed in radiation-emitting ("hot") patients injected with radionuclides for myocardial perfusion studies [29]. This leads to a significant exposure (up to 0.5 milliSievert, around 25 chest x-rays) per exam to the sonographer [30], with

Table 10.4 Summary of recommendations of the American Society of Echocardiography for training in stress echocardiography

	Fellows in training	Postfellowship training	Maintenance of skills
Qualifications for training	Level 2 training + ability to interpret resting wall motion	Level 2 training or equivalent	Not applicable
		Current active practice of echocardiography	
Conditions for training	Laboratory performing 40 stress echocardiography studies per month	Laboratory performing 40 stress echocardiography studies per month	Not applicable
	Supervisor with level 3 training and experience with more than 200 stress echocardiography studies	Supervisor with level 3 training and experience with more than 200 stress echocardiography studies	
Number of cases recommended	Participation in performance of at least 50 exercise echocardiography and/or pharmacological stress echocardiography studies	Participation in performance of at least 50 exercise echocardiography and/or pharmacological stress echocardiography studies	Interpretation of 15 stress echocardiography studies per month
	Interpretation of at least 100 stress echocardiography studies with supervision as above	Interpretation of at least 100 stress echocardiography studies with supervision as above	

Modified from Rodgers et al. [26]

Table 10.5 Additive skills necessary in order to perform, interpret, and report pharmacological stress echocardiography according to the Task Force of the American College of Cardiology/American Heart Association

1. Knowledge of advantages and disadvantages of the different agents
2. Knowledge of the pharmacokinetics and the physiological response to the different agents
3. Knowledge of the contraindications to the different agents
4. Knowledge of the side effects and complications of the different agents and how to manage them
5. Competence in cardiopulmonary resuscitation
6. Knowledge of the end points of pharmacological stress and indications for terminating the test

Modified from Ryan et al. [27]

Table 10.6 Summary of the European Association of Cardiovascular Imaging criteria for rating stress echocardiography laboratories

Basic standard	Advanced standard
Staff	
Designated head of stress echocardiography	Head maintains CME for stress echo
Performing a minimum of 100 studies/year per laboratory	More than 300 studies/year per laboratory
Studies performed by at least two people, one of whom is a clinician. At least one must have advanced life support or equivalent	
Head has substantial experience of TTE and stress echo	
Organization/equipment	
List of indications, provision of information to the patient, and written informed consent	Machine capable of changing mechanical index and having a full digital stress echo package
ECG and blood pressure monitoring capabilities	Audit of results against angiography or other independent standard
Established appropriate protocols	Advanced software dedicated to contrast imaging
Machine with second-harmonic imaging and tissue Doppler imaging software	Capacity for both pharmacological and exercise stresses
Resuscitation facilities readily available and record of complications	Additional quantification package should be available
Lockable drug cupboard	Standard operating procedures should be available
Contrast agent for LV opacification available	A history of training junior doctors
Provisions for continuing educational activities	

Modified from Popescu et al. [28]
CME continuing medical education, *LV* left ventricle, *TTE* transthoracic echocardiography

potential for significant cumulative risk in case of protracted exposure, especially worrying in women, in young people, during pregnancy [31], and in individuals who may require additional time scanning, such as novice sonographers including students and fellows.

The increased demand for stress echo activity posed by recent guideline recommendations [32, 33], growing concern about radiation exposure and the cost of alternative imaging techniques [31], and the expansion of indications and applications of stress echo well beyond coronary artery disease [34] can only be met with optimization of training, cardiology staff, and resources, ideally within the framework of a continuous structured quality improvement project, with a tailored teaching and training program, creation of a uniform procedural protocol, and implementation of regular internal audits [35–37].

Table of Contents Video Companion

See stress echo primer, tutorial, and cases 1–16.
See also in the section "Illustrative Cases: Case number 10" (by Prof. Bogdan Popescu, Bucarest, Romania).
See also in the section "Nuovo Cinema Paradiso Remastered: Rocky Horror Stress echo picture show."
See also in the section "Selected Presentations: The doctor factor in stress echocardiography; Stress echo: the heart of darkness."
Springer Extra Materials available at http://extras.springer.com/2015/978-3-319-20957-9

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Part II

Stresses: How, When and Why

Exercise Echocardiography

11

Luc A. Piérard and Eugenio Picano

11.1 Historical Background

Many tests have been proposed in combination with echocardiography, but only a few have a role in clinical practice. For the diagnosis of organic coronary artery disease, exercise remains the paradigm of all stress tests and the first which was combined with stress echocardiography. In the early 1970s, *M*-mode recordings of the left ventricle were used in normal subjects [1] and in patients with coronary artery disease [2]. Subsequently, two-dimensional (2D) echocardiography was used to document ischemic regional wall motion abnormality during exercise [3]. The technique was at that time so challenging [4] that with the introduction of dipyridamole [5] and dobutamine [6] as pharmacological stressors, many laboratories used pharmacological stress even in patients who were able to exercise. Large-scale, multicenter, effectiveness studies providing outcome data are available only with pharmacological [7, 8] not with exercise echocardiography, offering a more robust evidence-based platform for their use in clinical practice. Exercise echocardiography was only really applied as a clinical tool in the early 1990s [4], and it is now increasingly used for the diagnosis of coronary artery disease, the functional assessment of intermediate stenosis, and risk stratification. A series of successive improvements led to a progressively widespread acceptance: digital echocardiographic techniques, allowing capture and synchronized display of the same view at different stages [9], improved endocardial border detection by harmonic imaging [10], and ultrasound contrast agents that opacify the left ventricle [11]. In the USA, most laboratories use the post-treadmill approach with imaging at rest and as soon as possible during the recovery period [12, 13]. In Europe, a number of centers have implemented their stress echocardiography laboratory with a dedicated bed or table allowing bicycle exercise in a semisupine position and real-time continuous imaging throughout exercise [14, 15]. The diffusion of semisupine exercise imaging – much more user-friendly for the sonographer than the treadmill test – made image acquisition easier and interpretation faster [16–18]. Semisupine exercise gained its well-deserved role in the stress echocardiography laboratory for coronary artery

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disease diagnosis and, with growing frequency outside coronary artery disease, in the assessment of pulmonary hypertension, valve disease, cardiomyopathy, and heart failure [19, 20].

11.2 Pathophysiology

Exercise protocols are variable and include treadmill as well as upright and supine bicycle ergometry. All these forms of stress increase myocardial oxygen consumption and induce ischemia in the presence of a fixed reduction in coronary flow reserve [21]. Of the determinants of myocardial oxygen demand, heart rate increases two- to threefold, contractility three- to fourfold, and systolic blood pressure by 50 % [21]. End-diastolic volume initially increases to sustain the increase in stroke volume through the Frank–Starling mechanism and later falls at high heart rates (Fig. 11.1).

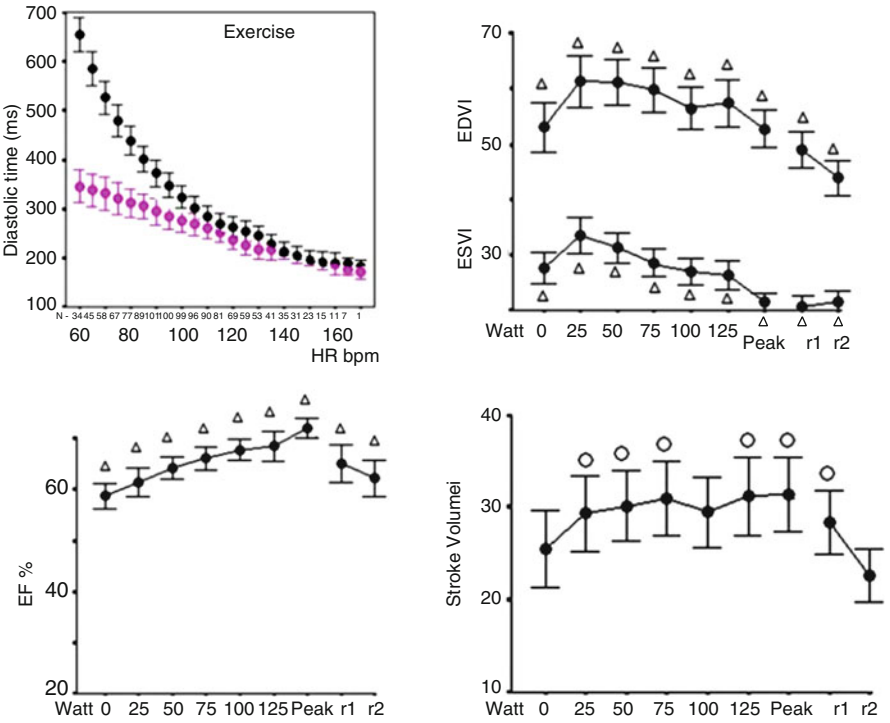

Fig. 11.1 The twofold increase in heart rate (*upper left panel*) is accompanied by a reduction of diastolic time. The shortening of diastole (*black dots*) is much more pronounced than shortening of systole (*purple dots*), but the former is much more critical for sub-endocardial perfusion, even in the absence of coronary artery disease. The trends of end-diastolic volume index (EDVI) and end-systolic volume index (ESVI), ejection fraction (EF) and stroke volume index (Svi) are shown in right upper panel, left lower panel and right lower panel respectively. (From Bombardini et al. [22])

Table 11.1 Exercise versus pharmacological stress

Parameter	Exercise	Pharmacological
Intravenous line required	No	Yes
Diagnostic utility of heart rate and blood pressure response	Yes	No
Use in deconditioned patients	No	Yes
Use in physically limited patients	No	Yes
Level of echocardiography imaging difficulty	High	Low
Safety profile	High	Moderate
Clinical role in valvular disease	Yes	No
Clinical role in pulmonary hypertension	Yes	No
Fatigue and dyspnea evaluation	Yes	No

Coronary blood flow increases three- to fourfold in normal subjects, but the reduction in diastolic time (much greater than shortening in systolic time) limits mostly the perfusion in the subendocardial layer – whose perfusion is mainly diastolic, whereas the perfusion in the subepicardial layer is also systolic [22]. In the presence of a reduction in coronary flow reserve, the regional myocardial oxygen demand and supply mismatch determines myocardial ischemia and regional dysfunction. When exercise is terminated, myocardial oxygen demand gradually declines, although the time course of resolution of the wall motion abnormality is quite variable [23]. Some induced abnormalities may persist for several minutes, permitting their detection on postexercise imaging. However, wall motion usually recovers very rapidly, and postexercise imaging can easily miss wall motion abnormalities. Regional and global function, although closely linked, may behave differently during stress. For example, if a small wall motion abnormality develops as a result of limited ischemia, the remainder of the left ventricle may become hyperdynamic, and the ejection fraction can increase despite the presence of an ischemic wall motion abnormality. In such a case, a regional abnormality will be present in the absence of global dysfunction. Alternatively, severe exercise-induced hypertension in the absence of coronary artery disease may lead to an abnormal ejection fraction response without an associated wall motion abnormality. There are distinct advantages and disadvantages to exercise versus pharmacological stress, which are outlined in Table 11.1. The most important advantages of exercise are that it is a stress familiar to both patient and doctor; it adds echocardiographic information on top of well-established and validated electrocardiographic and hemodynamic information, and it is probably the safest stress procedure. The disadvantages are the limited ability to perform physical exercise in many individuals, who are either generally deconditioned or physically impeded by neurologic or orthopedic limitations. In addition, stress echocardiography during physical exercise is more technically demanding than pharmacologic stress because of its greater difficulty and tighter time pressure [23].

11.3 Exercise Techniques

As a general rule, any patient capable of physical exercise should be tested with an exercise modality, as this preserves the integrity of the electrocardiogram (ECG) response and provides valuable information regarding functional status. Performing echocardiography at the time of physical stress also allows links to be drawn among symptoms, cardiovascular workload, and wall motion abnormalities. Exercise echocardiography can be performed using either a treadmill or bicycle protocol (Table 11.2). When treadmill exercise is performed, scanning during exercise is not feasible, and therefore most protocols rely on postexercise imaging [13]. It is imperative to complete postexercise imaging as soon as possible. To accomplish this, the patient is moved immediately from the treadmill to an imaging table and placed in the left lateral decubitus position so that imaging may be completed within 1–2 min. This technique assumes that regional wall motion abnormalities will persist long enough to be detected in the recovery phase. When abnormalities recover rapidly, false-negative results occur. The advantages of treadmill exercise echocardiography are the widespread availability of the treadmill system and the wealth of clinical experience that has accumulated with this form of stress testing. Information on exercise capacity, heart rate response, rhythm, and blood pressure changes are analyzed and, together with wall motion analysis, becomes part of the final interpretation. Bicycle exercise echocardiography is done with the patient either upright or recumbent (Fig. 11.2).

The patient pedals against an increasing workload at a constant cadence (usually 60 rpm). The workload is escalated in a stepwise fashion while imaging is performed. Successful bicycle stress testing requires the patient's cooperation (to maintain the correct cadence) and coordination (to perform the pedaling action). The most important advantage of bicycle exercise is the possibility to obtain images during the various levels of exercise (rather than relying on postexercise

Table 11.2 Exercise methods

Parameter	Treadmill	Upright bicycle	Supine bicycle
Ease of study for patients	Moderate	High	High
Ease of study for sonographer	Low	Moderate	High
Stage of onset of ischemia	No	Yes	Yes
Peak rate pressure product	High	High	High
Systolic blood pressure	Lower	Higher	Higher
Heart rate	Higher	Lower	Lower
Induction of coronary spasm	Higher	Lower	Lower
Preload increase	Lower	Lower	Higher
Ischemic strength	++ (+)	++ (+)	+++
Preferred modality in	USA	Europe	Echocardiography laboratory

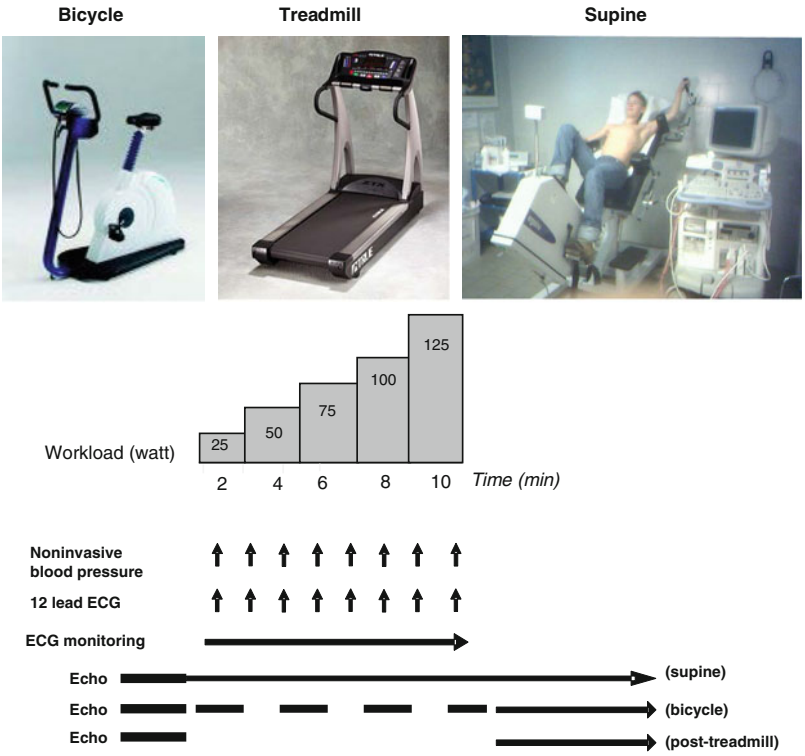

Fig. 11.2 Protocols of exercise stress echocardiography: upright bicycle (*left*); treadmill (*middle*); semisupine bicycle (*right*). Postexercise imaging is performed with treadmill only; at peak and postexercise with upright; and during, at peak, and after exercise with semisupine

imaging). With the patient in the supine position, it is relatively easy to record images from multiple views during graded exercise. With the development of ergometers that permit leftward tilting of the patient, the ease of image acquisition has been further improved. In the upright posture, imaging is generally limited to either apical or subcostal views. By leaning the patient forward over the handlebars and extending the arms, apical images can be obtained in the majority of cases. To record subcostal views, a more lordotic position is necessary and care must be taken to avoid foreshortening of the apex. When considering the various forms of exercise, it is important to appreciate fundamental differences. For most patients, both duration of exercise and maximum achieved heart rate are slightly lower in the supine position [24, 25], due primarily to the development of leg fatigue at an earlier stage of exercise. The limitation is overcome in part by the occurrence of ischemia at a lower workload with supine exercise. The earlier development of ischemia is the result of both a higher end-diastolic volume and higher mean arterial blood pressure for a given level of stress in the supine position [25, 26]. These differences contribute to a higher wall stress and an

associated increase in myocardial oxygen demand compared with an upright bicycle. Coronary spasms are provoked more frequently during treadmill than during bicycle exercise [27].

11.4 Safety and Feasibility

The safety of exercise stress is witnessed by decades of experience with ECG testing and stress imaging [28]. Also in exercise echocardiography registries collecting over 85,000 studies (25,000 in the international and 60,000 in the German registry), exercise echocardiography was the safest stress echocardiography test [29]. Death occurs on average in 1 in 10,000 tests, according to the American Heart Association statements on exercise testing based on a review of more than 1000 studies on millions of patients [28]. Major life-threatening effects (including myocardial infarction, ventricular fibrillation, sustained ventricular tachycardia, stroke) were reported in about 1 in 6000 patients with exercise in the international stress echocardiography registry – fivefold less than with dipyridamole echocardiography and tenfold less than with dobutamine echocardiography (Fig. 11.3). Although it is possible that patients referred for pharmacological stress are in general "sicker" than patients without contraindication to exercise, the available evidence suggests that while stress echocardiography is a safe method in the real world, exercise is safer than pharmacological stress [29], and dipyridamole [30] safer than dobutamine [31]. These conclusions are also in agreement with the preliminary results of the German

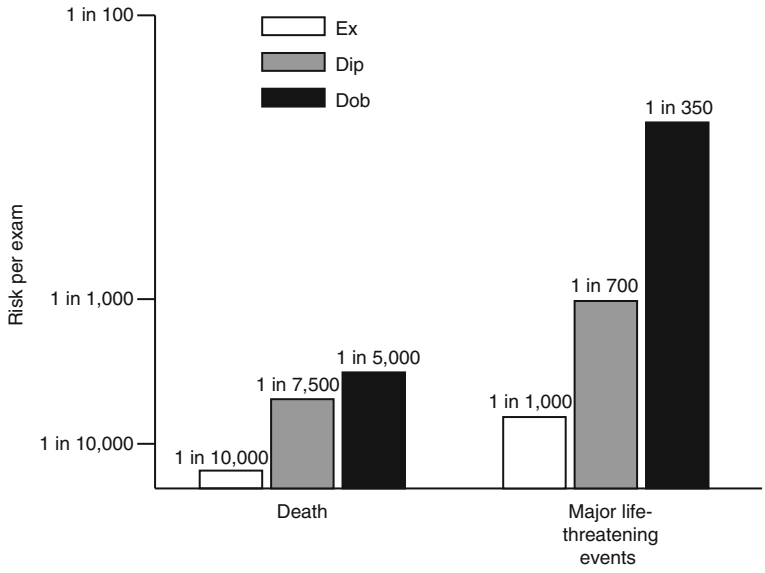

Fig. 11.3 Safety of stress echocardiography: highest for exercise, intermediate for dipyridamole, lowest for dobutamine stress (Original data from [29–32], summarized in [15])

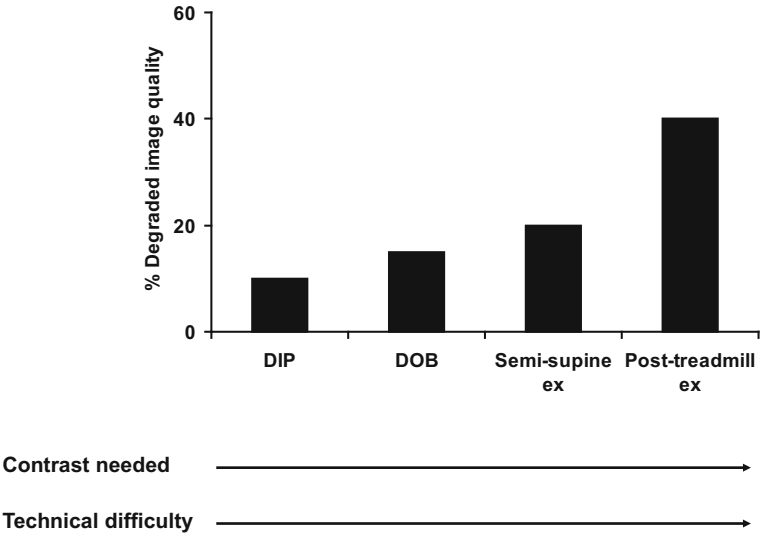

Fig. 11.4 The technical echocardiographic difficulties of different stresses. Factors polluting image quality are more frequent with post-treadmill and least frequent with pharmacological stresses

Stress Echocardiography Registry, published only in abstract form, which recruited more than 60,000 tests and reported a rate of complication of 0.6 % with exercise, 3.6 % with dobutamine, and 1.5 % with dipyridamole [32].

The feasibility of obtaining interpretable studies of good quality – relatively unchanged versus baseline images – is sufficient with post-treadmill, good for upright, and almost excellent with semisupine testing which should be the test of choice for exercise stress echocardiography. From the perspective of the stress echocardiography laboratory, there is evidence that semisupine exercise is easier, more feasible, and more informative than the other forms of exercise stress. It is also undisputed that semisupine exercise is more technically demanding than dobutamine and much more technically demanding than vasodilator stress (Fig. 11.4).

11.5 Diagnostic Results for Detection of Coronary Artery Disease and Myocardial Viability

For the detection of angiographically significant coronary artery disease repeatedly assessed in a series of continuously updated meta-analyses [33–37], the overall sensitivity and specificity of exercise echocardiography have been reported to be 83 and 85 %, respectively, according to the most updated meta-analysis of 55 studies with 3714 patients (Table 11.3) [37]. The specificity of exercise echocardiography is similar to dobutamine echocardiography, lower than dipyridamole echocardiography, and higher for all forms of stress echocardiography compared to stress

Table 11.3 Sensitivity and specificity of exercise echocardiography (*echo*) according to meta-analysis of 55 studies with 3714 patients

Test	No. of studies	Sensitivity % (95 % CI)	Specificity % (95 % CI)	lnDOR (95 % CI)
Exercise echo	55	82.7 (80.2–85.2)	84.0 (80.4–87.6)[a]	3.0 (2.7–3.3)
Adenosine echo	11	79.2 (72.1–86.3)	91.5 (87.3–95.7)	3.0 (2.5–3.5)
Dipyridamole echo	58	71.9 (68.6–75.2)	94.6 (92.9–96.3)[a]	3.0 (2.8–3.2)
State-of-the-art dipyridamole echo	5	81 (79–83)	91 (88–94)	3.1 (1.9–3.3)
Dobutamine echo	102	81.0 (79.1–82.9)	84.1 (82.0–86.1)[a]	2.9 (2.7–3.0)
Combined echo	226	79.1 (77.6–80.5)	87.1 (85.7–88.5)[a]	2.9 (2.8–3.0)
Combined SPECT	103	88.1 (86.6–89.6)[b]	73.0 (69.1–76.9)	2.8 (2.6–3.0)

Adapted from Heijenbrok-Kal et al. [37]
CI confidence interval, *lnDOR* natural logarith of the diagnostic odds ratio
[a]Nonoverlapping confidence intervals indicating a statistically higher specificity than the corresponding SPECT test
[b]Nonoverlapping confidence intervals indicating a statistically higher sensitivity than all other tests, except for adenosine and dipyridamole SPECT and a statistically lower specificity than all other tests except for exercise SPECT

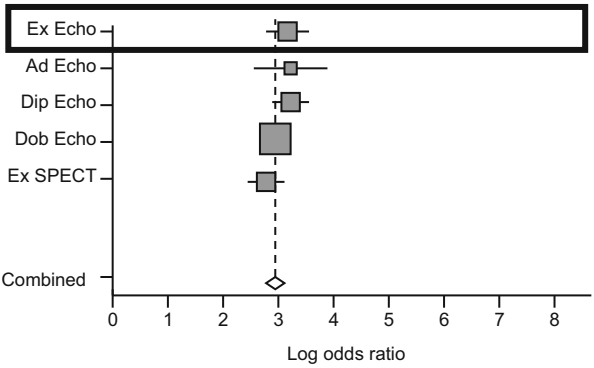

Fig. 11.5 The diagnostic accuracy of exercise echocardiography (*squared line*) versus other stress imaging tests. The value of the log odds ratio is a measure of overall diagnostic accuracy. The size of the box is smaller for smaller sizes, with higher confidence intervals (Modified from Heijenbrok-Kal et al. [37])

single-photon emission computed tomography (SPECT) [37]. The diagnostic accuracy is similar to other forms of stress imaging (dobutamine or dipyridamole stress echocardiography or stress SPECT) (Fig. 11.5).

Although the available information is only limited, exercise echocardiography can also be useful for detecting myocardial viability. Endogenous catecholamines produced during a low-level exercise test can also serve as a myocardial stressor to elicit contractile reserve in viable myocardium, with an accuracy comparable to low-dose dobutamine echocardiography [38]. A maximum exercise test can also identify a biphasic response suggesting the presence of viable myocardium at jeopardy [39].

11.6 Prognostic Value

The presence, site, extent, and severity of exercise-induced wall motion abnormalities have a clearly proven prognostic impact, as shown by over 20 studies on 5000 patients – ranging from patients with normal baseline function [40–43] to those evaluated early after an acute myocardial infarction [44–47], women [48], or hypertensive subjects [49]. The prognostic value of exercise stress echocardiography is high, comparable to other forms of pharmacological (dobutamine or dipyridamole) stress echocardiography and stress SPECT [50].

Among patients who have a normal exercise echocardiogram, prognosis is favorable and the coronary event rate is quite low [40]. An abnormal stress echocardiogram, defined as a new or worsening wall motion abnormality, substantially increases the likelihood of a coronary event during the follow-up period. This finding, coupled with the presence or absence of resting left ventricular dysfunction and the exercise capacity of the patient, provides a great deal of prognostic information in the individual patient. The prognostic value is incremental over clinical and exercise electrocardiographic variables [42, 50] (Fig. 11.6).

In patients evaluated for coronary artery disease, exercise echocardiography and exercise SPECT combined with the ECG variables provide comparable prognostic information and can be used interchangeably for risk stratification [50]. Other ancillary markers, beyond regional wall motion, can further stratify the prognosis during exercise echocardiography. In patients with a positive test result, the prognosis is more malignant, and in patients with a negative test result, the prognosis is less benign, with exercise-induced left ventricular cavity dilation [51] or severe mitral regurgitation [52, 53]. However, the systematic search of these ancillary markers of ischemia is unfeasible and technically challenging during exercise stress echocardiography and may shift the focus of imaging away from wall motion, which remains the cornerstone of diagnosis. Their greatest clinical value is outside coronary artery disease, in patients with heart failure [20] or valvular heart disease [19].

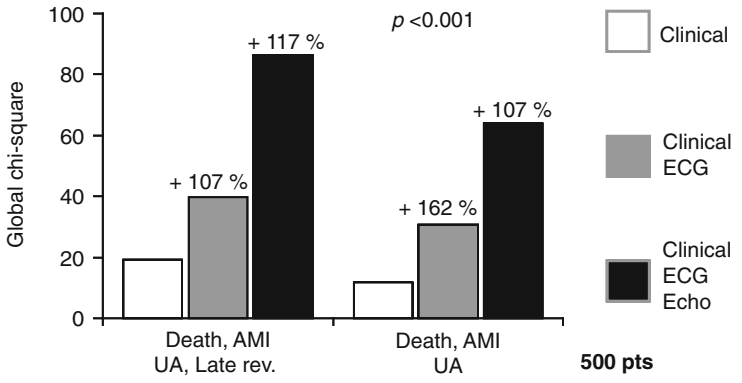

Fig. 11.6 The prognostic value of exercise echocardiography (Modified from Marwick et al. [42])

11.7 Exercise Echocardiography Outside Coronary Artery Disease

The baseline transthoracic echocardiogram performed at the time of SE permits recognition of many causes of cardiac symptoms in addition to ischemic heart disease, including dilated cardiomyopathy or hypertrophic cardiomyopathy, pulmonary hypertension, and valvular heart disease. As with CAD, also in these diseases, the application of exercise stress under controlled conditions can unmask structural defects which – although occult in the resting or static state – may occur under real-life loading conditions and lead to dysfunction detected by echocardiography.

Nowadays, in the SE laboratory, we can assess a variety of parameters beyond left ventricular function: valvular gradients and regurgitant flows and left and right heart hemodynamics including pulmonary artery systolic pressure, ventricular volumes, and extravascular lung water (see Fig. 1.6 in Chap. 1). From a practical viewpoint, it is not feasible to do everything in all patients, since there is little time during stress and there are so many things to see [54]. Therefore, the variables of potential diagnostic interest should be strategically tailored and prioritized to the individual patient based on the perceived incremental value of each (Table 11.4). Exercise is the test of choice for most applications – and bicycle semisupine exercise is technically easier than upright bicycle or post-treadmill, as it allows continuous monitoring and recording of the desirable parameters.

In general, many parameters used in stress echo applications beyond CAD can be more difficult to acquire but are easier to measure and more amenable to quantification than regional wall motion assessment; therefore, these applications may be less dependent upon the subjectivity of interpretation and operator experience [54]. The application of exercise stress echo is useful in many different conditions, from valvular (see Chap. 36) to congenital heart disease (see Chap. 37) to hypertrophic cardiomyopathy (see Chap. 34), to optimize risk stratification and timing of intervention [55], as discussed in detail in other chapters of this book.

11.8 Pitfalls

There are contraindications to exercise echocardiography, such as the classical contraindications to exercise stress, including unstable hemodynamic conditions or severe, uncontrolled hypertension. Additional relative contraindications to exercise stress is the inability to exercise adequately, and – specifically for exercise echocardiography – a difficult resting echocardiogram. These conditions are not infrequent, especially in an elderly population, since out of five patients referred for testing, one is unable to exercise, one exercises submaximally [14], and one has an interpretable but challenging echocardiogram, which makes pharmacological stress echocardiography a more practical option. Difficult echocardiograms can often be salvaged by contrast echocardiography for border enhancement of unreadable left ventricular segments at baseline and during stress.

Table 11.4 Applications of exercise stress echo beyond coronary artery disease

	A	U	I	Source	Cutoff values (ref)	Class rec/lev evidence
Dilated cardiomyopathy						
Contractile reserve	√			ESC 2012, EAE 2009	WMSI >0.25	EC
Symptomatic HCM						
Resting peak gradient <50 mmHg	√			ACCF/AHA 2011	>50 mmHg	IIa, B
Asymptomatic VHD						
Severe	√			ACCF/AHA 2011	PASP >60 mmHg	II, C
Severe MS	√			ACCF/AHA 2011	MG >15 mmHg, PASP >60 mmHg	I, C
Severe AR	√			ACCF/AHA 2011	LV reserve PASP increase	EC
Severe AS, normal EF		√		ACCF/AHA 2011	MG increase >20 mmHg	IIb, C (30)
Moderate AS, AR, MR, MS		√		ACCF/AHA 2011	Increase in degree of insufficiency/gradient Increase in PASP	EC
Mild MS, MR, AS, AR			√	ACCF/AHA 2011	Increase insufficiency/gradient Increase in PASP	EC
Symptomatic VHD						
Moderate MS	√			ACCF/AHA 2011	MG >15 mmHg, PASP >60 mmHg	I, C
Low flow, low gradient AS	√			ACCF/AHA 2011	True stenosis: SV >20 %, MG >40 mmHg, AVA <1.0 cm^2 and increase ≤0.3 cm^2	IIa, C
Moderate MR	√			ACCF/AHA 2011	Increase in MR severity, increase in PASP	EC
Mild MS, MR		√		ACCF/AHA 2011	Increase insufficiency/gradient Increase in PASP	EC
Severe AS, MS, MR			√	ACCF/AHA 2011	Increase in PASP	EC

(continued)

Table 11.4 (continued)

	A	U	I	Source	Cutoff values (ref)	Class rec/lev evidence
Pulmonary hypertension						
Suspected PAH in normal resting TTE		√		ACCF/AHA 2011	No accepted cutoff	EC
Reevaluation of exercise-induced PH on therapy		√		ACCF/AHA 2011		EC
Proven resting PH			√	ACCF/AHA 2011		EC
Suspected diastolic heart failure						
Symptoms, normal EF, inconclusive resting TTE		√		ESC 2012	E/e' >15	EC
Pediatric age group						
Isolated subaortic stenosis Aortic coarctation	√			ACC/AHA 2008	Increase in LVOT MG >30 mmHg Coarctation MG >20 mmHg and diastolic runoff	IIa, C
Heart transplant recipients						
Detection of cardiac allograft vasculopathy	√			ISHLT 2010	WMA	IIa, B

Modified from Ref. [54]

A Appropriate, *U u*ncertain, *I i*nappropriate, *EC e*xpert consensus, *As* aortic stenosis, *MG* mean gradient, *MS* mitral stenosis, *MR* mitral regurgitation, *PG p*eak gradient, *PAH* pulmonary arterial hypertension, *VHD* valvular heart disease

11.9 Clinical Guidelines

Exercise is the most physiologic stressor of all and thus is preferable in patients who are capable of exercising (Table 11.5). For coronary artery disease diagnosis, exercise echocardiography is the appropriate first-line test, skipping the exercise electrocardiography test, in patients with conditions making the ECG uninterpretable, such as left bundle branch block or Wolff–Parkinson–White syndrome or ST-segment abnormalities on baseline resting ECG [56, 57]. Exercise echocardiography is also the most suitable second-line stress test, when exercise ECG, performed as a first-line test reproduced ST-segment depression and/or angina or when the positive predictive value of these findings remains low (e.g., in women and/or hypertensive subjects).

Exercise stress echocardiography is frequently performed inappropriately, as with all other stress imaging tests, as a first-line test in patients with low pretest probability of disease and in whom ECG is interpretable [56, 57]. Exercise stress echocardiography has similar indications and contraindications to exercise SPECT, and similar diagnostic and prognostic accuracy as recognized by general cardiology guidelines [56, 57]. In a cost-conscious and radiation risk-conscious environment, this implies that stress echocardiography should be the preferred choice [58]. A unique advantage of exercise echocardiography over the other forms of stress is that it may offer helpful and tremendously versatile evaluation of valve function, of pulmonary hemodynamics, and of special subsets of patients, such as patients with heart failure, pulmonary hypertension, or valve disease. In all these patients, the physiologic nature of exercise stress and the staggering versatility of the echocardiographic technique allow one to tailor the most appropriate test to the individual patient in the stress echocardiography laboratory (Fig. 11.7).

Table 11.5 Indications to exercise stress echocardiography for diagnosis of coronary artery disease [56]

	Appropriate	Uncertain	Inappropriate
Intermediate pretest probability of coronary artery disease	√		
ECG uninterpretable	*v*		
Prior stress ECG uninterpretable or equivocal	√		
Repeat stress echocardiography after 2 years, in asymptomatic or stable symptoms		√	
Repeat stress echocardiography annually, in asymptomatic or stable symptoms		√	
Symptomatic, low pretest probability, interpretable ECG			√
Asymptomatic, low risk			√
Asymptomatic less than 1 year after percutaneous coronary intervention, with prior symptoms			√

Adapted from Montalescot et al. [56]

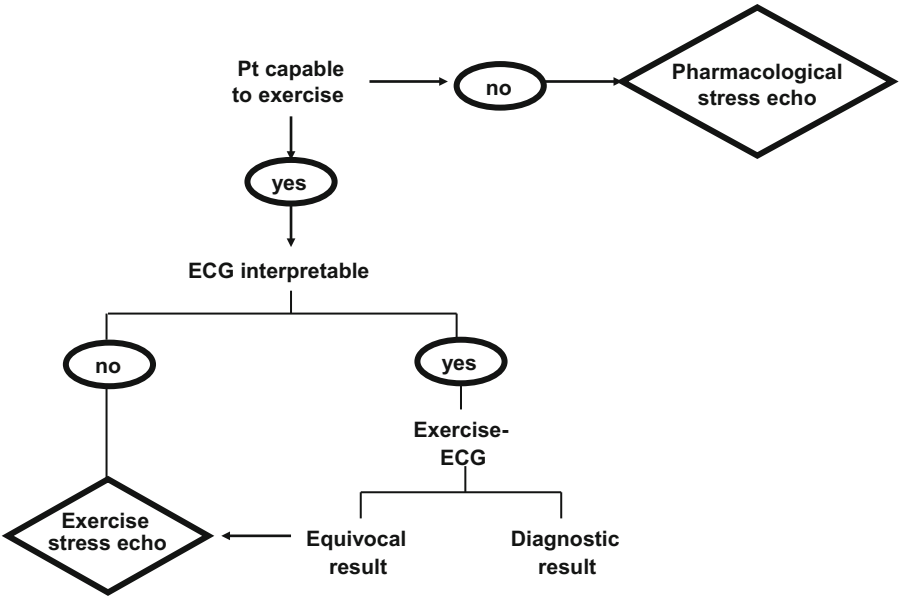

Fig. 11.7 The proposed algorithm for the use of exercise echocardiography

Table of Contents Video Companion

See also in the section illustrative cases: case number 9 (by Jesus Peteiro, La Coruna, Spain) and 10 (by Bogdan Popescu, MD, Bucarest, Romania); cases 29, 30, and 31 (by Maria Joao Andrade, Lisbon, Portugal)
Springer Extra Materials available at http://extras.springer.com/2015/978-3-319-20957-9

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Dobutamine Stress Echocardiography

12

Wilson Mathias Jr. and Eugenio Picano

12.1 Historical Background

Among exercise-independent stresses, the most popular are dobutamine and dipyridamole. Dobutamine is the prototype of pharmacological adrenergic or inotropic stress. It was initially proposed for the diagnosis of coronary artery disease in combination with perfusion imaging [1] and later with two-dimensional (2D) echocardiography by the Liège group [2]. Other sympathomimetic agents have been proposed for stress echocardiography, including isoproterenol [3] and epinephrine [4], but these drugs often bring more pronounced arrhythmogenic side effects. Following the demonstration of low-dose dobutamine as a test of myocardial viability in 1990 [5], in the subsequent decade dobutamine has been extensively adopted in pharmacological stress echocardiography. The evolution of dobutamine stress paralleled that of other pharmacological stresses. With echocardiography, it began at relatively "low" doses (20 μg kg^{-1} min^{-1}), which gave low sensitivity values [6]; later, more aggressive doses were adopted (up to 40 μg kg^{-1} min^{-1}) [7, 8], and finally it was coadministered with atropine [9], which overcame the limitation of less than ideal sensitivity to minor forms of coronary artery disease.

12.2 Pharmacology and Pathophysiology

Dobutamine is a synthetic catecholamine resulting from the modification of the chemical structure of isoproterenol. It acts directly and mainly on beta-1 adrenergic receptors of the myocardium, producing an increase in heart rate, enhancement of atrioventricular conduction, and increased contractility (Fig. 12.1). In fact, alpha-adrenergic activity can mediate systemic vasoconstriction and an increase in blood pressure and – at the coronary level – increased constriction up to coronary vasospasm, especially when the alpha-mediated vasoconstriction is enhanced by chronic or acute beta-blockade. Stimulation of beta-2 receptors on coronary arterioles may induce coronary arteriolar vasodilation. However, endothelial dysfunction and

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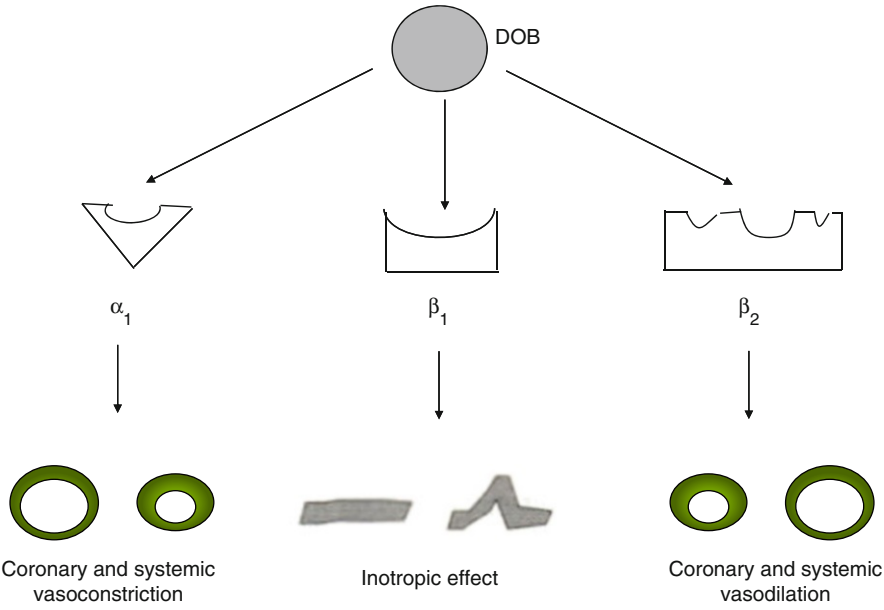

Fig. 12.1 The main cardiovascular receptor targets and physiologic effects of dobutamine

enhanced alpha-adrenergic tone contribute to the loss of dobutamine-induced vasodilation in coronary atherosclerosis [10]. The short half-life (2 min) of dobutamine allows rapid resolution of its effects once the intravenous infusion is discontinued. However, the alpha-mediated coronaro-constrictive and platelet-aggregating effects are not reversed, and may be potentiated, by beta-blockers and peak at 30–45 min after the end of infusion.

Dobutamine provokes ischemia mainly through the inotropic and chronotropic response to stimulation of myocardial beta-1 receptors determining an increase in myocardial oxygen demand (see Fig. 5.4 in Chap. 5). Heart rate increases two- to threefold, systolic arterial pressure increases 1.5- to twofold, and myocardial contractility increases four- to eightfold versus baseline. Other proischemic mechanisms are the flow maldistribution mediated by beta-2 receptors of coronary arterioles [11] and coronary vasospasm mediated by alpha-adrenoreceptors present on smooth muscle cells of epicardial arteries. The dobutamine dose usually employed for stress echocardiography testing causes a two- to threefold increase in coronary blood flow [12].

12.3 Methodology

The protocol displayed in Fig. 12.2 is the most widely used, the only one validated in a large-scale multicenter prospective trial [13], and it has been recently proposed as the state-of-the-art protocol by both the American [14] and European [15] recommendations. Doses lower than those shown in Fig. 12.2 are associated with

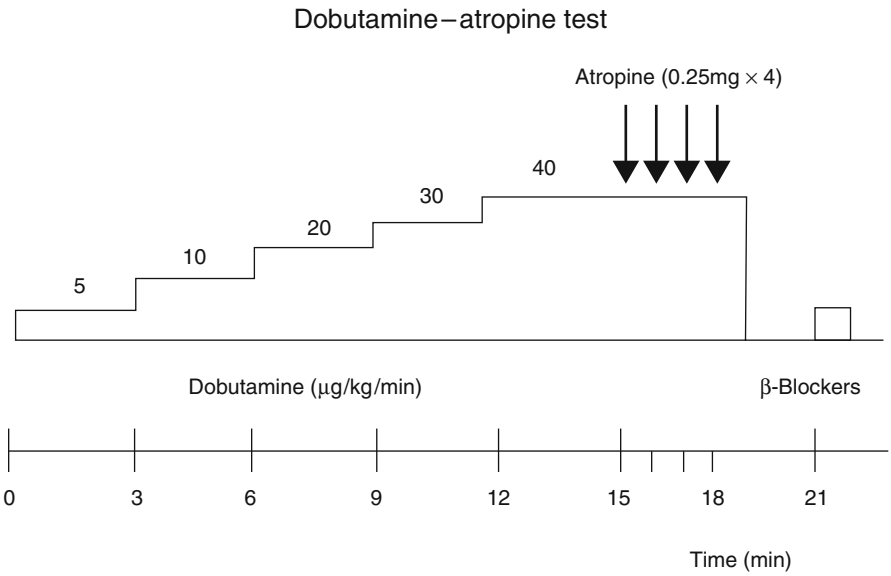

Fig. 12.2 Protocol of the dobutamine–atropine stress test. For viability detection in patients off beta-blockers, a 5-min step from 5 to 10 mcg is suggested

insufficient sensitivity, while higher doses are associated with an unacceptable high rate of side effects. For viability assessment, steps of 5 min are used, starting from 5 up to 10 mcg [5]. However, to fully recruit the inotropic reserve in patients with heart failure and usually with beta-blocker therapy, high doses (without atropine) are required [16].

Alternatively, on the pharmacology basis that atropine may take up to 3 min to achieve maximum effect, there are studies suggesting that an early administration of atropine, at a starting dose of up to 20 μg kg^{-1} min^{-1}, is more effective and equally accurate and may even be safer than a late atropine injection [17–20] and is also included in the American recommendations [14].

12.4 Feasibility and Safety

Minor but limiting side effects preclude the achievement of maximal pharmacological stress in about 10 % of patients [13, 21]. In order of frequency, these side effects are complex ventricular tachyarrhythmias (frequent, polymorphic, premature ventricular beats, couplets and triplets, nonsustained ventricular tachycardia), nausea and/or headache, hypotension (>30 mmHg drop in blood pressure) and/or bradycardia, supraventricular tachyarrhythmias (supraventricular tachycardia or atrial fibrillation), and hypertension. Limiting side effects are more often asymptomatic with dobutamine and more often symptomatic with dipyridamole [21]. Side effects usually disappear upon interruption of drug infusion, since the half-life is 2–3 min.

When symptoms or ischemia persist, IV beta-blockers – usually the short-acting drug esmolol – are given.

Both the patient and the physician should be aware of the rate of major complications that may occur during dobutamine stress. As concordantly shown by meta-analysis [22], single-center experiences [23–28], multicenter studies [13], and retrospective registries [29–31], major life-threatening side effects occur in 1 of 300–350 cases (Table 12.1).

The proliferating anecdotal reports of catastrophes also contribute in assessing the safety of the test. Cardiac rupture [32–35], ventricular fibrillation [36, 37], refractory coronary vasospasm [38, 39], myocardial infarction [40, 41], cardiac asystole [42, 43], and acute Tako-tsubo syndrome [44] have all been described during dobutamine testing. Tachyarrhythmias are the most frequent complication occurring during dobutamine stress echocardiography. In some cases they are subsequent to pharmacologically induced myocardial ischemia during the test and therefore are associated with a transient wall motion abnormality. However, in many cases they are independent of ischemia and can also develop at low dobutamine doses. The mechanism of their onset can be attributed to the direct adrenergic arrhythmogenic effect of dobutamine, through myocardial β-receptor stimulation, which is particularly evident in patients with ischemic heart disease. Dobutamine infusion can also lower the blood potassium level, thereby contributing to the genesis of ventricular ectopy through a depolarizing effect on the cell membrane [45] (Fig. 12.3).

Significant hypotension, sometimes associated with bradyarrhythmias, including asystole, is another frequent adverse reaction during dobutamine echocardiography.

Table 12.1 Life-threatening complications in early single center large experiences, multicenter studies (EDIC), and multicenter registries for dobutamine stress echocardiography

Author, year	Patients	Complications (s)
Single institution experience		
Mertes et al. 1993 [23]	1118	None[a]
Zahn et al. 1996 [25]	1000	1 VF, 1 LVF, 1 seizure
Secknus and Marwick 1997 [26]	3011	5 VT, 1 AMI, 1 prol ischemia, 1 hypo
Bremer et al. 1998 [27]	1035	1 VF, 1 VT
Poldermans et al. 1994 [24]	650	1 VF, 3 sustained VT
Mathias et al. 1999 [28]	4033	1 VFm 8 VT, 1 MI; 5 atropine intoxications
Multicenter registry		
Picano et al. (EDIC), 1994 [13]	2949	2 VF, 2 VT, 2 AMI, 1 prol ischemia, 1 hypo
Pezzano et al. (RITED) 1998 [29]	3041	2 VF, 1 asystole
Beckmann, 1999 [30]	9354	324 (2 VF)
Varga, 2006 [31]	35,103	63 (5 deaths)

AMI acute myocardial infarction, *VT* ventricular tachyarrhythmia, *VF* ventricular fibrillation, *LVF*, *VFm*, *MI* myocardial infarction, *prol* prolonged, *hypo* hypotension

[a]No life-threatening complications reported; however, minor and self-limiting adverse effects were documented

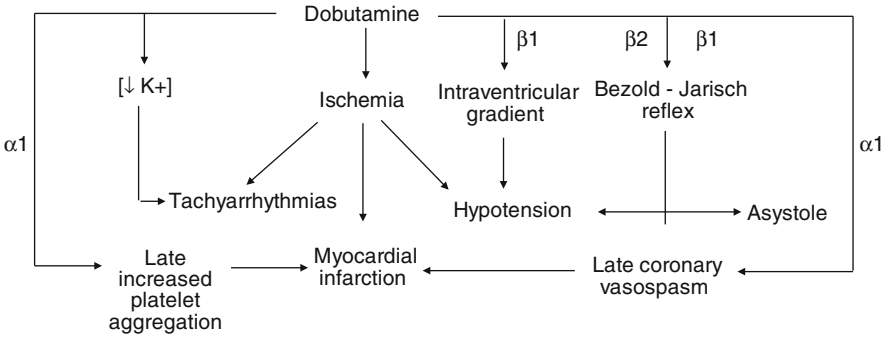

Fig. 12.3 Ischemia-dependent and ischemia-independent pathways of complications during dobutamine stress

In some cases this finding has been attributed to dynamic interventricular obstruction provoked by inotropic action of dobutamine, especially in hypertrophic hearts [46]. A vasodepressor reflex triggered by left ventricular mechanoreceptor stimulation (Bezold–Jarisch reflex) due to excessive inotropic stimulation may be an alternative mechanism [47]. These effects can be almost abolished if atropine is injected earlier.

Late and long-lasting transmural myocardial ischemia, with persistent ST segment elevation, is probably due to the coronary vasoconstrictive effect of dobutamine, through α-receptor stimulation, sometimes involving multiple coronary segments. Moreover, dobutamine can induce increased platelet aggregation, possibly provoking coronary occlusion, prolonged myocardial ischemia, and acute myocardial infarction on the anatomic substrate of a vulnerable, possibly noncritical, plaque unable to induce ischemia during stress [13, 48].

12.5 Diagnostic Results for Detection of Coronary Artery Disease

The accuracy in detecting angiographically assessed coronary artery disease has been consistently reported to be high, with sensitivity and specificity of 81 and 84 %, respectively, in a meta-analysis of 102 studies with over 7900 patients [49]. The diagnostic accuracy is similar to other forms of stress testing, such as exercise echocardiography [49, 50], dipyridamole echocardiography [49, 50], or stress SPECT [49]. In particular, the sensitivity and accuracy are identical to dipyridamole stress echocardiography when state-of-the-art protocols are used for both stresses (Fig. 12.4), as shown by two meta-analyses including 5 studies on 435 patients [50, 51].

One of the strategies in order to improve sensitivity of dobutamine stress echocardiography is a rapid injection of (5 mg in 1 min) metoprolol at peak stress with the acquisition of post-metoprolol images in a maximum interval of 3 min after the

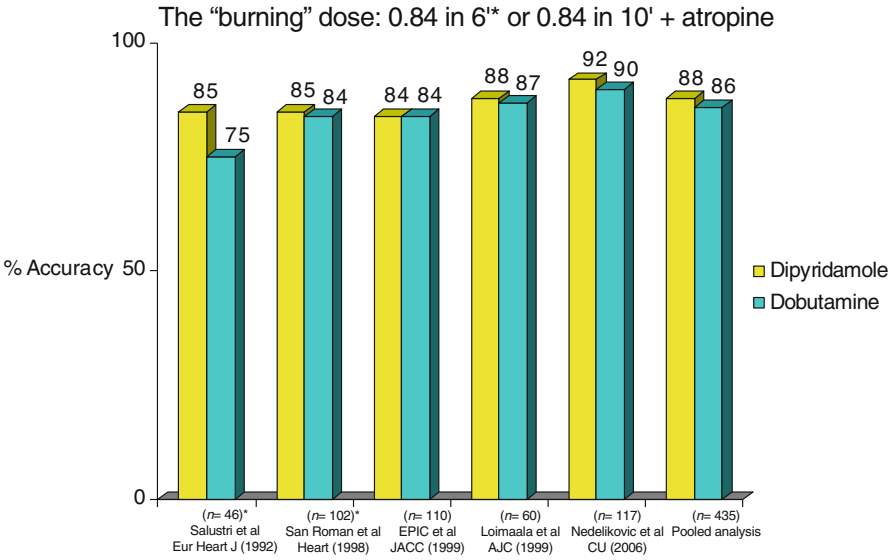

Fig. 12.4 The diagnostic accuracy for noninvasive detection of coronary artery disease of dobutamine echocardiography versus dipyridamole echocardiography (all protocols) and state-of-the-art (high dose with atropine or fast high dose) dipyridamole echocardiography (From meta-analysis of Noguchi et al. [50] and Picano et al. [51])

end of dobutamine infusion in negative studies where patients are not hypertensive at peak stress. This strategy may increase the sensitivity (mainly in single-vessel disease patients) up to 92 % without loss in specificity (Fig. 12.5) [52]. A possible mechanism is the unmasking of coronary vasospasm mediated by unopposed alpha-adrenoreceptors.

12.6 Identification of Myocardial Viability

Low-dose dobutamine recognizes myocardial viability with high specificity and good sensitivity, with excellent diagnostic [53] and prognostic [54] value. In patients with preserved global left ventricular function, myocardial viability identifies a greater risk to subsequent development of ischemia and nonfatal reinfarction early after acute myocardial infarction [55]. In patients with severe resting left ventricular dysfunction, a large amount of myocardial viability identified by low-dose dobutamine echocardiography is associated with a better survival [56]. This finding has been consistently described both in medically treated patients studied early after acute myocardial infarction [56] (a model of stunned myocardium) (Fig. 12.6) and in revascularized patients studied after chronic myocardial infarction (a model of hibernating myocardium) [57–59]. A contractile reserve identified by high-dose dobutamine (up to 40 mcg) identifies patients with dilated cardiomyopathy and better response to medical therapy and cardiac resynchronization therapy [60, 61].

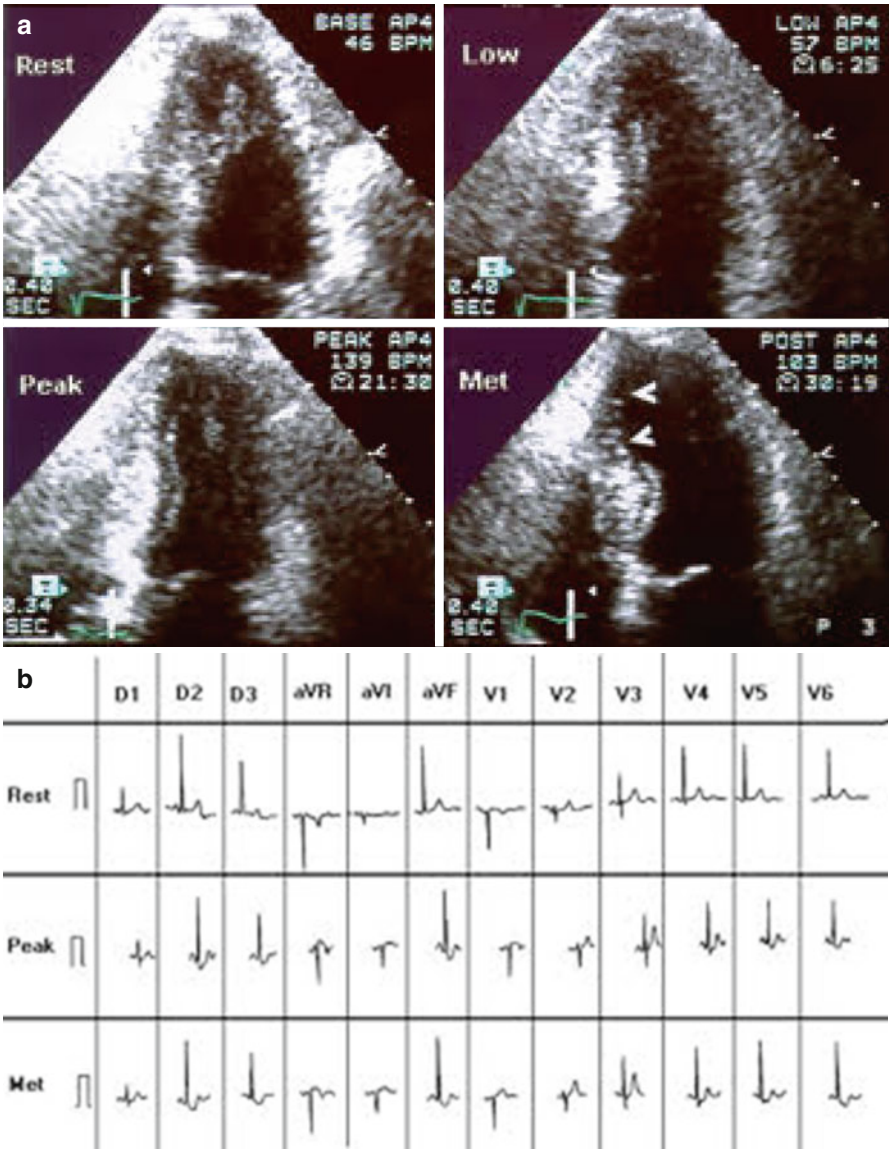

Fig. 12.5 (**a**) Example of a patient with a 90 % LAD stenosis without NWMA at peak developed only after metoprolol. Apical four-chamber view at end-systole with normal thickening at rest (HR of 46 beats min^{-1}, rate-pressure product of 6578 mmHg min^{-1} and LVESVI 15.7 ml m^{-2}) and low doses. At peak, HR was 139 beats min^{-1}, rate-pressure product was 20,850 mmHg min^{-1}, and LVESVI was 12.8 ml m^{-2}. After metoprolol (Met), there is a lack of thickening in the apical septum (*white arrows*) (HR of 103 beats min^{-1}, rate-pressure product of 15,450 mmHg min^{-1}, and LVESVI 33.3 ml m^{-2}). (**b**) EKG from patient in (a) demonstrating ST changes in leads D1, D2, aVF, V5, and V6 only during metoprolol

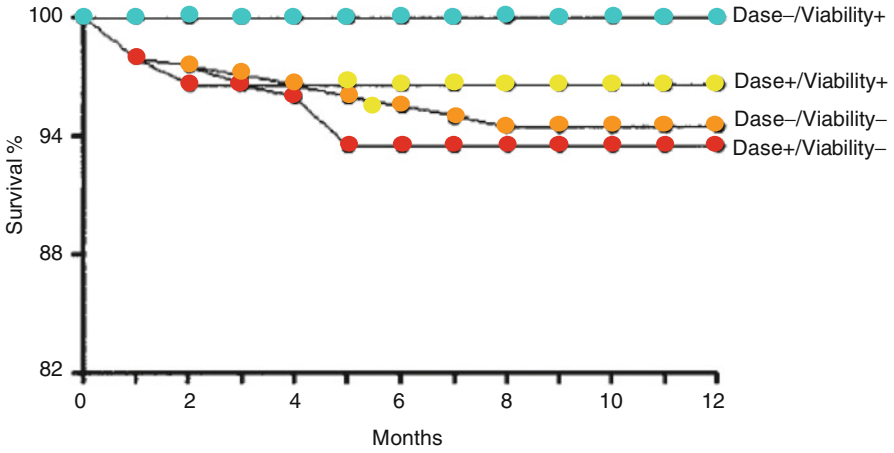

Fig. 12.6 Kaplan–Meier survival curves (considering only death as an end point) in patients stratified according to presence or absence of echocardiographically assessed viability and ischemia at low and high doses of dobutamine, respectively. Best survival is observed in patients with low-dose viability and no inducible ischemia; worst survival, in patients without viability and with inducible ischemia. *Viability* + and *viability* – indicate the presence or absence of myocardial viability at low-dose dobutamine, respectively; *Dase* + and *Dase*–, the presence or absence of myocardial ischemia at high-dose dobutamine, respectively (From Picano et al. [56])

Although the results of the STICH (Surgical Treatment for Ischemic Heart Failure) trial have cast doubt on the role of dobutamine stress echocardiography and other imaging modalities for the assessment of viability, the results are still predictive of a positive outcome [61]. When these are taken into consideration with previous studies [52–58], it becomes reasonable to recommend viability assessment when treating patients with coronary artery disease and left ventricular dysfunction [62].

12.7 Prognostic Value

The presence, site, timing, extent, and severity of dobutamine-induced wall motion abnormalities have a clear prognostic impact, as shown by over 50 studies on over 10,000 patients, including patients with or suspected coronary artery disease [63–72], evaluated early after acute myocardial infarction [73–77], and patients undergoing major noncardiac vascular surgery [78–85]. These studies concordantly show that dobutamine stress echocardiography results predict subsequent death, on the basis of coexistent fixed resting wall motion abnormalities, dobutamine dose required to induce ischemia (Fig. 12.7), and peak wall motion score index (Fig. 12.8). The prognostic value of dobutamine stress echocardiography is independent and additive to resting echocardiography and exercise electrocardiography and comparable to dipyridamole echocardiography [68, 86, 87] and stress SPECT [82, 88].

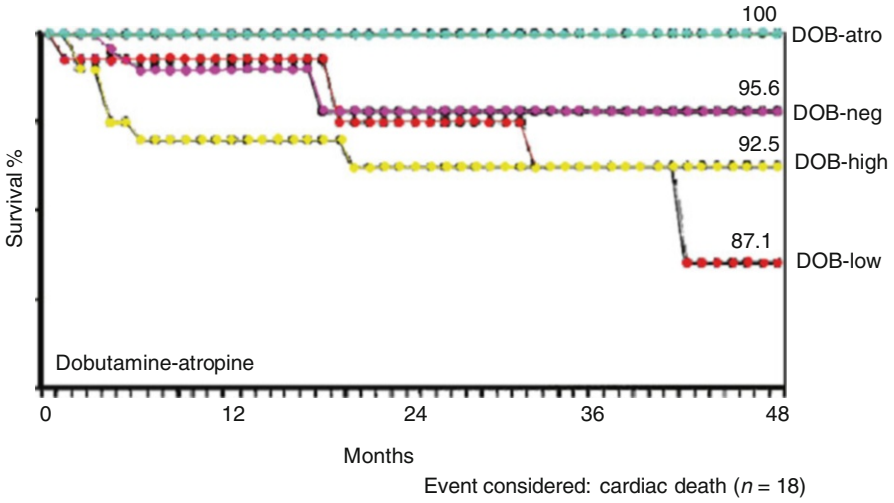

Fig. 12.7 Kaplan–Meier survival curves event-free of cardiac death in patients with negative and positive dobutamine echocardiography test results (*DOB*). Survival is worse in patients with positive DOB. In patients with positive DOB, a progressively worse survival is identified with positivity after atropine, high and low dose (From Pingitore et al. [68])

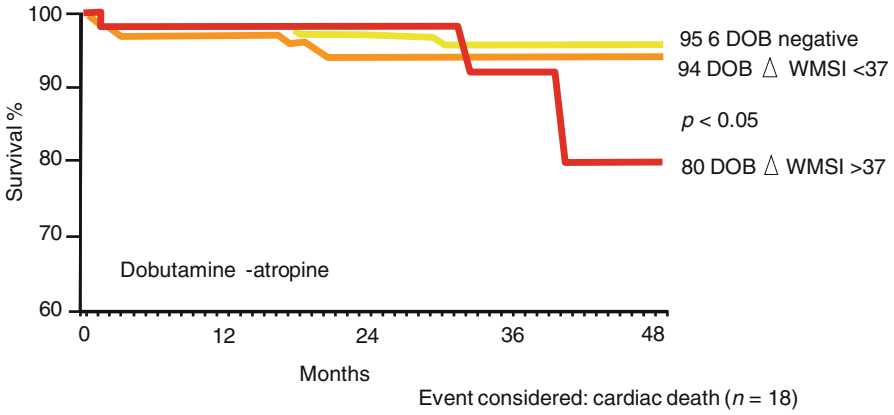

Fig. 12.8 Kaplan–Meier survival curves event-free of cardiac death in patients with negative and positive dobutamine echocardiography test results (*DOB*). In patients with positive DOB, a progressively worse survival is identified for patients with higher changes in peak wall motion score index (*WMSI*) (From Pingitore et al. [68])

12.8 Pitfalls

The limitations of dobutamine stress are related to feasibility, safety, technical difficulty of echocardiographic interpretation, suboptimal possibility to combine coronary flow reserve and wall motion information, and inability to predict physiologic

therapy-induced changes on exercise stress results. Minor but limiting side effects occur in 5–10 % of tests, and submaximal results have limited diagnostic and prognostic power. The test is less safe than other pharmacological stresses, such as vasodilators, and much less safe than exercise, with major life-threatening complications being 2–3 times more frequent with dobutamine than with dipyridamole and 4–5 times more frequent than with exercise. The echocardiographic image degradation during stress is less than with exercise, but significant, since high heart rate and hypercontractility make the wall motion interpretation more challenging. Changes exerted by anti-ischemic therapy (especially beta-blockers) on dobutamine stress are unrelated to physiologic effects of that same therapy on exercise, and therefore the test cannot be used to monitor pharmacological interventions in ischemic heart disease [89].

12.9 Indications and Contraindications

High-dose dobutamine is an appropriate choice for pharmacological stress echocardiography used for the detection of coronary artery disease, especially in patients with inability to exercise or contraindications to exercise [90] or with resting images of borderline quality which may make the more technically difficult exercise stress echocardiography a challenging task [91] (Table 12.2). It is also appropriate in intermediate-risk patients undergoing elective high-risk noncardiac surgery. Low-dose dobutamine is the first choice for identification of myocardial viability in patients with severe left ventricular dysfunction [90]. It is also appropriate in low-flow, low-gradient aortic stenosis to separate true from pseudosevere aortic stenosis [92]. Appropriateness is uncertain in intermediate-risk patients undergoing

Table 12.2 Appropriate and inappropriate indications to dobutamine stress echocardiography

	Appropriate	Uncertain	Inappropriate
Diagnosis of CAD in patient unable to exercise	√		
Diagnosis of viability in ejection fraction <35 %	√		
High-risk noncardiac surgery in intermediate-risk patient	√		
Low-flow, low-gradient aortic stenosis	√		
Need to evaluate antianginal therapy efficacy		√	
Intermediate-risk noncardiac surgery in intermediate-risk patient		√	
Prediction of CRT efficacy		√	
First-line test in patients able to exercise			√
Severe hypertension, malignant ectopy, inferior wall aneurysm early after AMI			√
Low-risk noncardiac surgery in low-risk patient			√

AMI acute myocardial infarction, *CAD* coronary artery disease, *CRT* cardiac resynchronization therapy

intermediate-risk noncardiac surgery [90, 93]. In women who cannot exercise, dobutamine stress echocardiography may be preferred than other modalities [93, 94]. Patients with a history of complex atrial (paroxysmal atrial fibrillation, paroxysmal supraventricular tachycardia) or ventricular arrhythmias (sustained ventricular tachycardia or ventricular fibrillation) or with moderate to severe hypertension should probably not undergo dobutamine stress testing and be referred for safer vasodilator stress [95].

12.10 Emerging and Promising Technologies

12.10.1 Coronary Flow and Microvascular Measurements

Dobutamine allows a combined dual imaging of wall motion and coronary flow reserve with either coronary flow velocity reserve, myocardial contrast echocardiography, or deformation parameters of left ventricular function. In a recent study, the outcomes of 651 patients with normal wall motion response during stress echocardiography with dobutamine or dipyridamole stress to evaluate coronary flow velocity reserve (CFVR) were evaluated in diabetic patients. CFVR was calculated simultaneously in the distal territory of the left anterior descending coronary artery. Diabetes increased risk only in patients with abnormal CFVR (<2.0) independently of the pharmacological stress technique used [96]. The use of CFVR was also evaluated in 20 patients with Tako-tsubo cardiomyopathy. The authors demonstrated that hyperemic CFVR increased significantly after recovery leading to a greater CFVR (2.9 + 0.3 vs. 2.1 + 0.4) and concluded that there was a transient impairment of CFR at the acute phase of TTC, which was due to a reduced vasodilating capacity [97]. Dynamic changes in microcirculatory blood flow at each stage of DASE can also be detected using real-time myocardial contrast echocardiography. The best parameter for detecting CAD in all stages was β reserve, which could highly accurately separate patients with from without coronary artery disease [98].

12.10.2 Myocardial Function and Deformation Parameters

The need for a more quantitative method for the interpretation of stress echocardiography depended on the development of new imaging modalities. Tissue Doppler and myocardial strain derived from Doppler measurements, or two-dimensional (strain and strain rate), has been considered an important alternative to better quantify regional contraction at rest or during stress [99, 100].

Tissue Doppler is feasible during stress tests, however is limited by the need of a high frame rate of at least 140 (s-1), and is angle dependent. These constraints limit the accurate deformation analysis of apical segments [101].

Classically, myocardial ischemia is defined as the transient reduction of myocardial thickening during induction of stress through pharmacological or exercise stress. However, myocardial ischemia can also cause early and late systolic

thickening, which unfortunately cannot be detected subjectively by the human eye, which has poor temporal resolution (30 frames per second), but can easily be measured by two-dimensional speckle tracking, a technique that is able to define deformation parameters known as Strain (fiber shortening) and Strain rate (fiber shortening over time) that are angle independent, making it more suitable for clinical practice. The results have been excellent in the experimental setting [102] and encouraging in the clinical realm [103], although some limitations do exist – as discussed in Chap. 23.

Real-time three-dimensional echocardiography during dobutamine stress has also been proposed to evaluate the extent and severity of CAD with good results and better specificity in multislice compared to multiplanar mode [104].

Table of Contents Video Companion

See stress echo primer, cases 8, 9, 10, 11, and 12.
See also, in the section illustrative cases, cases 11 (coronary artery disease), 32 to 35 (valvular heart disease), and 36 (heart transplant).
See also in the section "Nuovo Cinema Paradiso Remastered" the 2 short movies: Myocardial viability, a moonlight serenade, and Rocky Horror stress echo picture show.
See also in the section "Selected presentations: Angels in the stress echo lab."
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Dipyridamole Stress Echocardiography

13

Jorge Lowenstein and Eugenio Picano

13.1 Historical Background

Dipyridamole was the first pharmacological stress agent used for the diagnosis of coronary artery disease, with a pioneering indication proposed in Europe for the identification of ischemia during 12-lead ECG [1] and later in the USA by Lance Gould as hyperemic stress perfusion imaging [2]. Its main cardiac imaging applications stem from two fundamental properties, which are the two imaging sides of the same pathophysiological coin of coronary arteriolar vasodilation: the hyperemic effect and the proischemic effect [3]. The hyperemic effect is the conceptual basis for myocardial perfusion imaging, usually with radionuclide scintigraphy but today also with cardiovascular magnetic resonance [4]. The ischemic effect is the requisite for functional imaging, usually with two-dimensional (2D) echocardiography (Fig. 13.1), but today also performed with magnetic resonance [5].

The two entities – hyperemic stress and ischemic stress – are closely linked and can be considered as two different aspects of the same phenomenon, which requires endogenous adenosine accumulation as the common biochemical pathway (Table 13.1).

The predominance of the hyperemic over the ischemic manifestation will depend on the dose of dipyridamole (determining the amount of adenosine accumulation) and on the underlying coronary anatomy. With relatively low intravenous dipyridamole doses, in the presence of absent to moderate coronary artery disease, the hyperemic effect will prevail. With relatively high doses, in the presence of moderate to severe coronary artery disease, the ischemic effect will dominate. With echocardiography imaging that requires ischemia as a mandatory end point, testing began with relatively low doses (0.56 mg kg^{-1} over 4 min), which gave low sensitivity values [6]. Later, more aggressive doses were adopted (up to 0.84 mg kg^{-1} over 10 min) [7]. Finally, it was coadministered with atropine [8] or – more simply – with a high dose but a shorter infusion time (the accelerated protocol) [9], which overcame the limitation of less than ideal sensitivity to minor forms of coronary artery disease, especially in patients receiving antianginal therapy (Fig. 13.2). Experiences

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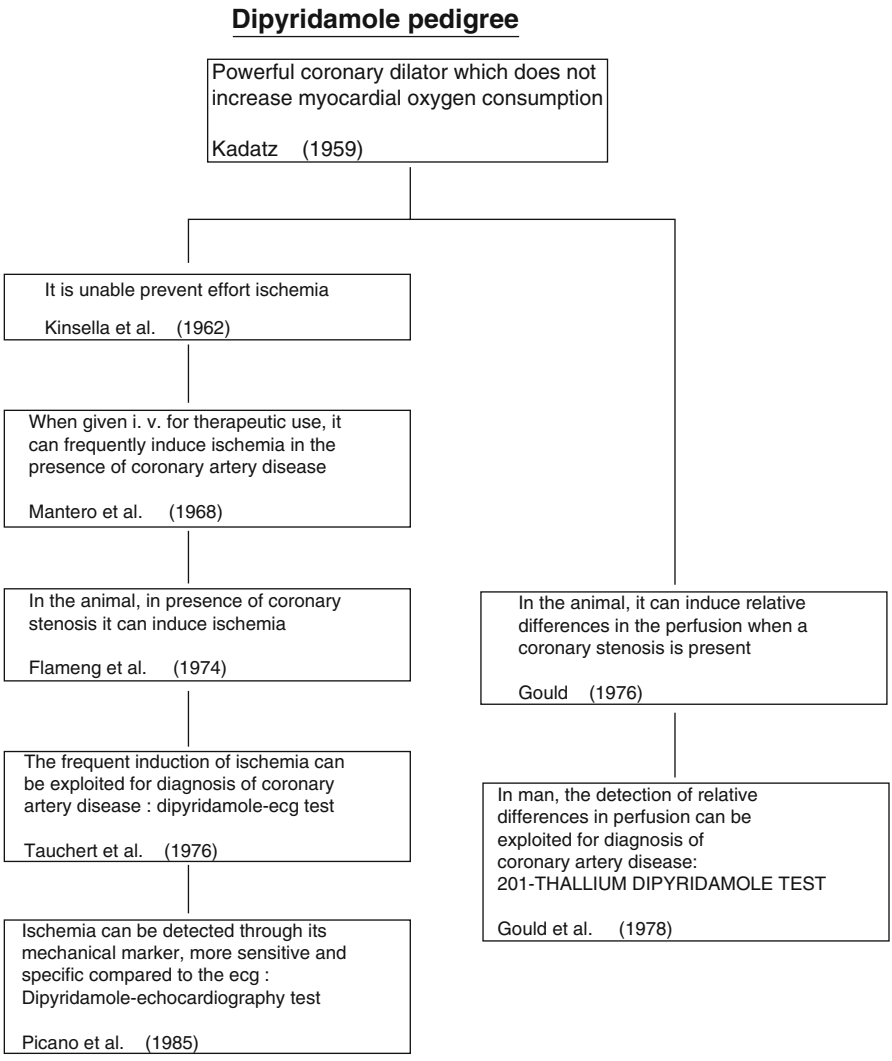


Fig. 13.1 Dipyridamole stress pedigree. *On the left*, the ischemic arm and on the right the hyperemic arm. The pioneer of dipyridamole as an exercise-independent stress test was Martin Tauchert, a German cardiologist who proposed dipyridamole ECG. Only years later did Lance Gould introduce the concept of vasodilator stress imaging, which did not conceptually require myocardial ischemia for test positivity. In recent years, it became clear that wall motion information can be ideally added to perfusion imaging, during contrast echocardiography or coronary flow imaging of the left anterior descending (LAD) artery. The two arms (hyperemic and ischemic) of dipyridamole stress are destined to merge with last-generation dual imaging stress echocardiography or stress cardiovascular magnetic resonance imaging (Modified from Picano [3])

Table 13.1 The dual nature of dipyridamole stress

Parameter	Hyperemic imaging	Ischemic imaging
End point	Flow heterogeneity	Wall motion abnormality
Ischemia required	No	Yes
Dominant technique	Radionuclide scintigraphy	2D echocardiography
Dose–effect response	Flat over 0.56 mg/kg	Steep up to 0.84 mg/kg
Optimal use	0.56 mg/kg	0.84 mg/kg

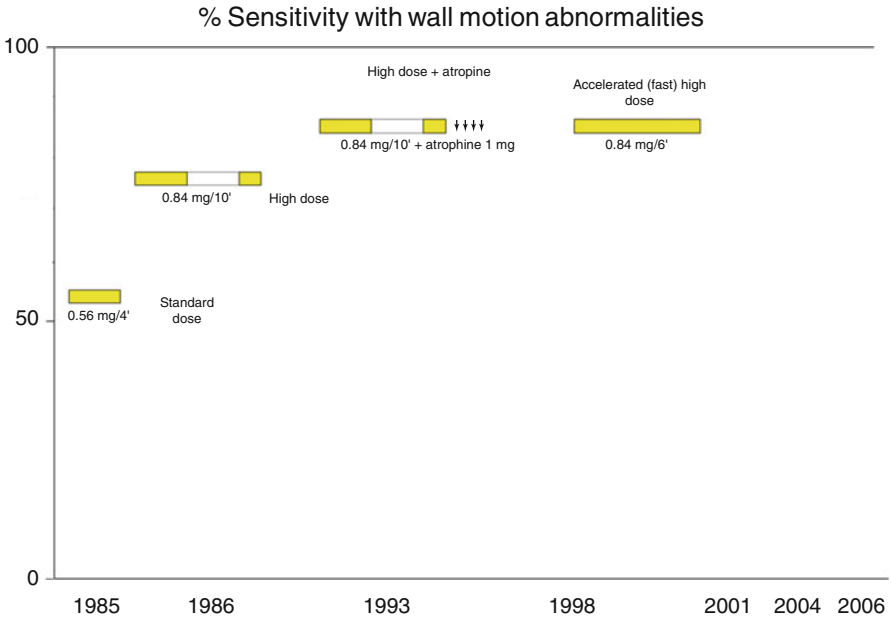


Fig. 13.2 Evolving dipyridamole stress echocardiography protocols over the years. The most sensitive and accurate protocols proposed over the last 15 years are the high dose (0.84 mg kg^{-1} in 10 min) with atropine up to 1 mg (recommended by the American Society of Echocardiography guidelines in 1998 and 2007) or the fast (or accelerated) high dose (0.84 mg kg^{-1} in 4–6 min). The latter is currently endorsed as the state-of-the-art protocol by the European Association of Echocardiography 2008 recommendations and is usually preferred since the imaging time is shorter and no multiple drug administration is needed

in some centers have used from the start (1988) high doses administered in a short time (syringe-based infusion of 0.84 mg/kg at a rate of 0.21 mg/kg/min during 4 min) with very good sensitivity and specificity and very scarce major collateral effects [10]. Later, some studies were reproduced with these doses, and today most centers worldwide use high doses delivered in 4–6 min, with the addition of atropine, which is very practical when coronary flow reserve is simultaneously assessed or when contrast is added for echocardiographic assessment of myocardial perfusion [11, 12].

The two lines of functional (wall motion) and hyperemic (coronary flow reserve) imaging are destined to converge conceptually and clinically with the diffusion of new-generation imaging technologies such as myocardial contrast echocardiography [13] and coronary flow velocity imaging [14], which will allow simultaneous assessment of flow and function at the same high, fast infusion protocol, which is currently recommended as state of the art by the European Association of Echocardiography [15]. The fast high-dose dipyridamole protocol is the best choice to kill "two birds with one stone," i.e., to image function and perfusion (two birds) in one sitting with a single stress (one stone). This approach is obviously simpler than the "two birds, two stones" approach (with separate testing of perfusion with low-dose adenosine or dipyridamole and function with dobutamine). It is, however, imperative that your "stone" (stress) is of sufficient weight (high cumulative dose) and thrown with sufficient speed (fast infusion rate) to kill the two diagnostic birds.

13.2 Pharmacology and Pathophysiology

Dipyridamole is a vasodilator test that reduces myocardial oxygen supply through flow maldistribution (steal) phenomena by stimulating $A2_A$ adenosinergic receptors present on the endothelial and smooth muscle cells of coronary arterioles. Acting indirectly, dipyridamole increases endogenous adenosine levels by reduction of cellular reuptake and metabolism. It acts as a prodrug, increasing the interstitial levels of adenosine by the combined effect of inhibition of cellular uptake of adenosine and inhibition of its breakdown by adenosine deaminase [3]. In our experience with a high dose, the peak is 1–2 min after the end of infusion and the half-time is 40 min, which suggests that the antidote aminophylline that blocks adenosine receptors should be routinely given at the end of the stress, even in negative cases. The dipyridamole dose usually employed for stress echocardiography testing (0.84 mg kg^{-1}) causes a three- to fourfold increase in coronary blood flow in normals [16] over resting values and a threefold increase in adenosine concentration in systemic venous blood [17]. It is necessary to take into account that the patients we receive in our laboratories are usually elderly, hypertensive, dyslipidemic, and with some degree of endothelial dysfunction. Thus, we define the magical number ≥ 2 as adequate response, and if this twofold diastolic flow velocity is not reached, significant obstruction of the epicardial artery corresponding to the territory explored and/or microvascular disease should be suspected.

Dipyridamole provokes ischemia mainly through steal phenomena [3], although the coadministration of atropine may also increase myocardial oxygen demand to a significant extent. Coronary collateral circulation represents a steal-prone coronary anatomy, probably providing the morphological background facilitating horizontal steal phenomena [18]. In the absence of collateral circulation, the most likely mechanism of dipyridamole-induced ischemia is the vertical steal [3]. The regional coronary flow in the ischemia-producing vessel remains unchanged when dipyridamole doses are increased from subischemic to ischemic [19], suggesting that an ischemic

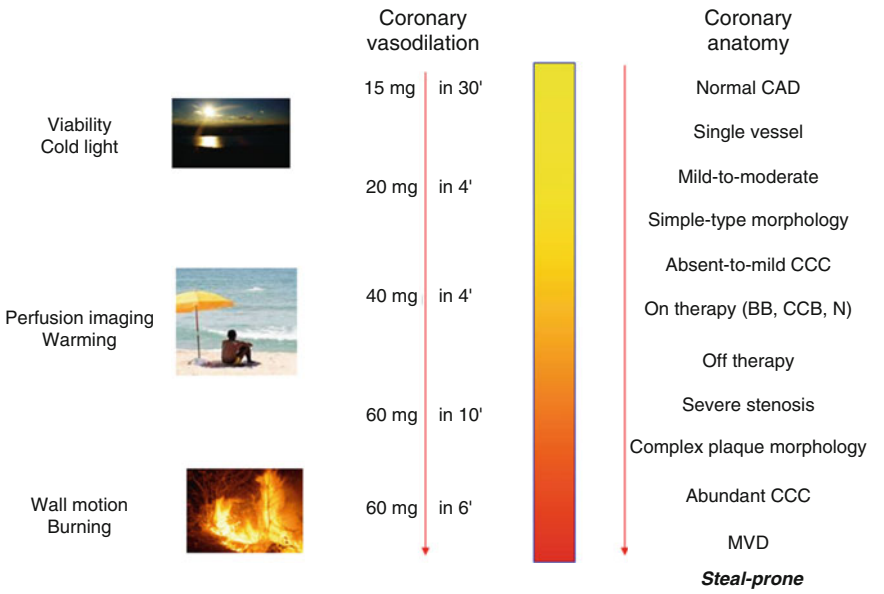


Fig. 13.3 The pathophysiological effects of dipyridamole at different dose windows and as a function of the underlying coronary anatomy in the individual patient. The proischemic, myocardial burning effects dominate at the higher doses; the cardioprotective, cold light effect at very low doses; and the warming hyperemic effect at intermediate doses (From Picano [22])

dysfunction develops for a transmural flow redistribution, causing hypoperfusion of the subendocardial layer. The flow increase is also considered to be important for the inotropic response of viable myocardium. In fact, the increased coronary flow reserve of hibernating myocardium is mirrored by the myocardial inotropic reserve in segments with resting dysfunction [20]. The cardioprotective effect on viable myocardium can also be evoked by very low, subhyperemic doses [21]. The three effects – viability, hyperemia, and ischemia – are elicited with different, increasing doses [21] observed one after the other during a single stress with dose titration [22]: Fig. 13.3. The exposure of vulnerable myocardium to the sunlight of coronary blood flow leads to three separate or sometimes overlapping effects: the "cold light" of the viability effect, the "warming" of regular-dose hyperemia, and the "burning" with high-dose ischemia.

13.3 Methodology

The standard or regular dipyridamole protocol consists of an intravenous infusion of 0.84 mg kg^{-1} over 10 min, in two separate infusions: 0.56 mg kg^{-1} over 4 min (standard dose), followed by 4 min of no dose, and, if still negative, an additional 0.28 mg kg^{-1} over 2 min. If no end point is reached, atropine (doses of 0.25 mg up to a maximum of 1 mg) is added, as recommended by the guidelines of the American Society

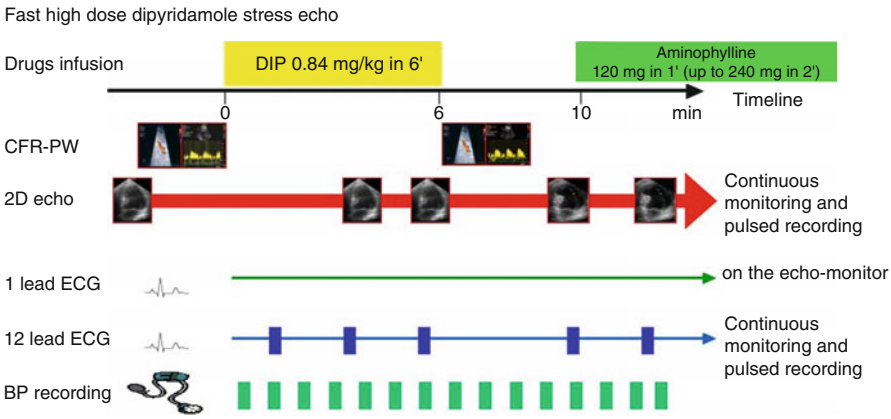


Fig. 13.4 The state-of-the-art protocol of high-dose, fast dipyridamole echocardiography test with dual imaging (wall motion and coronary flow reserve on the LAD coronary artery)

of Echocardiography for a decade [23, 24]. The same overall dose of 0.84 mg kg^{-1} can also be given over 6 min, as currently suggested by the 2008 recommendations of the European Association of Echocardiography [15], or in 4 min as used in many of our laboratories. Aminophylline (240 mg IV) should be available for immediate use in case an adverse dipyridamole-related event occurs and routinely infused at the end of the test, regardless of the result.

For a selective assessment of myocardial viability, a very low dose of dipyridamole (0.28 mg kg^{-1}) in 4 min has the same diagnostic accuracy as low-dose dobutamine [21, 25]. In special subsets of patients in whom a very high sensitivity for the diagnosis of coronary artery disease is required, high-dose dipyridamole (0.84 mg kg^{-1}) can be followed by maximal exercise [13, 26] or – less safely – by high-dose dobutamine [27]. Whenever suitable technology and dedicated expertise are available, it is recommended to perform dual imaging vasodilator stress echocardiography with combined wall motion and coronary flow reserve assessment with pulsed Doppler velocity imaging on the LAD coronary artery [11, 12, 14] (Fig. 13.4).

All caffeine-containing foods (coffee, tea, chocolate, bananas, and cola drinks) should be avoided for 12 h before testing, and all theophylline-containing drugs (aminophylline) should be discontinued for at least 24 h.

13.4 Feasibility and Safety

Minor but limiting side effects preclude the achievement of maximal pharmacological stress in less than 5 % of patients [28]. In order of frequency, they are hypotension and/or bradycardia, headache, dizziness, and/or nausea. Roughly two-thirds of the patients studied with the high-dose dipyridamole protocol experience minor side effects such as flushing and headache, which reflect the systemic vasodilatory effect

Table 13.2 Safety profile of pharmacological stress echocardiography

	Dobutamine	Dipyridamole
% submaximal tests	10 %	5 %
Side effects	1/300 exams	1/1000
VT, VF	++	+
High-grade AV block	+	++
Death	1/5000	1/10,000

VT ventricular tachycardia, *VF* ventricular fibrillation

of the drug. These side effects usually disappear following administration of aminophylline at the end of testing. On rare occasions, dipyridamole-induced ischemia becomes resistant to aminophylline [29]. In these cases, the marked late rise in the rate–pressure product during the test, which is due to sympathetic excitatory reflexes triggered by ischemia, exceeds the ischemic threshold on effort, maintaining ischemia when the flow maldistribution has been reversed by administration of aminophylline. In these cases, the administration of nitrates is necessary to reverse ischemia. Aminophylline is routinely given at the end of testing, also in negative cases, but on rare occasions it may trigger coronary vasospasm in about one-third of patients with variant angina: transient ST segment elevation is the usual pattern, and nitrates (not further aminophylline or beta-blockers!) should be given immediately to relieve spasm [30]. When atropine is administered during the study, the antidote aminophylline frequently produces tachycardia because it only inhibits dipyridamole, creating a dangerous situation in case ischemia was elicited. It is therefore necessary to rapidly inject cardioselective beta-blockers which also reverse the tachycardic effect of atropine.

Major life-threatening complications – i.e., myocardial infarction, third-degree atrioventricular block, cardiac asystole, sustained ventricular tachycardia, or pulmonary edema – occur in about 1 in 1000 cases, as shown by series encompassing over 35,000 patients with high-dose stress echocardiography techniques [28, 31]. The test induces major complications three times less frequently than dobutamine [32, 33] (Table 13.2).

13.5 Diagnostic Results for Detection of Coronary Artery Disease

The accuracy in detecting angiographically assessed coronary artery disease has been consistently shown to be high, with sensitivity and specificity 72 and 95 %, respectively, in a meta-analysis of 58 studies (all generations of protocols included) [34]. The diagnostic accuracy is similar to other forms of stress testing, such as exercise echocardiography or stress SPECT [35]. When state-of-the-art protocols are used for both stresses [36–39], the sensitivity, specificity, and accuracy of fast (or atropine-potentiated) high-dose dipyridamole are identical to dobutamine stress echocardiography, as shown by a meta-analysis including five studies with 435 patients [40]: Fig. 13.5.

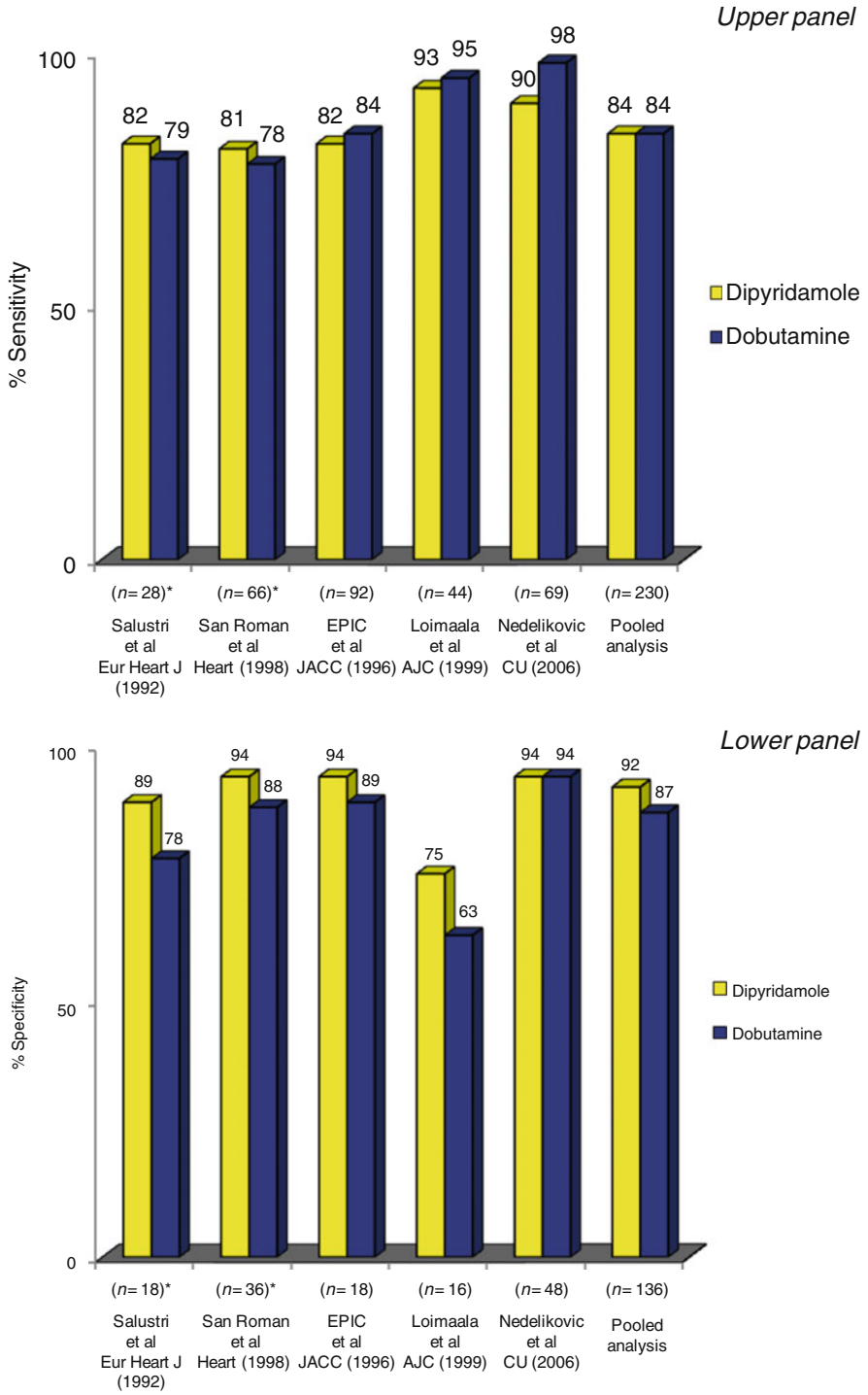


Fig. 13.5 Sensitivity (*upper panel*) and specificity (*lower panel*) for 5 individual studies and cumulative analysis of dipyridamole vs. dobutamine stress echocardiography. *Asterisk* indicates fast dipyridamole protocol; *no asterisk* is the high dose plus atropine protocol

13.6 Identification of Myocardial Viability

Very low dose (0.28 mg kg^{-1}) in 4 min dipyridamole recognizes myocardial viability with high specificity (higher than dobutamine) [21], good sensitivity (lower than dobutamine) [25], and excellent prognostic value (comparable to dobutamine) [41] (Fig. 13.6).

13.7 Prognostic Value

The prognostic value of dipyridamole stress echocardiography based on wall motion abnormalities has been extensively proven, confirmed, and reconfirmed in different subsets of patients with chronic coronary artery disease [42–45], recent myocardial infarction [46–52], or major noncardiac vascular surgery [53–58]. The prognostic value has been extensively demonstrated in special patient subsets, including hypertensives [59, 60]; elderly patients [61]; women [62]; patients with left bundle branch block [63], right bundle branch block, and/or left anterior hemiblock [64]; outpatients [65]; and patients with single-vessel disease [66] and in a chest pain unit [67, 68]. Dipyridamole stress results can predict subsequent cardiac death, mainly on the basis of two parameters: dipyridamole time (i.e., the interval between test onset and appearance of obvious dyssynergies) and peak wall motion score index (Fig. 13.7).

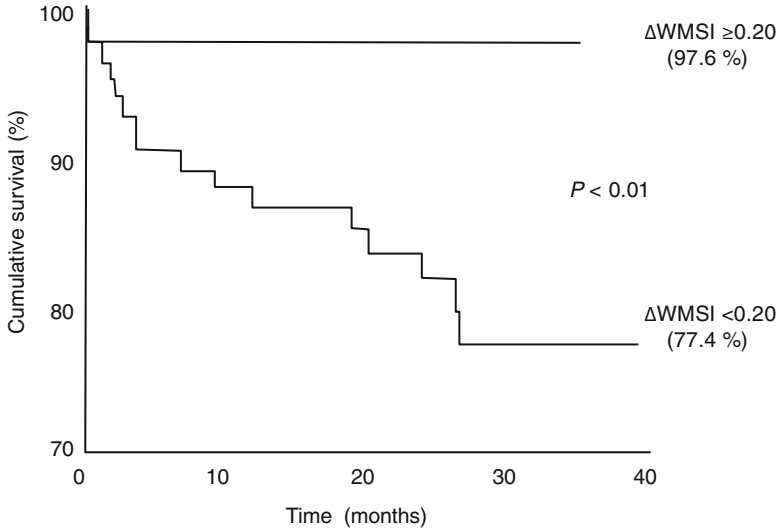


Fig. 13.6 Kaplan–Meier survival curves (with the end point as death only) in patients undergoing coronary revascularization. Myocardial viability could be distinguished by the number of segments which had improved, using as a cutoff value the difference between the resting wall motion score index and the low-dose dipyridamole wall motion score index (delta WMSI) set at 0.20. A small amount of viable myocardium is associated with a greater incidence of cardiac death ($p < 0.01$) (From Sicari et al. [41])

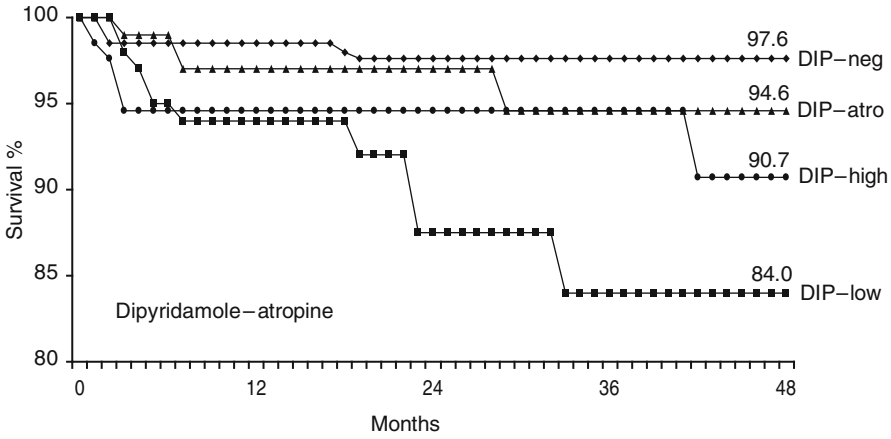


Fig. 13.7 Kaplan–Meier survival curves free of cardiac death in patients with negative and positive dipyridamole echocardiography tests (*DIP*). Survival is worse in patients with positive DIP. In patients with positive DIP, progressively worse survival is identified with positivity after atropine of high and low dose. DIP + low dose vs. DIP negative, $p < 0.0001$. Cardiac death ($n = 18$); follow-up 38 ± 21 months (Modified from Pingitore et al. [73])

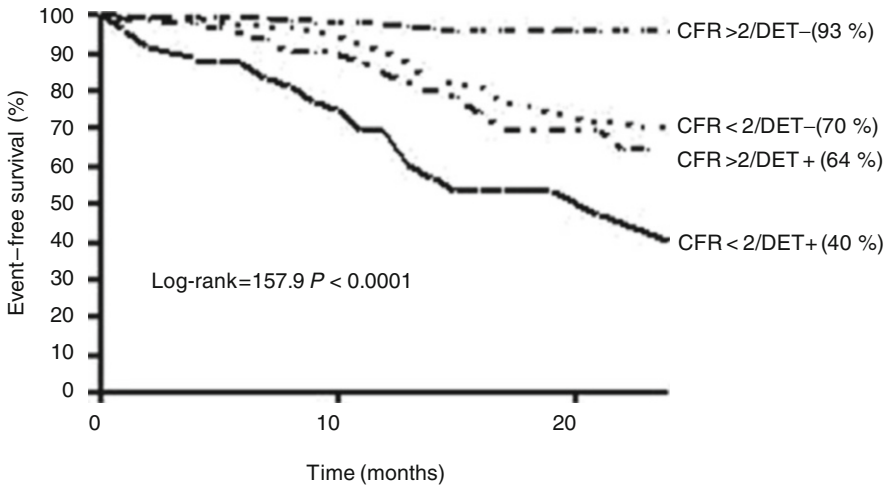
The prognostic value of dipyridamole stress echocardiography is independent of and additive to simpler clinical and laboratory variables such as resting echocardiography and exercise electrocardiography testing, and it has also been confirmed by prospective large-scale multicenter studies [43, 52]. Ongoing ischemic therapy at the time of testing not only lowers the diagnostic sensitivity in a way somewhat symmetrical to the effects on exercise testing [69] but also heavily modulates the prognostic value of pharmacological stress echocardiography. In the presence of concomitant anti-ischemic therapy, a positive test is more prognostically malignant, and a negative test less prognostically benign [70]. The prognostic value of dipyridamole stress echocardiography has also been evaluated in direct head-to-head comparisons with other forms of stress testing, and it was shown to be similar to dobutamine echocardiography [36, 71–73] and probably better than perfusion scintigraphy [50, 56].

13.8 The Added Value of Dual Imaging with Coronary Flow Reserve

The prognostic information supplied by vasodilator stress echocardiography based on wall motion (functional) imaging has been recently expanded with the systematic use of dual imaging with combined wall motion and coronary flow reserve assessment [11, 14, 74–77]. The use of coronary flow reserve as a stand-alone diagnostic criterion suffers from two main limitations: firstly, it is not always possible to obtain information from the 3 main coronary arteries, and, secondly, the coronary flow reserve cannot distinguish between microvascular and macrovascular coronary

diseases [78]. Therefore, it is more interesting (and clinically plausible) to evaluate the additive value over conventional wall motion for prognostic stratification. From the pathophysiologic viewpoint, wall motion positivity requires ischemia and epicardial artery stenosis as a necessary prerequisite, whereas coronary flow reserve can be normal only if microvascular integrity is also preserved. The combination of conventional wall motion analysis with 2D echocardiography and coronary flow reserve with pulsed Doppler flowmetry of the mid-distal LAD artery has been shown to provide an added and complementary power of prognostication in patients with known or suspected coronary artery disease [79–81], normal coronary arteries [82], diabetes [83, 84], hypertension [85], left bundle branch block [86], idiopathic dilated cardiomyopathy [87], or hypertrophic cardiomyopathy [88]. A reduced coronary flow reserve is an additional parameter of severity in the risk stratification of the stress echocardiographic response, whereas patients with a negative test for wall motion criteria and normal coronary flow reserve have a favorable outcome during dipyridamole stress echocardiography (Fig. 13.8).

Similar data have been obtained with the more complex and costly, but more informative since it evaluates all coronary territories and not only LAD artery, myocardial contrast echocardiography in patients with coronary artery disease [89] and with dilated cardiomyopathy [90].



Subjects at risk

CFR > 2/DET−	598	371	168	135
CFR < 2/DET−	208	140	57	42
CFR > 2/DET+	104	40	15	10
CFR < 2/DET+	187	33	11	7

Fig. 13.8 The additive prognostic value of wall motion and coronary flow reserve (Modified from Rigo et al. [79])

13.9 Third-Generation Stress Echocardiography

It is possible that in the near future we will collectively use three tools during a unique stress echo with dipyridamole potentiated with atropine to evaluate three different objectives: 2D echo for the semiquantitative assessment of regional wall motion, supported by the usual practice, and at the same time qualitative and subjective analyses, with color pulsed Doppler for LAD coronary flow reserve assessment, and strain 2D for the expected quantitative evaluation of the left ventricular longitudinal function. All this in only one imaging test which is fast, safe, free from radiation, objective and inexpensive, and with high diagnostic precision [91].

During the era of stress echo, there are three important periods: Paleolithic, which was the 2D echocardiography period; Neolithic, where 2D echocardiography was combined with the evaluation of coronary flow reserve by transthoracic echocardiography; and the present, with the advent of wall motion quantitative evaluation through advanced technological systems that translate the obtained data into numbers and transfer them to a bull's-eye diagram (Table 13.3). Probably this should be the scientific and clinical perspective of the echocardiographic community in the next years [92].

This model may be useful with any pharmacological stress agent, but undoubtedly dipyridamole stress echocardiography is the most suitable one.

13.10 Indications and Contraindications

Fast, high-dose dipyridamole stress echocardiography is an appropriate choice for pharmacological stress echocardiography used for the detection of coronary artery disease, especially in patients with inability to exercise or contraindications to exercise, or with resting images of borderline quality, making exercise echocardiography especially challenging. It is technically easier than exercise or dobutamine, since the image quality is less degraded by tachycardia, hyperventilation, and hypercontractility: "from the technical viewpoint, dipyridamole is the elementary school, dobutamine the secondary school, and exercise the university in the stress echo cursus studiorum" [93]. It is equally accurate, and technically easier [94] and safer, than dobutamine stress echocardiography: as clearly stated by the 2008 EAE recommendations, "exercise is safer than pharmacological stress. Among pharmacological stresses, dipyridamole is safer than dobutamine" [15]. It is subjectively better tolerated by the patients than adenosine

Table 13.3 The three generations of stress echocardiography

Stress generation	First	Second	Third
Era	Paleolithic	Neolithic	Modern
Tool	2D Echo	LAD pulsed Doppler	Strain 2D
Objective	Wall motion disorders	Coronary flow reserve	Longitudinal, radial, and torsion stress
Evaluation	Qualitative	Quantitative	Quantitative
Period	Early 1980s	Late 1990s	2010
State	Clinical state	Advanced clinical standard	In validation process

[95]. Dipyridamole stress echocardiography is also appropriate in intermediate-risk patients undergoing elective high-risk noncardiac surgery. Appropriateness is uncertain in intermediate-risk patients undergoing intermediate-risk noncardiac surgery. For the identification of myocardial viability in patients in whom low-dose dobutamine is unsafe or not tolerated, low-dose dipyridamole can be an effective alternative, although the appropriateness of the specific indication is restricted by limited experience. Patients with second- or third-degree atrioventricular block or with sick sinus syndrome should not receive dipyridamole (unless they have a functioning pacemaker). Also, patients with bronchial asthma or a tendency to bronchospasm are not indicated for dipyridamole testing (Table 13.4).

Although according to the literature it is not a frequent complication, it is better to avoid dipyridamole stress echocardiography in patients presenting severe bilateral carotid disease with unknown Willis polygon circulation, due to the theoretical possibility of producing circulatory steal and the potential risk of brain ischemia.

Patients using dipyridamole (and possibly the novel oral antiplatelet agent ticagrelor) chronically should not undergo adenosine testing for at least 24 h after withdrawal of therapy, because their blood levels of adenosine could be unpredictably high. Withdrawal of long-term theophylline or caffeine for at least 24 h is also required in order to have adenosine receptors free.

The main differences between dipyridamole and dobutamine stress echocardiography are reported in Table 13.5. Inotropic and vasodilator stresses should both be used in a stress echocardiography laboratory, for several reasons. Basically, each test has different limitations and specific advantages: a versatile use of both makes it possible to tailor

Table 13.4 Contraindications to dipyridamole stress echocardiography

	Absolute	Relative
Active bronchospasm	√	
> or equal 2nd-degree AV block	√	
SBP <90 mmHg	√	
Methylxanthine use		√
Remote history of reactive airway disease		√
Chronic dipyridamole therapy, recent (<12 h) coffee, tea, chocolate ingestion		√

AV atrio-ventricular, *SBP* systolic blood pressure

Table 13.5 Pharmacological test for detection of coronary stenosis

	Vasodilator	Dobutamine
Receptor target	A2A adenosine	Alpha-1, beta-1, beta-2 adrenergic
Hemodynamics	Reduces supply	Increases demand
Physiological targets	Coronary arterioles	Myocardium
Cellular target	Smooth muscle cells	Myocytes
Antidote	Aminophylline	β-blockers
Stress	Dipyridamole (adenosine)	Dobutamine
Contraindications	Asthmatic disease, bradyarrhythmias	Tachyarrhythmias, uncontrolled hypertension

the stress to the individual patient. Whatever type of stress is the laboratory's first choice, in the case of submaximal results due to limiting side effects, the second choice should be used, to avoid the inaccuracies of nondiagnostic submaximal testing.

13.11 Pitfalls

In spite of many advantages in terms of high accuracy, excellent safety profile, and robust evidence base supporting the prognostic value in several patients' subsets, dipyridamole is still relatively underused among pharmacological stresses in the USA and UK. This may be due to lack of commercial availability or high drug cost in some countries and established cultural imprinting in mainstream cardiological knowledge that vasodilators produce little, if any, myocardial ischemia and are more suitable for perfusion imaging – although with adequately high, state-of-the-art protocols there is no sensitivity difference – and there may be a specificity advantage, versus exercise or dobutamine.

We see some advantages with dipyridamole stress echocardiography and suggest using it as the drug of choice (Table 13.6) in patients in whom safety is essential (in case of hypertension, ventricular arrhythmias, atrial fibrillation, pacemaker, or when overstimulation cannot be performed), in those with associated cardiac pathology (complete left bundle branch block, left ventricular hypertrophy), and in patients with dynamic subvalvular obstruction, known vasospasm, or need to assess coronary flow reserve in various territories or associated to myocardial contrast. It is also worth mentioning that it is useful in laboratories with lower infrastructure and it is the ideal stress agent for those who are initiating in the technique of stress echocardiography.

The strengths and weaknesses of dipyridamole with respect to dobutamine, the other major pharmacological stress agent, can be seen in Table 13.7.

Table 13.6 Drug of choice as pharmacological stress agent

Dipyridamole	Dobutamine
When safety is essential in patients with: Hypertension Atrial fibrillation (moderate or high ventricular response) Ventricular arrhythmias	Patients where beta-blockers cannot be interrupted and coronary flow reserve is not possible to assess
Patients with pacemaker (when overstimulation is not possible)	In case of presumed single-vessel disease
Patients with subvalvular dynamic obstructions	In case of manifest ventricular dysfunction (ejection fraction <35 %)
Patients with coronary spasm	Patients with decompensated severe COPD, asthma, or bronchospasm
When it is necessary to evaluate coronary flow reserve in several territories	Patients receiving aminophylline or derivatives
When myocardial contrast is used	Patients with low-flow, low-gradient aortic stenosis
In laboratories with lower infrastructure and less experience	

Table 13.7 Relative strengths of the two pharmacological stress agents most used in clinical practice

Dipyridamole	Dobutamine
Fast study	More physiological study
Not very expensive in many countries	Better press in the US literature
Requires less technology and experience	Larger experience in many laboratories
Greater feasibility	Very good tolerance
Lower complication rate	Recognize insufficient test response
Excellent specificity	Suitable for viability studies
Very good prognostic value in different clinical scenarios	Better sensitivity to assess single-vessel disease
Very adequate to assess multi-vessel coronary flow reserve	Adequate to evaluate coronary flow reserve in the LAD territory

Nevertheless, we are convinced that the current echocardiography laboratory should have the possibility of using all the stress echocardiography modalities, as there is a scope for each stress agent according to the pathology and the indications and contraindications of each specific patient. In addition, the ever-changing shape of pharmacological stress echo will likely remodel once again in the near future, and we will shift from the current second-generation vasodilator stress echo (with wall motion and coronary flow reserve in one setting) to the third-generation stress echo, which will incorporate also quantitative wall motion analysis once the currently limiting technical problems have been overcome.

13.12 Clinical Guidelines

Dipyridamole stress echocardiography is the pharmacological test of choice for the assessment of inducible ischemia in patients unable to exercise [96, 97], especially when dobutamine is contraindicated or yielded submaximal, nondiagnostic results. It is the stress test of choice when available technology and expertise allow to have a combined simultaneous assessment of coronary flow and myocardial function in a one-stop-shop stress test [15].

Table of Contents Video Companion

See stress echo primer, cases 1 to 8.

See also, in the section illustrative cases, cases number 1 to 8 (by Maria Joao Andrade, MD, Carnaxide, Lisbon, Portugal) and cases 13 to 18 (by Jorge Lowenstein, MD, Buenos Aires, Argentina, and Quirino Ciampi, MD, PhD, Benevento, Italy).

See also in the section "Selected presentations: Angels in the stress echo lab."

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Adenosine and Regadenoson Stress Echocardiography

14

Sharon L. Mulvagh, Sahar S. Abdelmoneim, and Eugenio Picano

14.1 Background

Various pharmacologic stress agents are currently available, including adenosine, dipyridamole, and most recently regadenoson. These agents have a common mechanism, mediated through activation (nonselective or selective) of adenosine A2A receptors with resultant coronary vasodilation. Adenosine and dipyridamole have been the mainstays of vasodilator myocardial perfusion imaging (MPI) for almost two decades [1]. Radionuclide scintigraphy [2], positron emission tomography [3], and magnetic resonance imaging [4] have been the modalities traditionally utilized for myocardial perfusion imaging. Adenosine stress testing is a procedure in which patients are exposed to an intravenous infusion of adenosine while simultaneous monitoring of symptoms, hemodynamic parameters, electrocardiogram, and imaging occurs [5]. Adenosine is a second-generation vasodilator adenosinergic stress agent, evolving from the first-generation prototype, dipyridamole, which acts by triggering accumulation of endogenous adenosine [6] (Table 14.1). Perfusion imaging with scintigraphy is the dominant application of adenosine stress testing with up to 63 % of overall perfusion studies performed with adenosine and 30 % with dipyridamole in the USA [7]. The 2009 update of the American Society of Nuclear Cardiology guidelines for nuclear cardiology procedures illustrates the different protocols in place for these vasodilator agents [8].

Conventional stress echocardiography is based on functional imaging, to detect regional wall motion abnormalities (RWMA) as a diagnostic criterion to indicate the presence of ischemia [9]. When utilized in this manner, vasodilator stress echocardiography is reported to be less sensitive than radionuclide scintigraphy. Increasing the dose of the vasodilator stress can improve the diagnostic sensitivity [10]. However, ultrasound contrast enhancement permits not only improved endocardial border definition for RWMA assessment but also uniquely enables myocardial perfusion imaging improved during stress echocardiography [11, 12]. Ultrasound contrast enhancement also allows for improved Doppler coronary flow velocity imaging [13], which is currently recommended in combination with wall motion assessment during vasodilator stress echocardiography [14]. With adequate

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Table 14.1 Three generations of adenosinergic stress

	Prototype	First clinical application	Mediator	Stimulated receptors	Half-life
First generation	Dipyridamole	1980	Endogenous adenosine	A1, A2A, A2B, A3	Hours
Second generation	Adenosine	1990	Exogenous adenosine	A1, A2A, A2B, A3	Seconds
Third generation	Regadenoson	2000	Selective adenosine agonist	A2A (A1)	Minutes

dosing, adenosine stress echocardiography therefore also has the potential "to kill multiple birds with one stone," i.e., to assess wall motion, myocardial perfusion, and coronary flow reserve simultaneously in one sitting, with a single stress agent [15, 16]. This approach is a recommended option for the evaluation of stable coronary artery disease, by the European Association of Echocardiography [14].

The clinical appeal of adenosinergic stress may be further enhanced by third-generation vasodilator agents, i.e., selective A2A adenosine agonists, such as regadenoson [17], binodenoson, and apadenoson. The latter two are currently being investigated in phase 3 studies. Regadenoson (generic name code: CVT-3146) is a short-acting third-generation adenosinergic stress agent. In April 2008, regadenoson (Lexiscan, Astellas Pharma US, Inc. Deerfield, IL) [18] was the first selective A2A agonist approved by the US Food and Drug Administration for use as a vasodilator in conjunction with radionuclide perfusion imaging and is today by far the most used pharmaceutical stress for MPI imaging, making 83 % of all stresses and an estimated 2–3 million tests performed per year in the USA only. Its counterpart, Rapiscan (Rapidscan Pharma Solutions EU Ltd, London, UK), was authorized by the European Commission with the same indication in 2010. The affinity of regadenoson for human adenosine A2A receptors exceeds that for adenosine A1 receptors by more than nine-fold, and its affinity for A2B and A3 receptors is minimal. Given its selectivity, this A2A receptor agonist has the potential to increase the safety and tolerability of adenosine stress, especially in asthmatic patients. Data shown from two major trials (The Adenoscan Versus Regadenoson Comparative Evaluations for Myocardial Perfusion Imaging [ADVANCE-MPI and ADVANCE-MPI 2] trials [19]) demonstrated the non-inferiority of regadenoson as compared to adenosine for detection of ischemia and the overall decreased symptoms including flushing, chest pain, and dyspnea.

14.2 Pharmacology and Pathophysiology

14.2.1 Adenosine Receptors

Adenosine is a nucleoside, i.e., a purine-based adenine bound to sugar ribose [20] acting through its specific receptors located on the outer surface of the cell membrane. It is produced inside the cell, so it is diffused, driven by the concentration

gradient, to extracellular space to activate its receptors, which can be divided into two major subtypes: (1) A1 inhibitory receptors and (2) A2 stimulatory receptors. The A1 receptors predominate in the myocardium, whereas the A2 receptors are found in the coronary arteries (endothelial and smooth muscle cells). Probably the chemistry signal that induces adenosine synthesis is the oxygen supply-demand ratio via the variation of the potential of phosphorylation. In fact, in the case of insufficient oxygen supply, there is a reduction in the potential of phosphorylation and the consequent increment of free adenosine monophosphate (AMP) in the cytoplasm that is available as a substrate of 5′-nucleotidase [21]. The increment of 5′-nucleotidase determines an increased production of adenosine. A2A receptors play a key role in mediating inappropriate arteriolar vasodilation leading to hyperemia and – in presence of critical coronary stenosis – to subendocardial ischemia for vertical and horizontal steal phenomena and regional wall motion abnormality [6]. The human adenosine A2A receptor gene has been localized on chromosome 22q, and several genetic polymorphisms have been identified [22] as potentially responsible, at least in part, for the heterogeneity in response to coronary flow during stress imaging [23] (Fig. 14.1). The main physiological effects of endogenous adenosine, classified according to involvement of A1, A2, or A3 receptors, are presented in Table 14.2.

14.2.2 Adenosine Metabolism

When adenosine binds with phosphate it becomes a nucleotide, i.e., adenosine monophosphate (AMP), adenosine diphosphate (ADP), and adenosine triphosphate (ATP).

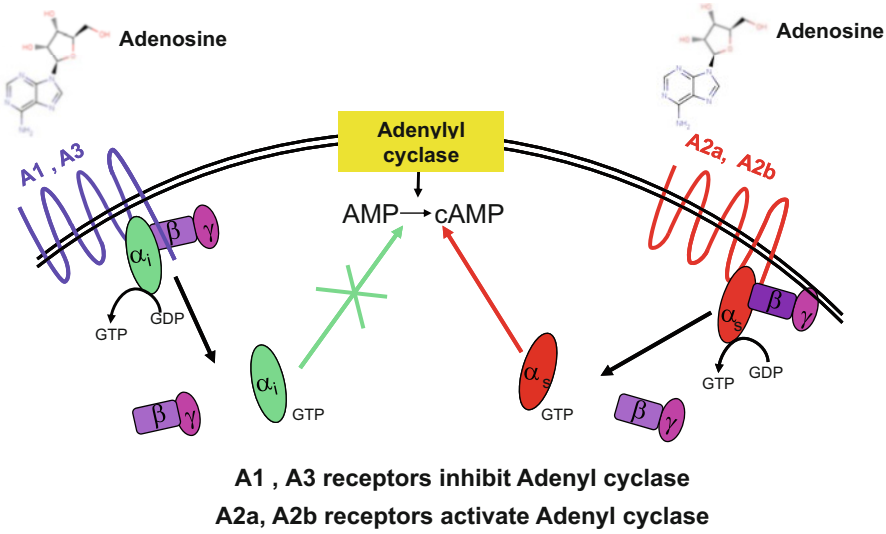


Fig. 14.1 The molecular structure of adenosine receptors

Table 14.2 Adenosine receptors: a view from the imaging laboratory

Receptor	Effect	Desired diagnostic end point
A1	Atrioventricular block Bradycardia Preconditioning	
A2A[a]		Coronary vasodilation
A2B[a]	Bronchoconstriction due to mast cell degranulation	
A3	Anti-inflammatory effects (peripheral blood mononuclear cells)	

[a]Jacobson [24]. Additional effect of stimulation as follows: *A2B* and *A2A* peripheral vasodilation, *A1* renal vasoconstriction, *A2A* sympathetic surge (carotid body)

Actually, one of the pathways of adenosine generation is degradation of those nucleotides, which under normal conditions contribute only up to 10 % of the endogenous adenosine in the heart. Approximately 90 % of adenosine in the heart is created by the *S*-adenosyl homocysteine hydrolase pathway [2]. A certain amount is also generated by degradation of extracellular AMP. Extracellular adenosine returns into the cell by reuptake through cell membrane by facilitated diffusion, where in a very short time it is degraded by enzyme adenosine deaminase to inosine, which is biologically inactive. It is the end stage of adenosine degradation in myocytes, but in the endothelial cells, adenosine is broken down from inosine to hypoxanthine and uric acid. At physiological concentrations, adenosine is predominantly salvaged, i.e., metabolized to adenosine 5-monophosphate (AMP) by the enzyme adenosine kinase. At higher concentrations such as those following administration of diagnostic doses, adenosine is deaminated to inosine [2]. Dipyridamole blocks adenosine reuptake with a resultant increase of adenosine in extracellular space and greater activity on the receptor site. Theophylline and other methylxanthines (such as caffeine) block adenosine receptors in a dose-dependent manner [2] (see Fig. 5.3 in Chap. 5). When patients receiving adenosine (140 μg kg^{-1} per min) for controlled hypotension were pretreated with clinical doses of dipyridamole (to reduce the dose requirements of adenosine), the arterial plasma concentration was shown to be 2.5 μM, a level ten times the normal level [25].

14.2.3 Hemodynamic Effect

The adenosine effects listed in Table 14.3 substantiate the proposed potential clinical uses of adenosine listed in Table 14.4. Cardiac stress imaging is the most important diagnostic application of adenosine infusion. The intravenous infusion of adenosine induces a slight increase in heart rate and cardiac output and a slight decrease in systemic pressure. The mild tachycardia occurs in spite of the direct, negative chronotropic and dromotropic effects of adenosine for stimulation of A1 myocardial receptors; it is a consequence of adrenergic activation, occurring either through direct stimulation of sympathetic excitatory arterial chemoreceptors [26] or indirectly through systemic vasodilation. In normal subjects, the coronary blood flow increases to four to five times the baseline flow following adenosine – an

Table 14.3 Cardiovascular effects of exogenous adenosine administered intravenously in humans

Vagal inhibition (low doses), increase in heart rate
Inhibition of the sinus node and AV conduction in high doses, bradycardia, AV block
Antiadrenergic effect
Vasodilatation in all arteriolar beds, except vasoconstriction in renal preglomerular arterioles; decrease in reperfusion injury
Hyperventilation (explained by interaction with carotid chemoreceptors)

Table 14.4 Potential clinical uses of adenosine

Paroxysmal supraventricular tachycardia
Exercise-induced ventricular tachycardia
Controlled hypotension during intracranial vascular surgeries
Afterload reduction in congestive heart failure
Antiplatelet aggregation (cardiopulmonary bypass, hemodialysis)
Reduction of reperfusion injury
Diagnosis and prognosis of coronary artery disease

increase comparable to that caused by high-dose dipyridamole and substantially higher than that induced by exercise or dobutamine, during which coronary blood flow increases about three times the baseline value [27] . The maximal coronary dilatory effect is reached within 2 min of adenosine administration and wears off rapidly within 2.5 min after the infusion is stopped. Adenosine can induce elevation in pulmonary capillary wedge pressure and/or left ventricular end-diastolic pressure only in presence of myocardial ischemia [28]. In comparison to the newer selective A2A receptors agonist, regadenoson was shown to be >100 times potent than adenosine in increasing the coronary blood flow [29]. The decrease in mean arterial blood pressure was similar between regadenoson and adenosine (13 and 18 mmHg, respectively). However, the increase in heart rate was higher with regadenoson than adenosine. It was suggested that the A2A-mediated sinus tachycardia was related to the direct sympathetic excitation and less due to baroreceptor reflex mediation [30].

The power and time course of the coronary vasodilator effect of adenosine and other newer synthetic adenosine-receptor agonists are shown in Fig. 14.2 [17].

14.2.4 Pharmacologic Comparison of Vasodilator Agents (Adenosine, Dipyridamole, and Regadenoson)

Pharmacologic differences between the three vasodilator stress agents are outlined in Table 14.5. Regadenoson has, in theory, attractive features close to the "ideal" agent for its rapid onset of action and adequate duration of effect allowing image acquisition and fewer side effects due to its selective stimulation of A2A receptors specifically responsible for coronary vasodilation, avoiding undesirable effects of A1, A2B, and A3 receptor stimulation (such as dyspnea, headache, and flushing). As a matter of fact,

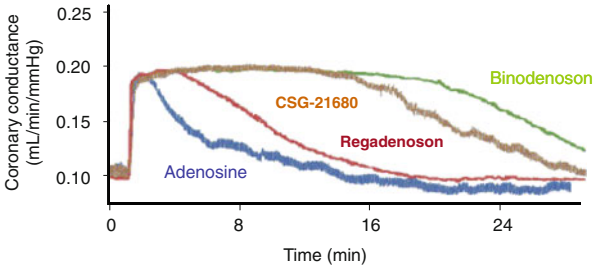


Fig. 14.2 The vasodilatory effect of adenosine and newer selective A2A receptor agonists (Adapted from Zoghbi [9])

the incidence of these side effects is not substantially reduced when compared to adenosine, although their severity is decreased, and in particular it may offer a safer option in patients with a bronchoreactive component of lung disease [31].

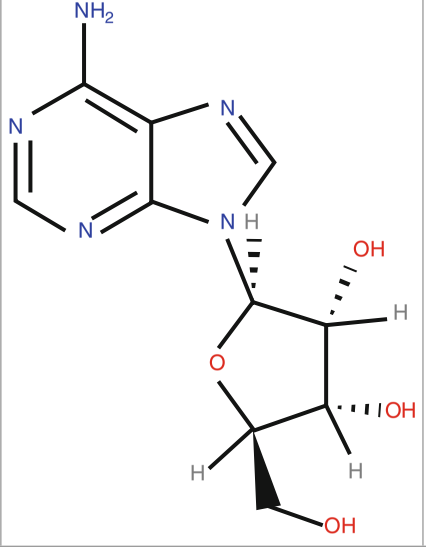
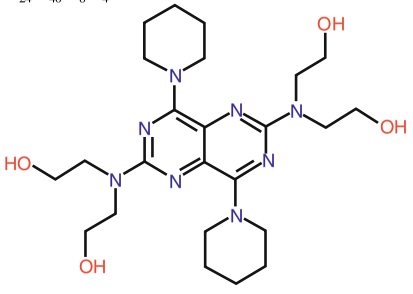
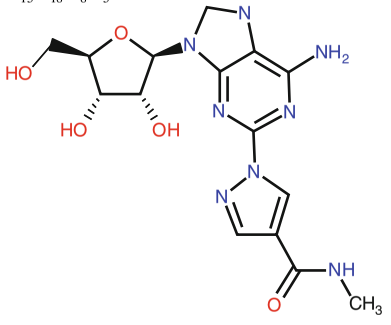
14.3 Methodology

For echocardiographic imaging, the dose is usually started at 100 μg kg^{-1} per minute and is gradually increased to a target of 140–200 μg/kg^{-1} per min [10] (Fig. 14.3). When side effects are intolerable, down titration of the dose is also possible. Some authors suggest infusing adenosine for no more than 90 s, taking into account that the maximal hyperemic effect is already reached at 30–60 s [32, 33]. The short adenosine infusion seems to be effective, safer, and better tolerated than the standard dosage, but it has the disadvantage that there is not enough time to perform a complete assessment of left ventricular wall motion. Although not routinely advised, adenosine injection of 2.5-mg bolus produces an increment in coronary flow reserve similar to that obtained by a 3-min venous infusion [34]; however, intense hyperpnea can result, which is uncomfortable to the patient, and can interfere with the technical acquisition of adequate echocardiographic images.

Similar to dobutamine, administration of adenosine requires an infusion pump, whereas dipyridamole may be injected with a handheld syringe. As with dipyridamole, test sensitivity can be potentiated using a handgrip [34], which can be added to adenosine or to ATP infusion [35].

Regadenoson is currently administered as a bolus of 0.4 mg in a 5-mL solution (without weight-based dose adjustment) injected over 10 s followed by a 5-mL saline flush to ensure appropriate drug delivery. The optimum time for image acquisition for perfusion imaging is 2–10 m after drug infusion. Regadenoson stress echo enables combined assessment of myocardial perfusion imaging and wall motion analysis. In the absence of coronary stenoses, regadenoson induces a two- to threefold increase in coronary blood flow and increased wall thickening. The addition of atropine – as described with adenosine and dipyridamole – may be used to potentiate the stress [36–40]. Suggested protocol for regadenoson myocardial perfusion stress echocardiography is shown in Fig. 14.4 [36].

Table 14.5 Pharmacologic properties between the three vasodilator stress agents

	Adenosine	Dipyridamole	Regadenoson
Trade name	Adenoscan/Adenocard	Persantine	Lexiscan (in the USA) Rapiscan (in Europe)
Company	Astellas Pharma US, Inc. Deerfield, IL	Boehringer Ingelheim Pharmaceuticals, Inc Ridgefield, CT	Astellas Pharma US, Inc. Deerfield, IL/Rapidscan Pharma Solutions EU Ltd, London, UK
Indications	Pharmacologic stress in MPI Treating PSVT	Pharmacologic stress in MPI Orally to treat thrombotic states	Pharmacologic stress in MPI
Molecular formula	Endogenous vasodilator of purine derivatives $C_{10}H_{13}N_5O_4$ 	Pyrimidine derivative $C_{24}H_{40}N_8O_4$ 	Purine derivative $C_{15}H_{18}N_8O_5$ 

(continued)

Table 14.5 (continued)

	Adenosine	Dipyridamole	Regadenoson
Mechanism of action	Nonselective A2A receptor activation	Inhibit adenosine reuptake, increasing availability of adenosine	Selective A2A receptor activation
Administration	Intravenous infusion	Intravenous infusion	Intravenous bolus
Half-life	<10 s	30–60 min	Triphasic (2–4 min, 30 min, 120 min)
Time to peak	30 s	7–15 min	1–4 min
Excretion	Cellular intake	Glucuronide conjugates and unchanged drug in feces	57 % of drug unchanged in urine

MPI myocardial perfusion imaging, *PSVT* paroxysmal supraventricular tachycardia

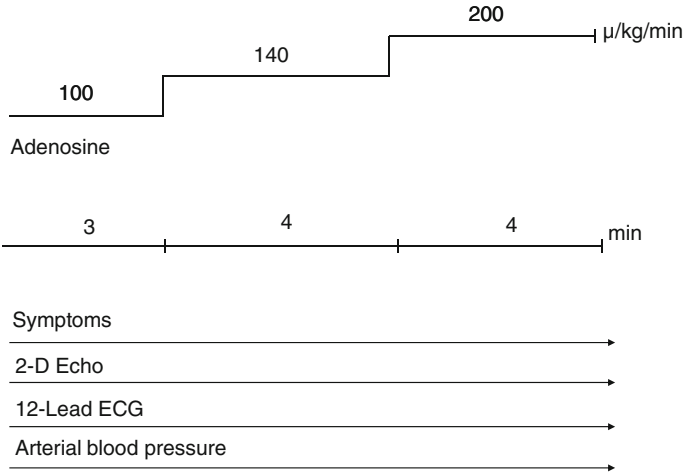


Fig. 14.3 Protocol of adenosine stress echocardiography

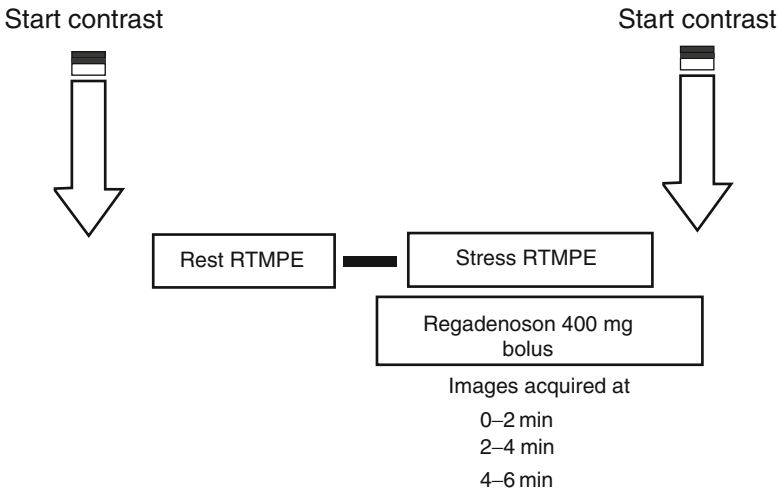


Fig. 14.4 Protocol of regadenoson real-time myocardial perfusion echocardiography (RTMPE) (Adapted from Porter et al. [36])

14.4 Tolerability and Safety

Side effects are not infrequent and may be limiting in a significant number of patients – up to 20 % [41]. However, in contrast to dipyridamole, side effects from adenosine and regadenoson rapidly dissipate and rarely cause significant complications; this is due to the very short half-life of adenosine and regadenoson. The most frequent limiting side effects for adenosine-mediated vasodilator stressors include high-degree

atrioventricular block, arterial hypotension, intolerable chest pain (sometimes unrelated to underlying ischemia, possibly induced for direct stimulation of myocardial A1 adenosine receptors), shortness of breath, flushing, and headache. All side effects disappear upon termination of adenosine infusion. On very rare occasions, an infusion of aminophylline is required. The quality of side effects is similar to that experienced by the same patients during dipyridamole stress, but these effects are quantitatively more pronounced during adenosine stress. Although side effects are frequent, the incidence of major life-threatening complications (such as myocardial infarction, ventricular tachycardia, and shock) has been shown to be very low, with only one nonfatal myocardial infarction in approximately 10,000 cases. Among pharmacological stress tests [41–44], adenosine is probably the least well tolerated subjectively, but at the same time possibly the safest (see Table 14.6), on the basis of the large experience gained in nuclear cardiology with myocardial perfusion imaging [41], although – as happens with dipyridamole – coronary vasospasm may occur during or after adenosine stress, which may lead to serious adverse outcomes if unrecognized [45, 46].

Despite of the theoretical benefit, regadenoson stress has shown similar side effects compared to adenosine; most reactions resolve within 30 min. However, the severity of symptoms is less, and tolerability score is greater after regadenoson stress when compared to adenosine [17].

In post-marketing experience, the most common side effects reported for regadenoson include headache (26 %), chest tightness (13 %), nausea (6 %), and abdominal pain (5 %); atrioventricular block, syncope, and seizure were reported in <1 % of patients [18]. Importantly, regadenoson is given as a single rapid bolus, whereas both adenosine and dipyridamole are infused over minutes. This is of important implications in terms of physician and patient time.

In November 2013, the US Food and Drug Administration Communication warned health safety professionals of the rare but serious risks of heart attack and

Table 14.6 Side effects of pharmacological stress protocols

Stress protocol	Dipyridamole 0.56 mg kg^{-1}	Dipyridamole 0.84 mg kg^{-1}	Adenosine 140 mcg kg^{-1} per min	Regadenoson 400 mcg/5 mL bolus	Dobutamine 40 mcg kg^{-1} per min ± atropine
Reference	Lette et al. [42]	Picano et al. [43]	Cerqueira et al. [41]	Iskandrian et al. [17]	Picano et al. [44]
No. of patients	73,806 (9066 with 0.75 or 0.84 mg kg^{-1})	10,451	9256	784 <0.10 %	2949
Major side effects	0.04 %	0.07 %	<0.10 %		0.4 %
Fatal MI*	0.01 %	0.01 %	0 %	0 %	0 %
Nonfatal MI[a]	0.017 %	0.02 %	0.01 %	0 %	0.07 %
VT/VF	0.008 %	0.01 %	0 %	0 %	0.05 %

MI myocardial infarction, *VT* sustained ventricular tachycardia, *VF* ventricular fibrillation
[a]In November 2013, some cases of MI were reported with regadenoson and adenosine

death with either regadenoson or adenosine. Regadenoson and adenosine can provoke myocardial ischemia up to myocardial infarction and – rather unexpectedly for regadenoson due to its relatively weak effect on A1 receptors – advanced atrioventricular blocks up to cardiac asystole. Furthermore, there was an increase in the incidence of seizures noted in the post-marketing experience. Hence, changes to the drug labels and updated recommendations for avoiding the use of these agents in patients with signs or symptoms of unstable angina or cardiovascular instability and to reflect that regadenoson may lower seizure threshold were implemented [47].

In principle, the application of the stress with echo should increase the safety, due to the possibility to detect ischemia in real time and stop the test with administration of aminophylline as soon as the diagnostic end point has been reached.

14.5 Indications and Contraindications

The merits and limitations of adenosine and regadenoson in comparison with the prototype vasodilator dipyridamole are shown in Table 14.7. The list of contraindications of adenosine and regadenoson is identical to that for dipyridamole (Table 13.4 in Chap. 13). Exogenous adenosine has an even more pronounced negative chronotropic and dromotropic effect than endogenous adenosine [17], making the appearance of advanced atrioventricular blocks more frequent with adenosine than with dipyridamole for equivalent doses. Adenosine is a direct alternative to dipyridamole – the prototype of vasodilator adenosinergic stress. Like dipyridamole, antianginal drugs lower adenosine stress echocardiography sensitivity, whereas concomitant therapy with oral dipyridamole potentiates the cardiovascular effects of adenosine. The safety record and short half-life make adenosine especially indicated in patients with severe aortic stenosis [48] or elderly patients [49], who may be especially vulnerable to complications during dipyridamole or dobutamine stress. Possibly, emerging application of regadenoson across varying clinical populations included regadenoson use in patients with moderate and severe chronic obstructive pulmonary disease [37, 50] who have an indication to stress imaging and may want to avoid adenosine-induced bronchoconstriction and respiratory compromise, although in these patients the use of the bronchodilator dobutamine might be more reasonable.

Table 14.7 Adenosine versus dipyridamole and regadenoson for vasodilator stress testing

	Dipyridamole	Adenosine	Regadenoson
Half-life	Hours	Seconds	*Minutes*
Aminophylline requirement	Always	Rarely	Sometimes
Echocardiographic difficulty	Mild	Moderate	Mild
Limiting side effects	5 %	10–20 %	5 %
Patient tolerance	Good	Fair	Good
Prognostic value	Extensive	Initial	In progress

Table 14.8 Diagnostic accuracy of adenosine echocardiography with regional wall motion abnormalities

Authors	Reference	Year	Patients	Dose	Sensitivity (%)	Specificity (%)
Zoghbi et al.	[9]	1991	73	100–140	85	92
Edlund et al.	[51]	1991	54	60–200	89	Na
Martin et al.	[52]	1992	37	140	76	60
Marwick et al.	[54]	1993	97	180	86	71
Amanullah et al.	[58]	1993	40	140	74	100
Heinle et al.	[59]	1993	42	140	56	NA
Case et al.	[53]	1994	26	140	96	100
Takeishi et al.	[55]	1994	61	140	51	Na
Tawa et al.	[34]	1995	67	180	64	91
Djordjevic et al.	[10]	1996	58	200	92	88
Anthopoulos et al.	[49]	1996	120	140	66	90

14.6 Diagnostic Accuracy of Regional Wall Motion Abnormalities for Detection of Coronary Artery Disease and Myocardial Viability

The full range of sensitivities has been reported [34, 51–55] with higher values coming from expert centers evaluating patients with previous myocardial infarction and multivessel disease (Table 14.8). Higher adenosine dose [10] and/or the combination with a handgrip [34] showed higher sensitivity without significant loss in specificity. On the basis of a published meta-analysis on 11 studies, adenosine stress echocardiography, based on wall motion abnormalities, showed the same sensitivity (79 %), specificity (91.5 %), and accuracy as exercise echocardiography, dipyridamole echocardiography, and dobutamine echocardiography, with superior specificity when compared to SPECT stress imaging [56]. Some initial data suggest that adenosine infusion may elicit an inotropic response in viable myocardium with resting dysfunction [57], thereby representing an alternative to dobutamine for the recognition of viability through pharmacological stimulation.

14.7 The Value of Myocardial Perfusion During Adenosine Stress Echocardiography

The use of ultrasound contrast enhancement with stress echocardiography (SE) was shown to improve the diagnostic accuracy of stress echo for the diagnosis of CAD [60]. Myocardial perfusion echocardiography with ultrasound contrast enhancement during vasodilator stress (analyzed visually and quantitatively) was shown to enhance the diagnostic performance over wall motion analysis alone for detection of coronary artery disease (CAD). Reported diagnostic accuracy measures for qualitative myocardial perfusion echocardiography during vasodilator stress are shown in Table 14.9. In addition, the diagnostic accuracy of quantitative myocardial

Table 14.9 Clinical evidence of selected studies for the evaluation of myocardial perfusion during vasodilator stress echocardiography

Study	No. of patients	Type of SE	Reference/cutoff	CAD prevalence	Reported diagnostic yield
Moir et al. (2004) [61]	85	ESE-Dipyridamole	CA [≥50 %]	42 (51 %)	Sensitivity: WM :74 %; MPE&WM: 91 % Specificity: WM: 81 %; MPE&WM: 70 %
Tsutsui et al. (2005) [62]	36 (16 had CA)	Dipyridamole	SPECT CA [≥50 %]	SPECT 20 (56 %) CA 13 (36 %)	MPE vs. SPECT: Sensitivity: 70 %; Specificity: 81 % MPE vs. CA: Sensitivity: 67 %; Specificity: 92 %
Xie et al. (2007) [63]	40	Adenosine	SPECT CA [>50 %]	29 (72.5 %)	MPE vs. SPECT: Sensitivity: 76 %; Specificity: 94 % MPE vs. CA: Sensitivity: 78 %; Specificity: 86 %
Abdelmoneim et al. (2010) [64]	91 (88 were feasible for analysis)	Adenosine	SPECT	42 (46 %)	MPE vs. SPECT: Sensitivity: 88 %; Specificity: 85 % WM vs. SPECT: Sensitivity: 62 %; Specificity: 96 %
Arnold et al. [65]	65	Adenosine	CA [≥50 %] And MRI		MPE vs. CA: Sensitivity: 82 %; Specificity: 85 % MPE vs. MRI: Sensitivity: 85 %; Specificity: 74 %

ESE exercise stress echocardiography, *MPE* myocardial perfusion echocardiography, *MCA* microbubble contrast agents, *MRI* magnetic resonant imaging, *CAD* coronary artery diseases, *CA* coronary angiography

perfusion echocardiography-derived myocardial blood flow reserve from selected studies is shown in Table 14.10.

14.8 Prognostic Value of Adenosine Stress Echocardiography

Data on the prognostic value of adenosine stress echocardiography findings are limited to date, but consistent with the larger evidence collected with perfusion imaging with nuclear and CMR techniques [71, 72], and it is expected that adenosine-induced wall motion abnormalities on echocardiography would have a prognostic role. A positive viability response with wall motion recovery in segments with resting dysfunction identified a lower risk subset in patients with acute myocardial infarction who underwent primary coronary angioplasty after an acute myocardial infarction [73]. In asymptomatic type-2 diabetics, a reduced coronary flow reserve was associated with poor glycemic control and higher risk of subsequent events [74].

Table 14.10 Studies of quantitative real-time myocardial perfusion echocardiography during adenosine stress in patients with known or suspected coronary artery disease

Feature	Korosoglou et al. (2004) [66]	Malm et al. (2006) [67]	Kowatsch et al. (2007) [68]	Osorio et al. (2007) [69]	Vogel et al. (2008) [70]	Abdelmoneim et al. (2010) [64]
Contrast agent	SonoVue[a]	Optison[b]	PESDA	PESDA	SonoVue[a]	DEFINITY[c]
No. of patients	47	53	54	71	48	79
Reference test	SPECT and CA	CA	CA	CA	CA	SPECT
Prevalence of CAD, %[d]	62	44	46	35	77	48
Diagnostic accuracy of MBF reserve						
Cutoff	2.3	2.06	2.6	1.68	1.94	1.90
AUC	NA	0.780	0.780	NA	0.928	0.779
Sensitivity, %	80	77	76	84	89	73
Specificity, %	78	69	67	87	92	72

Abbreviations: *AUC* area under the receiver-operating characteristic curve, *CAD* coronary artery disease, *MBF* myocardial blood flow, *NA* not available, *PESDA* perfluorocarbon-exposed sonicated dextrose albumin, *SPECT* single-photon emission computed tomography

[a]SonoVue (sulfur hexafluoride microbubbles); Bracco Diagnostics; Milan, Italy

[b]Optison (perflutren protein-type A microspheres); GE Healthcare, Princeton, New Jersey

[c]DEFINITY (perflutren lipid microspheres); Lantheus Medical Imaging, Inc, North Billerica, Massachusetts

[d]Prevalence of disease was calculated on the number of patients reported to have the disease on the basis of the reference test

A prognostic role of myocardial perfusion during SE has been demonstrated in studies with different pharmacologic stressors [75]. In a study enrolling patients with known or suspected CAD and comparing dipyridamole perfusion echocardiography with simultaneous SPECT, during mean follow-up period of 14 months, abnormal perfusion echocardiography was found to be an independent predictor of adverse cardiac outcome (odds ratio, OR 23, 95 % CI 6–201, $p < 0.001$) and further provided an incremental prognostic value over clinical variables, LV systolic function, inducible wall thickening abnormalities, and SPECT results [76]. Furthermore, the isolate reduction in coronary flow reserve derived from RTMPE during adenosine stress in patients with known or suspected CAD and normal resting left ventricular function adds independent and incremental prognostic information over clinical and resting echocardiography variables in predicting events [77].

14.9 Emerging Applications of Regadenoson Vasodilator Stress

Since the regadenoson approval in 2008, it became a well-established pharmacological stress agent with myocardial perfusion imaging in many subsets of patients. Emerging regadenoson applications in stress perfusion echocardiography (with ultrasound contrast enhancement) are on the horizon. Porter et al. [36] performed the first clinical study of real-time myocardial perfusion stress echocardiography using DEFINITY ultrasound contrast agent (Lantheus Medical Imaging, Inc.) continuous infusion at rest and every 2 min, for up to 6 min after regadenoson bolus in patients referred for quantitative coronary angiography. Sensitivity, specificity, and accuracy for detecting significant coronary stenosis (>50 % diameter) using qualitative myocardial perfusion stress echocardiogram with regadenoson were demonstrated to be 80 %, 74 %, and 78 %, respectively, compared to 60 %, 70 %, and 66 % in wall motion analysis alone ($p < 0.001$ for sensitivity) with highest sensitivity when imaging was performed in the first 2–4 min after regadenoson administration [36]. Further application includes quantifying myocardial blood flow from myocardial perfusion echocardiography replenishment curves. As shown in a preclinical study [38] in ten dogs with myocardial perfusion echocardiography (SonoVue, Bracco Diagnostics; Milan, Italy), demonstrating a regadenoson-induced increase in myocardial blood flow decreased proportionally to coronary stenosis severity, with optimal time for myocardial perfusion imaging in stress echocardiography between 3 and 10 min after regadenoson bolus. This was further confirmed in a clinical study demonstrating an [78] accurate detection of significant LAD stenosis (>70 % with 74 % sensitivity and 67 % specificity). Figure 14.5 shows an example of perfusion defect on regadenoson myocardial perfusion echocardiography.

Prognostic regadenoson data are lacking given its recent approval; however, it will be forthcoming as experience with this agent increases.

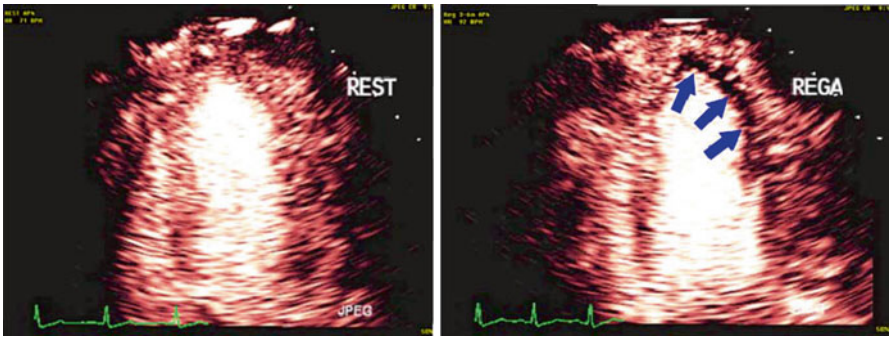


Fig. 14.5 Myocardial perfusion defect detectable with real-time myocardial perfusion echocardiography using Optison contrast agent showing resting image (*left*) with normal myocardial perfusion and at peak stress (*right*); an apical anterior myocardial perfusion defect (*blue arrows*) on end-systolic (two-chamber view) images obtained following a regadenoson bolus injection

14.10 Practical Aspects

14.10.1 Cost-Effectiveness

The choice of one vasodilator stressor over the other depends on patient characteristics, drug cost, and the physician's preference. Cost plays a major role in that regard. In some countries, an additional limitation of adenosine is its exorbitant cost: in the USA, adenosine costs $179, dipyridamole $95, and dobutamine $1 per exam. In one study [79], the mean cost of the vasodilator stress agent was $154 ± 127 with adenosine and $10 ± 2 with dipyridamole ($p < 0.001$). When the cost of adverse effects and monitoring was included, the total cost rose to $160 ± 27 and $19 ± 3 with adenosine and dipyridamole, respectively ($p < 0.001$). In Europe, adenosine costs €100, dipyridamole €3, and dobutamine €9. However, it is also possible to have a generic formulation of adenosine from the hospital pharmacy at a very low cost of around €1 [14].

Currently, there is no cost-effectiveness analyses performed for the vasodilator stressor regadenoson. However, regadenoson appears to have many of the attributes of an ideal pharmacologic stress agent, and it is expected to assume that the less complex administration of regadenoson (fixed bolus dose) [17] will simplify the work flow and result in a potential milder adverse effects which in turn lead to increased patient satisfaction and efficacy of the tests, all resulting in improved cost-effectiveness.

In one study [52], it was found that among adenosine, dipyridamole, and dobutamine, adenosine was the test most disliked by the patients.

14.11 Clinical Guidelines

The American Society of Echocardiography guidelines [50] provided the rationale for the uses of vasodilator stress echocardiography, although not commonly applied in the USA. Similarly, the European Association of Echocardiography

documented the clinical value of vasodilator stress echocardiography [14]. In 2013, the ESC guidelines on stable angina affirmed the necessity of pharmacological stress testing echocardiography in patients who are unable to exercise adequately. Furthermore, they recommended the use of regadenoson or dobutamine as an alternative stressor in cases where adenosine is contraindicated especially in asthmatic patients [80]. Similarly, the use of vasodilator stress echocardiography has been acknowledged in the 2013 ACC/AHA Appropriateness Use Criteria for the Detection and Risk Assessment of Stable Ischemic Heart Disease TTE [81].

Table of Contents Video Companion

See also in the section "Illustrative cases: case numbers 17 and 18" (by Prof Ana Djordjevic-Dikic).

See also in the section "Selected presentations: Pharmacological and myocardial effects of adenosine and dipyridamole."

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Pacing Stress Echocardiography

15

Edyta Plonska and Eugenio Picano

15.1 Historical Background

High-rate pacing is a valid stress test to be used in conjunction with echocardiography; it is independent of physical exercise and does not require drug administration. It has evolved over the last 35 years, starting from an invasive (intravenous) right atrial pacing modality combined with an ionizing imaging technique such as radionuclide ventriculography [1], moving to a semi-invasive modality combined with two-dimensional (2D) echocardiography, using a transnasal [2] or transoral [3] catheter for transesophageal left atrial pacing, and finally evolving to a totally non-invasive modality with external programming in patients with a permanent pacemaker for right atrial or ventricular pacing [4].

15.2 Pathophysiology

The pathophysiological rationale of pacing stress is obvious, with the stress determined by a controlled increase in heart rate, which is a major determinant of myocardial oxygen demand, and thereby tachycardia may exceed a fixed coronary flow reserve in the presence of hemodynamically significant coronary artery disease. Cardiac volumes decrease [5] and blood pressure does not change significantly during pacing, whereas contractility increases only minimally (see Fig. 5.4 in Chap. 5), possibly due to the Bowditch Treppe or staircase phenomenon [6], i.e., the increase in contractility due to the increase in heart rate [7, 8]. At increased heart rate, the coronary flow is decreased through reduction in diastolic duration in the presence of coronary stenosis. Heart rate is a major factor influencing transmural blood flow distribution and regional function, because when coronary vasodilation is maximal, there is an inverse relationship between the heart rate level and subendocardial perfusion [9]. The drop in the subendocardial-to-subepicardial flow ratio associated with rapid atrial pacing in the presence of a tight coronary stenosis is critical to the development of regional dysfunction, because regional percent systolic thickening is linearly and tightly related

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to subendocardial, but not to transmural flow [9]. In experimental dog models, pacing stress shows a good sensitivity, only marginally lower than high-dose dobutamine or dipyridamole stress, for detection of significant coronary stenoses by stress echocardiography [10]. In patients with permanent right ventricular pacing, perfusion defects can often be found in the inferior and apical wall, which are probably the earliest activated sites under right ventricular apical pacing [11, 12]. The regional coronary flow reserve can be impaired in the dominant coronary artery perfusing these regions, whereas it is usually normal in the left anterior descending coronary artery. This abnormality is at least partially responsible for the low specificity of stress myocardial scintigraphy [13]. In patients with permanent pacemakers, chronic right ventricular pacing also induces asymmetric thickness of the left ventricular wall and redistribution of left ventricular mass [14]. In fact, asynchronous electric activation of the left ventricle decreases mechanical load in early vs. late activated regions of the ventricular wall. Accordingly, chronic right ventricular pacing induces redistribution of left ventricular mass, with thinning of early vs. late activated myocardium. Septal motion during right ventricular pacing can vary according to the site of stimulation and heart rate. Preejection septal beaking is observed – similarly to what can be found in other patients with relatively delayed left ventricular activation, caused by left bundle branch block or type B Wolff–Parkinson–White syndrome (Fig. 4.8 in Chap. 4). The preejection period septal beaking is not due to early activation and unopposed contraction of the interventricular septum, but rather it occurs in response to an altered transseptal pressure gradient. When pacing causes the right ventricle to be activated before the left, right ventricular pressure begins to increase in systole before left ventricular pressure, altering the normal left-to-right transseptal pressure gradient [15]. Coincident with the early unopposed increase in right ventricular pressure, the septum abruptly moves posteriorly toward the left ventricle. With the subsequent onset of left ventricular contraction, left ventricular pressure increases, the normal transseptal pressure gradient is restored, and the septum returns in the anterior direction toward its end-diastolic position. In the ejection phase, a ventricularly paced left ventricle can show a normal posterior motion and thickening (more frequent with pacing from the right ventricular apex) or a flat or paradoxical (anterior) motion (more frequent with pacing from right ventricular outflow or right ventricular inflow) [11]. The interpretation can be easier in the first case than in the second case, especially considering that in 30 % of patients, a normal or flat motion can become paradoxical at high pacing rates over 120 per min.

15.3 Methodology

The main features of different pacing techniques are summarized in Table 15.1. Pacing can be atrial or ventricular. The paced chamber is the left atrium in transesophageal pacing and the right atrium or the right ventricle in permanent pacemaker stimulation.

All have good diagnostic results. However, intravenous atrial pacing [1] requires catheterization, which nullifies its utilization in the echocardiography laboratory. Utilization of the transesophageal approach as a stress test for ischemia has become

Table 15.1 Pacing mode and contractile pattern in pacing stress echocardiography

	Paced chamber	Noninvasiveness	Septal movement	Simplicity of echocardiographic reading
Permanent PM atrial mode	Right atrium	++	Normal	++
Permanent PM ventricular mode	Right ventricle	++	Paradoxical (60 %)	±
Permanent PM biventricular	Right and left ventricle	++	Normal	++
Transesophageal	Left atrium	±	Normal	++
Transvenous	Right atrium	–	Normal	++

++ excellent, + good, – poor

possible, thanks to recent improvements in this technique, enabling effective atrial capture at a relatively low threshold, which has reduced patient discomfort [2], and transoral stimulation with 10-French catheters [3]. The results reported have been good, but semi-invasiveness substantially limits the applicability of this approach. In a more clinically plausible approach, the presence of a permanent pacemaker can be exploited to conduct a pacing stress test in a totally noninvasive way by programming the pacemaker to increasing frequencies [4]. The paced chamber is the right atrium in atrial stimulation and the right ventricle in ventricular stimulation mode. The diffusion of biventricular pacing also expands the domain of application of pacing stress echocardiography, since this pacing mode induces a physiological contraction of the septum, making echocardiography interpretation easier. The interpretation must consider that regional wall motion in the septum is differently affected by the pacing mode (Fig. 15.1).

In the atrial and biventricular stimulation mode, the normal, physiological electrical activation sequence is preserved; therefore, the septal wall motion is normal and there are no special interpretation problems. Roughly two out of three patients with permanent pacemakers are studied in the right ventricular pacing mode. In approximately 30 % of right ventricular-paced patients, the septal wall motion is normal [14, 15], but in the majority of them, an anterior systolic interventricular septal motion (paradoxical motion) is present at baseline. In this case, it is necessary to focus on wall thickening rather than endocardial excursion, and on nonseptal regions of the left anterior descending territory to identify left anterior descending stenosis, but this interpretation will always be a challenge, especially at high heart rates. Now, to avoid apical right ventricular pacing, ventricular lead is rather implanted in midseptal position or close to right ventricular outflow tract. Pacemaker stress echocardiography can only be used with patients with a permanent pacemaker, a large and expanding population in today's cardiology practice [4]. In addition, this test is especially useful in patients with a permanent pacemaker. In fact, the noninvasive diagnosis of coronary artery disease in patients with a permanent pacemaker is an extremely difficult task, since the induced rhythm by right ventricular pacing makes the electrocardiogram uninterpretable and stress scintigraphy is plagued by an exorbitant number of false-positive results [12].

With external programming of the pacemaker, pacing is started at 110 bpm and increased every 2 min by 10 bpm until 85 % of the target heart rate (220 minus years of

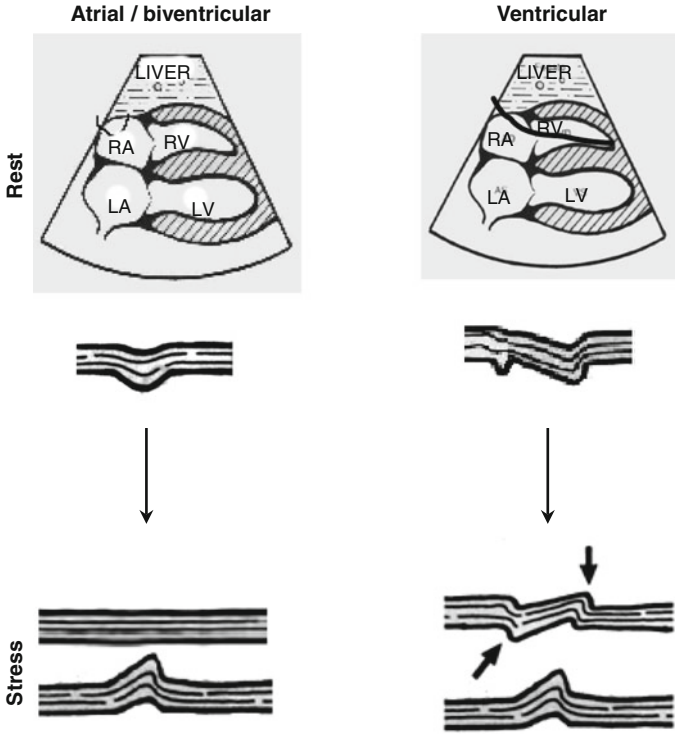

Fig. 15.1 Different types of baseline septal motion and stress-induced ischemia according to the pacing mode (AAI/DDD vs. VVI). *RV* right ventricle, *IVS* interventricular septum, *LA* left atrium, *LV* left ventricle, *RA* right atrium, *AAI* atrial stimulation mode, *VVI* ventricular stimulation mode

age for men; 200 minus years of age for women) is achieved (Fig. 15.2) or until other standard end points are reached. The same protocol can also be followed in an accelerated fashion, with faster steps (20–30 s each) up to the target heart rate. Left ventricular segmental contractility can be also assessed during two-step rapid pacing at the rate of 100 bpm and then at 85 % of maximal age-predicted heart rate. The examination is done with the patient supine or in left lateral decubitus position. Two-dimensional echocardiographic images are obtained before pacing and throughout the stress test, the last recording being obtained after 3 min pacing at the highest rate reached (usually 150 bpm) or the target heart rate. Blood pressure and the electrocardiogram are monitored throughout the examination. Left ventricular wall motion abnormalities are evaluated at rest, during pacing, and immediately after pacing interruption.

15.4 Clinical Results and Comparison with Other Stress Echocardiography Tests

Good diagnostic results have been obtained with invasive pacing stress echocardiography, with good sensitivity and specificity [16–19]. As with other stress echocardiography tests, the positivity can be effectively titrated in the time and space

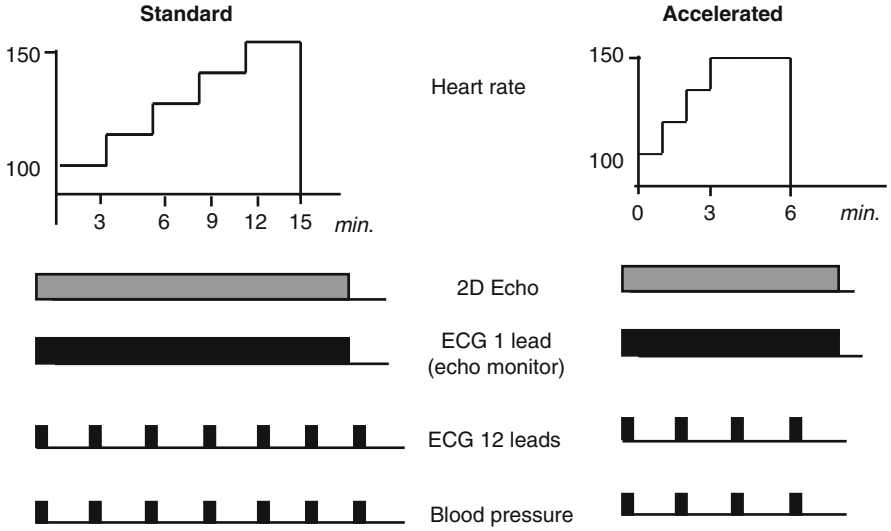

Fig. 15.2 Protocol of pacing stress echocardiography: standard (*left*) or accelerated (*right*)

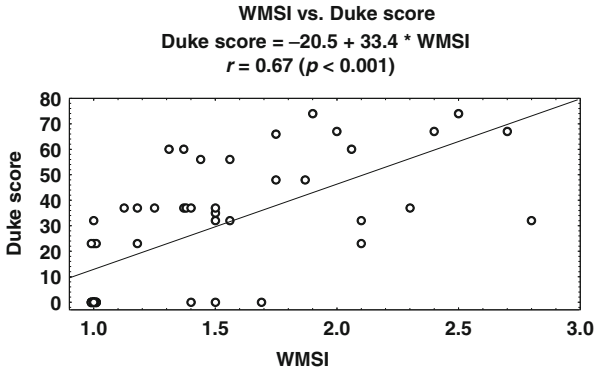

Fig. 15.3 Extent and severity of coronary artery disease (expressed by the prognostically validated Duke score) is predicted by peak wall motion score index (*WMSI*) during pacing stress echocardiography

domain [4], and more severe degrees of underlying coronary artery disease are associated with a lower heart rate, necessary to induce ischemia and with more extensive wall motion abnormality (Fig. 15.3).

Pacing-induced ischemia is also helpful in risk stratification of the patient with known or suspected coronary artery disease [20–23].

Noninvasive pacemaker stress echocardiography has several advantages in comparison to conventional diagnostic techniques. The relative merits and limitations of noninvasive pacemaker stress echocardiography vs. pharmacological stress echocardiography are reported in Table 15.2.

Table 15.2 Pacing vs. pharmacologic stress echocardiography

	Pacemaker	Pharmacological
Patient tolerability	Very high	High
Stress imaging time	5–10 min	10–20 min
Safety	Very high	High
Intravenous line	Usually not required	Required
Clinical experience	Initial	Extensive
Applicability	Patients with permanent pacemaker	All patients

The ability to instantly lower the rate and terminate stress results in high test safety. Pacemaker stress echocardiography is rapid and can be conducted at bedside and is therefore well tolerated by the patient and user friendly for the physician. In contrast to physical stress, it does not require patient capability to exercise; contrary to pharmacological stress, it does not require an intravenous line and the additional cost (and risk) of drug administration. The stress echocardiography imaging during pacing represents high quality. Imaging time is also shorter, because the median time of pacing is less than 10 min with the accelerated protocol, which compares favorably with the approximately 10 min of imaging time for dipyridamole and about 20 min for dobutamine–atropine. In patients with a permanent pacemaker, 2D echocardiography during pacing is a useful tool in the detection of coronary artery disease.

15.5 Pitfalls

Myocardial oxygen consumption as high as that reached with exercise is not obtained by atrial pacing because cardiac volumes decrease and blood pressure does not change significantly, such that in some patients with mild coronary artery disease, wall motion abnormalities may not develop. At a high rate, there are fewer video frames during the ejection period and less time to appreciate a regional wall motion abnormality. Only one half of patients can be stressed in an atrial stimulation or biventricular mode that preserves the physiological sequence of contraction of the left ventricle. In patients with ventricular stimulation of long duration, specificity can perhaps be lowered. The external programming of the permanent pacemaker is simple and fast, but it requires technology (external programmer) and expertise not readily available in the echocardiography laboratory – also requiring minimum cooperation and coordination with the pacemaker laboratory – which is usually, but not always and anywhere, easy to obtain. Perfusion changes are of limited diagnostic value during pacing stress since they are present especially in the septal and apical regions independently of underlying coronary stenoses for the associated nonischemic wall motion abnormalities [24, 25]. Diastolic function can also be assessed during atrial pacing [26], and echocardiography might allow to do it noninvasively.

Table 15.3 Indications to pacing stress in patients referred for stress echocardiography

	Appropriate	Uncertain	Inappropriate
Patients with implanted pacemaker (atrial or biventricular mode)	√		
Patients with implanted pacemakers (ventricular mode)		√	
Patients without implanted pacemaker (transesophageal)			√

15.6 Clinical Indications

Because of its safety and repeatability, noninvasive pacing stress echocardiography can be the first-line stress test in patients with permanent pacemakers [27, 28], especially if the stimulation can be performed in the most physiological and less technically challenging atrial or biventricular mode (Table 15.3). In the recent "Stress Echocardiography in Clinical Practice" Survey from UK, pacing stress echocardiography was performed in a large number (40 %) of echocardiography departments participating in the study [29].

Table of Contents Video Companion

See in the section "Illustrative cases: case number 41 (by Prof Edyta Plonska)." Springer Extra Materials available at http://extras.springer.com/2015/978-3-319-20957-9

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Ergonovine Stress Echocardiography for the Diagnosis of Vasospastic Angina

16

Jae-Kwan Song and Eugenio Picano

Coronary artery spasm has been considered one of the major mechanisms causing *dynamic* stenosis of epicardial coronary arteries, which can evoke acute myocardial ischemia. Vasospastic angina caused by coronary artery spasm has a wide clinical spectrum: one of its typical clinical manifestations is variant angina. Coronary vasospasm has also been documented to contribute to the development of unstable angina or acute myocardial infarction [1]. Classically, coronary artery spasm is diagnosed by an invasive provocative procedure during diagnostic coronary angiography. Since various noninvasive diagnostic tests for fixed atherosclerotic stenosis of epicardial coronary arteries (exercise ECG, stress echocardiography, and nuclear tests) are being used in routine daily practice, it would be useful to establish a reliable, noninvasive, and safe diagnostic method to document coronary artery spasm in the management of patients with vasospastic angina.

The rare episodic nature of coronary artery spasm makes it extremely difficult to document spontaneous coronary vasospasm in clinical practice. The noninvasive stress tests currently used are ergonovine [2], acetylcholine [3], and systemic alkalosis by hyperventilation [4]. Of these, spasm-provocation testing using ergonovine is considered the gold standard for diagnosis of coronary artery spasm because of its high sensitivity and specificity. Acetylcholine seems to have comparable diagnostic validity for intracoronary administration, but its short half-life for the abundant pseudocholinesterase in human plasma makes intravenous injection inadequate for spasm provocation.

16.1 Basic Considerations

Ergonovine maleate is an important oxytocin alkaloid and a member of the ergobasine group, an amine alcohol derivative of lysergic acid. This drug can induce coronary vasoconstriction in patients who have undergone heart transplantation, which suggests that it does not act via the central nervous system. This drug is believed to stimulate α-adrenergic and 5-hydroxytryptamine (serotonin) receptors [5]. After

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intravenous injection, the half-life of the distribution phase is between 1.8 and 3 min, and the half-life of the disappearance phase is between 32 and 116 min [6]. This rapid mode of action explains why coronary spasm most often occurs between 2 and 4 min after the injection. The use of ergonovine in incremental doses starting with an intravenous injection of 0.05–0.1 mg followed by small increments of 0.1–0.15 mg at 5-min intervals up to a maximum cumulative dosage of 0.35 or 0.4 mg is generally recommended [1]. This general guideline is based on the finding that the cumulative doses (0.1 + 0.2 + 0.3 + 0.4 mg) at 5-min intervals have the same effects as a single dose of 0.4 mg [1]. The provocative test with ergonovine performed in the cardiac catheterization laboratory has a high sensitivity (98 %) and specificity (98.7 %) [7].

16.2 Protocol

For a diagnosis of vasospastic angina, the possibility of significant fixed atherosclerotic stenosis of major epicardial coronary arteries is usually ruled out by means of the exercise stress test and/or pharmacological stress echocardiography. All cardioactive drugs (β-receptor blocker, calcium channel blocker, and nitrates) should be discontinued for at least five half-lives; however, nitroglycerin should be administered sublingually as necessary. Resting hypertension is usually controlled using angiotensin-converting enzyme inhibitors; uncontrolled hypertension is a contraindication of this test.

It should be remembered that some drugs, especially long-acting calcium channel blockers, may have persistent effects on coronary vasomotor tone as long as 2–3 weeks after discontinuation [8, 9].

Figure 16.1 shows the classic protocol of ergonovine echocardiography. A bolus injection of ergonovine (50 μg) is administered intravenously at 5-min intervals until a positive response is obtained or a total dose of 0.35 mg is reached. The 12-lead

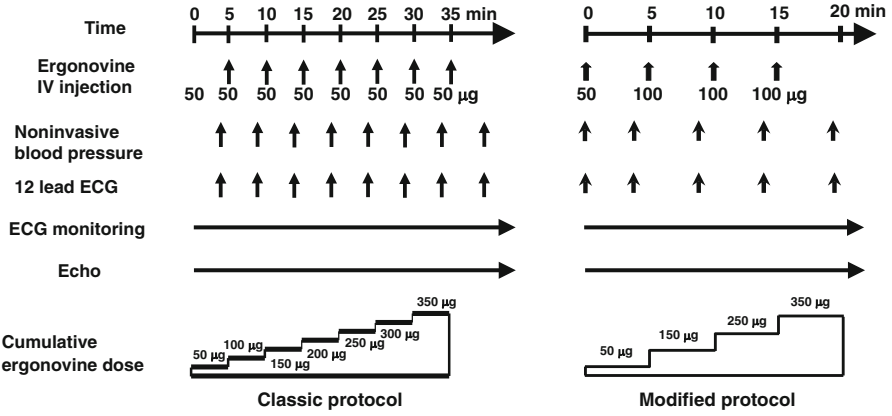


Fig. 16.1 Classic (*left*) and modified (*right*) protocols for ergonovine echocardiography

ECG is recorded after each ergonovine injection and left ventricular wall motion is monitored continuously. Positive criteria for the test include the appearance of transient ST-segment elevation or depression greater than 0.1 mV at 0.08 s after the J point (ECG criteria) or reversible wall motion abnormality by two-dimensional echocardiography (ECG criteria). The criteria for terminating the test are as follows: positive response defined as ECG or echocardiographic criteria, total cumulative dose of 0.35-mg ergonovine, or development of significant arrhythmia or changes in vital signs (systolic blood pressure >200 mmHg or <90 mmHg). An intravenous bolus injection of nitroglycerin is administered as soon as an abnormal response is detected; sublingual nifedipine (10 mg) is also recommended to counter the possible delayed effects of ergonovine. These drugs can be administered as needed. The protocol can be modified just to decrease the test time (Fig. 16.1), with bolus doses of 50, 100, 100, and 100 μg every 5 min up to a cumulative dose of 350 μg.

16.3 Noninvasive Diagnosis of Coronary Artery Spasm: Clinical Data

Bedside ergonovine echocardiography has been reported to be accurate and safe [8–18] (Figs. 16.2 and 16.3). The sensitivity of echocardiographic criteria (detection of reversible regional wall motion abnormalities) is higher than 90 %, which is far greater than that of ECG criteria (ST-segment displacement, 40–50 %). Characteristic ST-segment elevation during ergonovine testing occurred in about one third of patients with variant angina [16]; the lower sensitivity with ECG criteria can be partially explained by an earlier development of regional wall asynergy during myocardial ischemia in the so-called pre-electrocardiographic phase rather than a true false-negative finding [10–13]. The earlier detection of ischemia with higher sensitivity is very important from the safety point of view, as the vicious cycle of the ischemic cascade can be terminated earlier and the risk associated with prolonged ischemia reduced. According to a single-center report of ergonovine echocardiography performed on 1,372 patients [16], the test showed very high feasibility (99.1 %); transient arrhythmias – including sinus bradycardia ($n=10$), ventricular premature beats ($n=10$), short-run ventricular tachycardia ($n=2$), and atrioventricular block ($n=4$) – developed in 1.9 % (26/1,372) of the patients studied. All of these arrhythmias were transient and promptly reversed with the administration of nitroglycerin and nifedipine, as described earlier. Although intracoronary nitroglycerin could not be used to reverse coronary vasospasm in this protocol, there were no serious complications such as development of myocardial infarction or fatal arrhythmia during the test [8, 9].

Unlike other stress tests for fixed atherosclerotic stenosis of coronary artery, this test shows high sensitivity even in patients with single-vessel spasm [16]; the transmural nature of supply ischemia due to coronary artery spasm may explain this difference.

As this test also showed very high specificity (>90 %) for the diagnosis of coronary artery spasm before coronary angiography, invasive coronary angiography and spasm-provocation testing can be avoided for the diagnosis of vasospastic angina [16, 18].

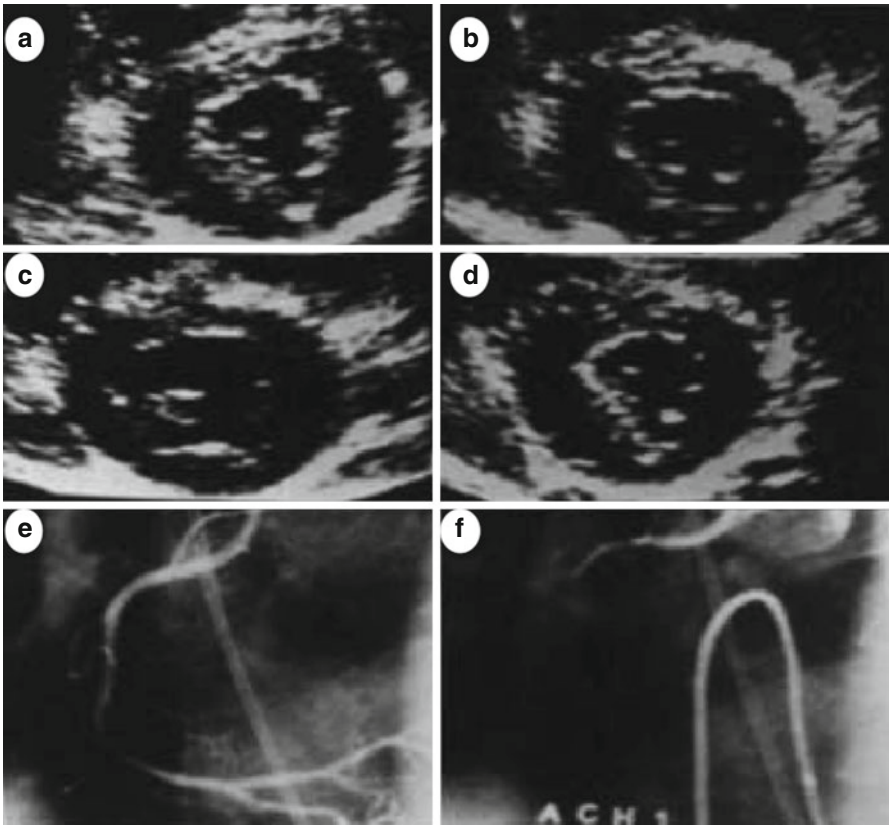


Fig. 16.2 Representative examples of (**a**–**d**) ergonovine stress echocardiography and (**e**, **f**) coronary angiography in a 53-year-old man with early-morning chest pain. Treadmill test results were negative up to stage 4 of the Bruce protocol, and ergonovine echocardiography was done. Left ventricular wall motion at end-systole recorded in the parasternal short-axis view was demonstrated in quad-screen format. (**a**) Basal status. (**b**) Left ventricular wall motion after injection of 0.05-mg ergonovine. (**c**) Regional loss of systolic myocardial thickening in the mid-inferior segment with an ergonovine dose of 0.1 mg and (**d**) recovery of regional wall motion abnormality with nitroglycerin, a finding suggestive of myocardial ischemia in the region of the right coronary artery due to coronary vasospasm. (**e**) Coronary angiogram taken 2 days later revealed a normal right coronary artery. (**f**) Intracoronary injection of acetylcholine (ACH) provoked total occlusion of the proximal right coronary artery, which was compatible with coronary vasospasm (From Song et al. [9], with permission)

16.4 Special Safety Considerations

Issues regarding the safety of spasm-provocation testing are summarized in Table 16.1.

Ergonovine echocardiography testing, undertaken either in the catheterization laboratory or at the bedside, is a risky and challenging procedure, demanding a high

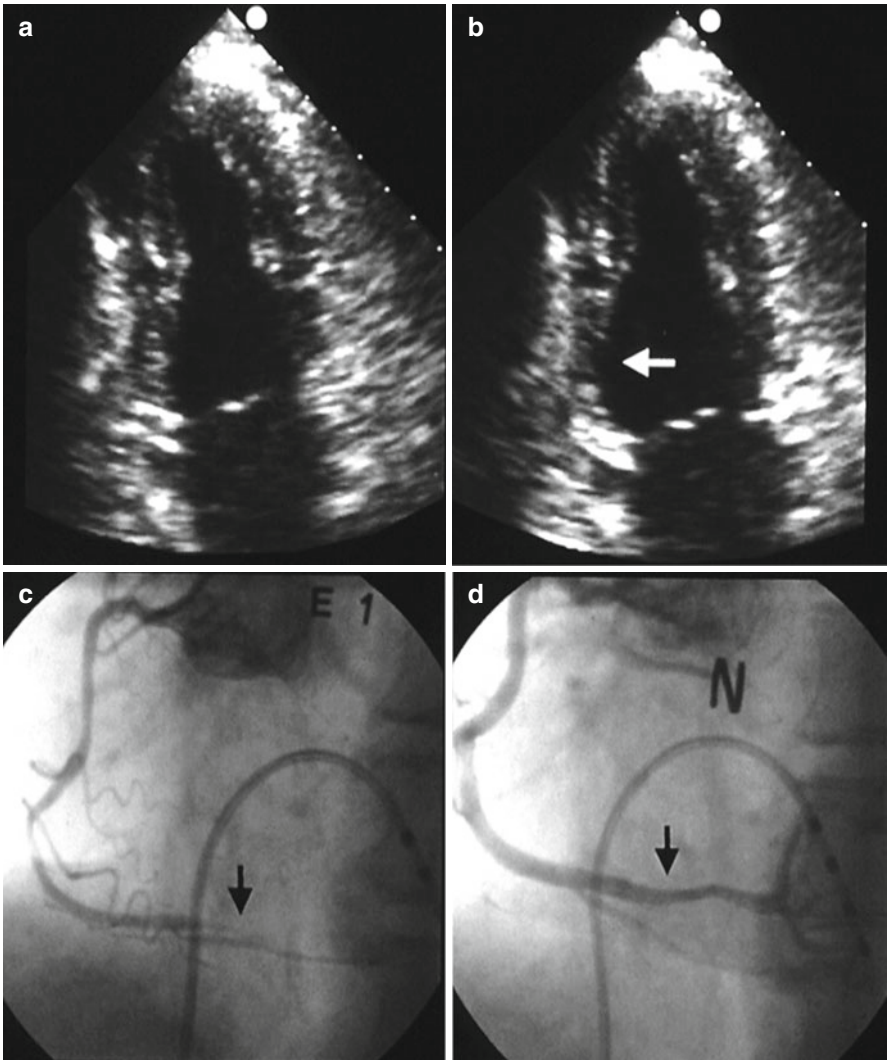


Fig. 16.3 Representative example of ergonovine echocardiography (**a**, **b**) and invasive spasm-provocation testing during diagnostic coronary angiography (**c**, **d**) in a 47-year-old man. Left ventricular wall motion at end-systole recorded in the apical two-chamber view was demonstrated (**a**, **b**). Compared with the basal status (**a**), prominent loss of systolic thickening in the inferior wall developed with an ergonovine dose of 0.15 mg (**b**, *white arrow*), which was compatible with myocardial ischemia due to coronary artery spasm in the right coronary artery territory. Coronary angiogram taken 3 days later revealed no significant fixed disease. Intravenous injection of ergonovine (*E1*) provoked total occlusion of the distal right coronary artery (*C*), and the angiogram after injection of nitroglycerin (*N*) showed completely normal right coronary artery and relief of total occlusion (**d**) (Adapted from Song et al. [16], with permission)

Table 16.1 Potential advantages and disadvantages of spasm-provocation testing in the catheterization laboratory and at the bedside

	Advantages	Disadvantages
Provocation test during angiography	Angiographic demonstration of reversible vasoconstriction	Relatively late and insensitive ischemic markers (chest pain, electrocardiographic changes)
	Direct intracoronary injection of nitroglycerin	Invasive, perturbs vasomotor tone
	Temporary pacemaker backup	Injecting contrast agent into coronary circulation
		Continuous monitoring of whole ischemic process impossible
Bedside ergonovine echocardiography	Detection of regional wall motion abnormalities: sensitive and specific marker of myocardial ischemia, continuous monitoring, early detection and termination of ischemic cascade	Intracoronary injection of nitroglycerin impossible
	Noninvasive, does not perturb vasomotor tone	Temporary pacemaker backup impossible
	Repeat and follow-up studies	Dependent on acoustic window

degree of skill on the part of the operator [8]. Angiographic demonstration of reversible total occlusion of one of the major epicardial coronary arteries is in itself enough for a diagnosis of coronary vasospasm. If, however, angiography reveals only moderate vasoconstriction, as occurs more frequently in the daily clinical practice of provocation testing, other indexes of myocardial ischemia are necessary before a definite diagnosis of coronary vasospasm can be made. In the catheterization laboratory, the development of chest pain and electrocardiographic changes, well known as relatively late events in ischemic cascade, are classic markers of myocardial ischemia. The usual 3- to 4-min wait after each injection of the drug before repeat angiography without sensitive monitoring of ischemic cascade in the catheterization laboratory may also contribute to the potential danger of the procedure. This is because the development of serious arrhythmia or myocardial infarction depends on the duration of the preceding myocardial ischemia during spasm provocation.

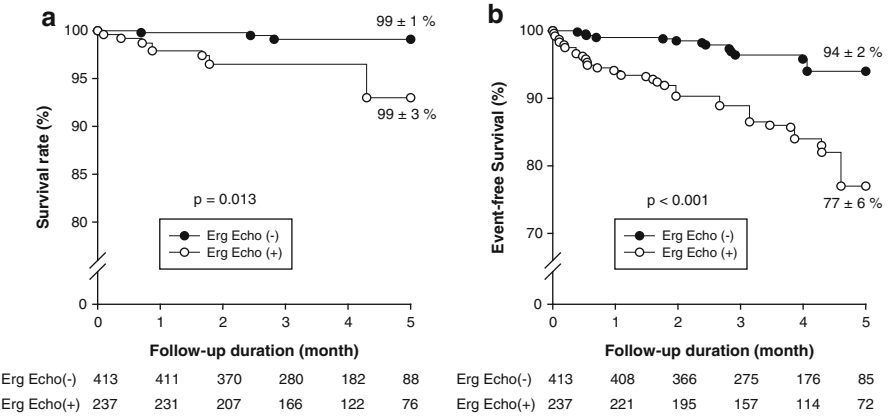
In addition to concerns about disturbing vasomotor tone with the catheter, injecting a contrast agent into the coronary circulation during a severe ischemic episode may increase the risk of the procedure. Myocardial imaging rather than angiography has been proposed as a more sensitive, more specific, and safer method of identifying coronary vasospasm by some physicians. The importance of intracoronary nitroglycerin for reversing an intractable vasospasm that is not responsive to sublingual and intravenous nitroglycerin has been reported [19, 20], but other published investigations indicate that intracoronary nitroglycerin is not a prerequisite for spasm-provocation testing [8–18].

The most important advantage of ergonovine echocardiography is its capacity for detecting regional wall motion abnormalities, which are sensitive and specific

markers of myocardial ischemia, even before the appearance of chest pain or electrocardiographic changes. During ergonovine echocardiography, the wall of the left ventricle can be continuously monitored, with early termination of myocardial ischemia based on the detection of regional wall motion abnormality; this is a potential and theoretical advantage of the test. In our study [8, 16], less than half of the patients with definite wall motion abnormalities showed ECG changes suggestive of myocardial ischemia, which is compatible with the premise described above. Further multicenter investigation is needed to determine whether early detection and termination of myocardial ischemia based on regional wall motion abnormalities can completely obviate the need for temporary pacemaker backup. Continuous monitoring of the ventricular wall motion without interruption during ergonovine echocardiography can contribute to the detection of multivessel coronary spasm involving the right and left coronary arteries. This is almost impossible during invasive spasm-provocation testing in the catheterization laboratory, as termination of spasm in one coronary artery territory is necessary. Simultaneous catheterization of both coronary ostia for demonstration of potential multivessel spasm is not a routine procedure due to low clinical feasibility.

16.5 Potential Clinical Impact

Noninvasive ergonovine stress echocardiography is an effective and reasonably safe way of diagnosing coronary vasospasm in routine clinical practice for patients visiting the outpatient clinic [16] or for those admitted to the coronary care unit under the clinical impression of unstable angina pectoris [15]. Although clinical usage of spasm-provocation testing has decreased significantly in Western countries and spasm-provocation testing is no longer a routine diagnostic procedure, one outcome study [21] reveals significantly higher mortality and event rates with a positive result of ergonovine stress echocardiography (Fig. 16.4) in patients with near-normal coronary angiogram or in those with negative stress test results for significant fixed stenosis. These results demonstrate the powerful prognostic implication of noninvasive ergonovine stress echocardiography in routine daily practice for differential diagnosis of chest pain syndrome. As this test provides an effective and powerful means of risk stratification on the basis of the presence of provocable ischemia in patients with no evidence of significant fixed coronary stenosis, either by direct invasive or noninvasive (by 64-slice computed tomography) coronary angiography or by noninvasive stress testing, consideration of ergonovine stress echocardiography for complete differential diagnosis of mechanisms of myocardial ischemia should be encouraged in various clinical scenarios involving patients with chest pain syndrome [22], such as patients with angiographically normal coronary arteries and a history of angina at rest, aborted sudden death [23], flash pulmonary edema [24], or suspected left ventricular apical ballooning syndrome [25]. The usefulness of the ergonovine test in monitoring the efficacy of antianginal therapy has been documented [26], but its clinical value remains uncertain. It is probably inappropriate to use the test in patients in whom the diagnosis is already established by clinical history or with concomitant ischemia in the presence of



Erg Echo(-)	413	411	370	280	182	88
Erg Echo(+)	237	231	207	166	122	76

Erg Echo(-)	413	408	366	275	176	85
Erg Echo(+)	237	221	195	157	114	72

Fig. 16.4 Survival (**a**) and event-free survival rates (**b**) according to the results of ergonovine echocardiography (*Erg Echo*) in patients with near-normal coronary angiogram or negative stress test results for significant fixed stenosis. (−), negative test; (+), positive test (Adapted from Song et al. [21])

angiographically documented coronary artery disease. The test can be less safe in patients with uncontrolled hypertension and previous stroke [27]. It is also important to consider vasospasm – and, if appropriate, vasospasm testing – in several clinical settings remote from the cardiology ward when ergometrine-containing or serotonin-agonist drugs are routinely given and may occasionally precipitate "out-of-the-blue" cardiological catastrophes mediated by coronary vasospasm: ergometrine given in the obstetric clinic to reduce uterine blood loss in the puerperium phase [28–33] or bromocriptine given for milk suppression [34, 35], sumatriptan or ergometrine used in neurology for migraine headaches [36–39], 5-fluorouracil and capecitabine (an oral 5-fluorouracil prodrug) given as chemotherapy in (breast and colon-rectal) cancer [40–44], and, with increasing frequency, cocaine as a cause of chest pain in the ER [44, 45]. In all these conditions, it is essential to think of vasospasm so as to recognize it.

16.6 Pitfalls

In spite of the contrary evidence in the literature [16, 18, 46], there is concern on the safety of noninvasive intravenous ergonovine provocative testing, and – according to ESC guidelines 2013 [47] – as fatal complications may occur with intravenous injection of ergonovine, due to prolonged spasm involving multiple vessels, the intracoronary route is preferred.

16.7 Clinical Guidelines

Provocative testing with intravenous ergonovine is not recommended in patients without known coronary artery anatomy nor in patients with high grade obstructive lesions on coronary arteriography. Diagnostic tests proposed in suspected vasospastic angina are listed in Table 16.2 [47].

Table 16.2 Diagnostic tests in suspected coronary vasospasm

Recommendations	COR	LOE
An ECG is recommended during angina if possible	I	C
Coronary arteriography is recommended in patients with characteristic episodic resting chest pain and ST-segment changes that resolve with nitrates and/or calcium antagonists to determine the extent of underlying coronary disease	I	C
Ambulatory ST-segment monitoring should be considered to identify ST deviation in the absence of an increased heart rate	IIa	C
Intracoronary provocative testing should be considered to identify coronary spasm in patients with normal findings or nonobstructive lesions on coronary arteriography and the clinical picture of coronary spasm to diagnose the site and mode of spasm	IIa	C

From Montalescot et al. [47], ESC guidelines 2013
COR class of recommendation, *LOE* level of evidence

In out-of-hospital cardiac arrest, there is no evidence of heart disease in 5 % of patients. In them, according to 1997 guidelines, "ergonovine test during coronary angiography is recommended but not mandatory" [48]. Recent data from the Japanese Coronary Spasm Association suggest a 6 % incidence of coronary vasospasm in survivors of out-of-hospital cardiac arrest from cardiac cause [49]. These patients who survived cardiac arrest are a high-risk population in spite of maximal medical therapy and should be identified. This represents about 10 % of indications to ergonovine testing in the stress echo lab [46], but more extensive experience is needed to bring this currently "off-label" indication into guidelines. In the guidelines for diagnosis of coronary spastic angina by the Japanese Circulation Society, drug-induced coronary spasm provocation testing with ergonovine (or acethylcholine) is recommended only with invasive evaluation during cardiac catheterization, with class 1 indication in patients in whom vasospastic angina is suspected on the basis of symptoms, but in whom coronary spasm has not been diagnosed by non-invasive evaluation (including exercise-ECG test, Holter and hyperventilation test) [50].

Table of Contents Video Companion

See stress echo primer, cases 13 to 16.
See also, in the section "Illustrative cases: case number 12" (by Jae-Kwan Song, MD, Seoul, South Korea).
See also in selected presentations: Vasospasm in the echo lab: witches are back.
Springer Extra Materials available at http://extras.springer.com/2015/978-3-319-20957-9

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Hyperventilation, Handgrip, Cold Pressor, and Squatting Stress Echocardiography

17

Rodolfo Citro and Eugenio Picano

17.1 Hyperventilation Test

Hyperventilation tests have been mainly used in clinical practice as a provocative test for coronary artery vasospasm in patients with suspected or documented vasospastic angina [1–4]. The rationale for the use of hyperventilation testing for this purpose is based on the demonstration that, in susceptible patients, hyperventilation may trigger a vasospasm of a major epicardial coronary artery associated with chest pain and ischemic electrocardiographic changes similar to those observed during spontaneous anginal attacks [1].

Prolonged, vigorous overbreathing decreases plasma hydrogen ion concentration, leading to metabolic alkalosis, which can trigger coronary artery spasm [1]. The increase in arterial blood pH reaches the peak at the end of hyperventilation, while ST-segment elevation usually develops during the recovery phase early after the end of the test, when arterial pH is already decreasing toward baseline but is still significantly elevated compared to the basal values [4].

Another mechanism of coronary spasm in this setting can ensue, with increases in intracellular concentration of calcium ions following a decrease in the concentration of hydrogen ions, which compete with calcium for active transmembrane transport [5] (Fig. 17.1). The increase in intracellular calcium concentration can in turn elicit a vasospastic constriction of smooth muscle cells in susceptible coronary epicardial arteries [5].

The patient hyperventilates for 5 min, with increased frequency (30 per min) and depth of breathing (Fig. 17.2). The time window of positivity usually occurs 1–5 min after the end of hyperventilation, therefore without degrading the quality of echocardiographic imaging.

The sensitivity of the test is markedly affected by the spontaneous activity of the disease; when spontaneous attacks occur frequently, a positive response to hyperventilation is observed in more than 80 % of patients, while the sensitivity of the test decreases to 50 % or less in patients with less active disease [1, 3, 4, 6–10]. Since hyperventilation may produce chest pain and pseudoischemic changes in

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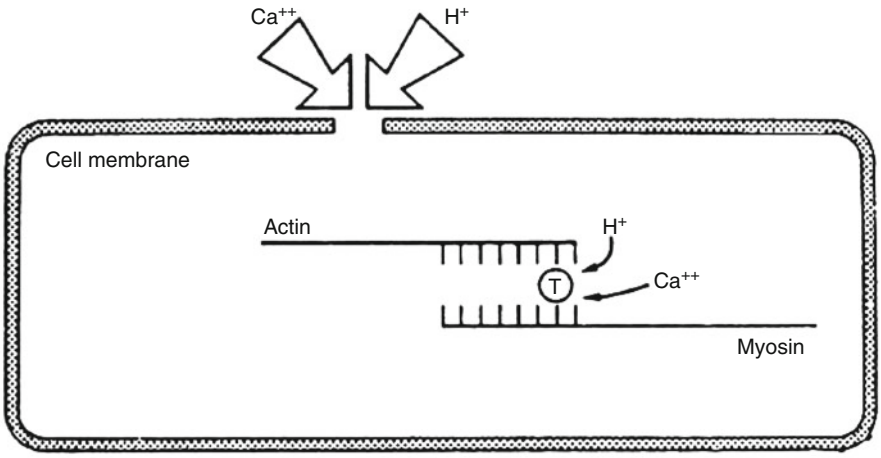

Fig. 17.1 The mechanism of contraction induced by alkalosis in a smooth muscle cell. With a reduced concentration of hydrogen ions, more calcium enters the cell from the outside and more intracellular calcium reaches the regulatory troponin site, triggering contraction (Modified from [5], with permission)

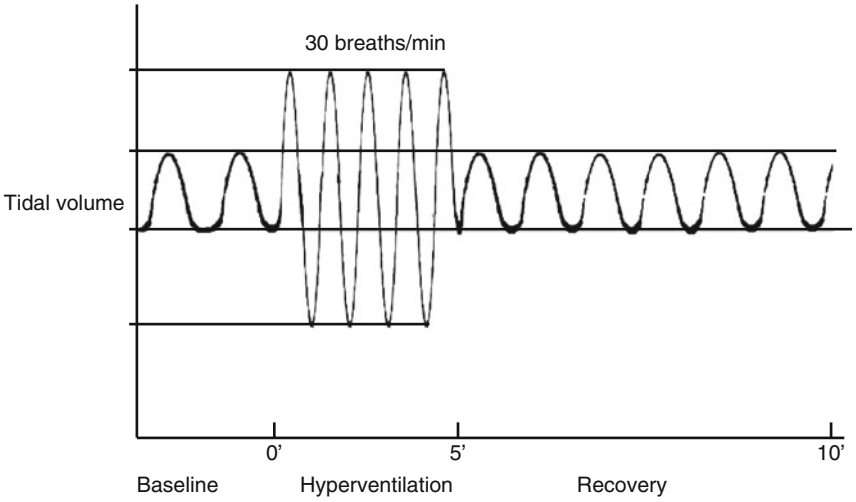

Fig. 17.2 Protocol of the hyperventilation stress echocardiography test

vasospasm, echocardiographic monitoring during the test can be particularly useful to demonstrate normal regional wall motion and thickening and therefore rule out the diagnosis of vasospastic myocardial ischemia. In patients with variant angina, hyperventilation can also be used to predict the ability of antianginal drugs to prevent spontaneous attacks and to select an effective medical treatment [8]; moreover, if the test yields negative results during long-term follow-up, this may indicate a spontaneous remission of the disease [8].

The hyperventilation test has shown excellent safety and satisfactory feasibility associated with good sensitivity (slightly lower than ergometrine) and specificity for the diagnosis of vasospastic angina (Table 17.1). It is considered slightly safer than the ergonovine test because the stimulus to vasospasm wanes as soon as the intracellular pH returns to normal; however, one should be aware that consequences of ischemia are largely independent of the form of provocation [11, 12]. Both total duration of the test and the imaging time are shorter with hyperventilation (about 10 min) than with ergonovine (approximately 20 min) (Table 17.1).

It can therefore be a useful test for the diagnosis of vasospastic angina in outpatients and in patients with contraindications to ergometrine such as arterial hypertension or previous stroke (Table 17.1). It may unmask the vasospastic origin of symptoms in patients with syncopal angina [13, 14]. A case of reproducible postcoital hyperventilation-induced coronary vasospasm, within minutes to hours of sexual activity, was described in a woman with chest pain and idiopathic recurrent pulmonary edema, reproduced by hyperventilation test and abolished by calcium-antagonists and nitrates [15]. However, hyperventilation is demanding for the patient who may not be able to complete it and is contraindicated in epilepsy. In patients with typical symptoms, a positive response to hyperventilation is diagnostic, thus avoiding the need to perform ergometrine testing. In patients with a negative or nondiagnostic response to hyperventilation but with symptoms suggesting vasospastic angina, ergonovine testing might be performed since the sensitivity of the hyperventilation test in patients with sporadic symptoms is suboptimal and a negative response cannot rule out the presence of vasospastic angina. In the guidelines for diagnosis of coronary spastic angina by the Japanese Circulation Society, non-invasive coronary spasm provocation testing with hyperventilation test is recommended in patients suspected of having vasospastic angina with a low (class IIa) or high (class IIb) frequency of attacks, but in whom coronary spasm has not been diagnosed by non-invasive evaluation (including exercise-ECG test, Holter and hyperventilation test) [16].

Hyperventilation testing can also be used to assess the efficacy of medical therapy, such as endothelium-protective estradiol supplementation in variant angina [17].

Novel, promising approaches combine mild hyperventilation followed by exercise [17] or the cold pressor test [18–21] to enhance the test sensitivity for vasospasm detection. Conceptually, this approach is similar to the combined stress approach for the

Table 17.1 Tests for coronary vasospasm

	Hyperventilation	Ergometrine
Sensitivity	++	+++
Specificity	+++	+++
Safety	+++	++[+]
Imaging time	10 min	20 min
Arterial hypertension	Yes	No
Epilepsy	No	Yes
Previous stroke	Yes	No
Physically deconditioned	No	Yes

diagnosis of minor forms of fixed coronary artery stenosis. In the latter case, a vasodilator stress reducing subendocardial flow supply through steal phenomenon (dipyridamole) is administered, and if the stress is negative, a second additive stressor (exercise or dobutamine), with a different mechanism of action, is administered on the shoulder of the first one to increase myocardial oxygen demand [22, 23]. In the diagnosis of coronary vasospasm, there is a hierarchy of testing for stressor potency with ergometrine being the most potent, hyperventilation the intermediate, and exercise and cold pressor the least potent [9] (Fig. 17.3). Since hyperventilation acts in a different fashion than exercise and cold, the sensitivity for vasospasm critically increases with the combination of hyperventilation and either the cold pressor or exercise test (Fig. 17.3).

17.2 Handgrip Stress Echocardiography

Handgrip (HG) is an isometric exercise stress test with hemodynamic effects on both the systemic and coronary circulation. HG induces sympathetic activation and catecholamine release resulting in increased preload, heart rate, and end-systolic wall stress with a modest increment in myocardial oxygen consumption [23].

In normal conditions, the coronary tone depends on the balance between vasoconstriction and vasodilation mediated by α and β-receptors, respectively, and by

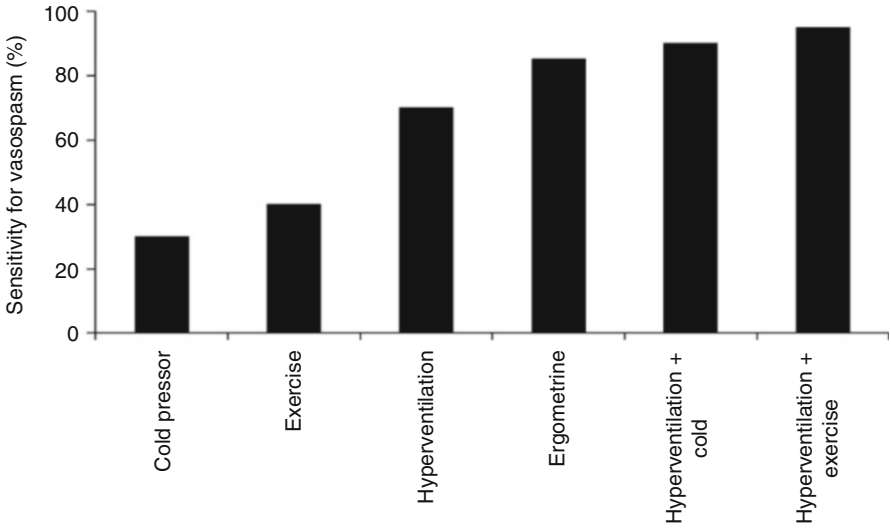

Fig. 17.3 The hierarchy of test sensitivity for the diagnosis of coronary artery disease. The continuous transverse line indicates the fixed ceiling of coronary flow reserve, which is not reduced in this ideal case of pure vasospastic angina. The *dashed lines* indicate the fluctuations of coronary tone. They occur spontaneously (*far left*, variant angina) or can be provoked by stress testing. The power of stress testing is indicated by the depth of the *dashed line*. Only tests arriving below the line of oxygen consumption at rest evoke ischemia. Cold and exercise are relatively weak stressors when used alone, but they can critically potentiate the sensitivity of hyperventilation

endothelial function integrity. Conversely, atherosclerosis of the coronary arteries causes endothelial dysfunction with the loss of β-receptor vasodilatation response and predominance of the α-receptor-mediated vasoconstriction effect [24–26].

Owing to its ability to increase cardiac workload and vasoconstriction on atherosclerotic coronary arteries, HG has been proposed as a useful test to detect myocardial ischemia in patients with known or suspected coronary artery stenosis. However, HG has a low sensitivity and specificity for detecting the presence of coronary artery disease (CAD) if used alone. Isometric exercise has been proposed in addition to conventional exercise stress test as it is easy to perform during echocardiography [27–30].

At present, no univocal or standardized study protocol has been defined yet. The majority of studies reported the combination of HG with dobutamine stress echocardiography. First, the maximum isometric muscular effort of the patient is preliminary measured [31]. The subject holds the dynamometer in the hand to be tested, with the arm at right angles and the elbow by the side of the body. The handle of the dynamometer is adjusted if required – the base should rest on first metacarpal (heel of palm), while the handle should rest on middle of four fingers. When ready, the subject squeezes the dynamometer with maximum isometric effort, which is maintained for about 5 s. No other body movement is allowed. The subject should be strongly encouraged to give a maximum effort. Dobutamine is performed according to a standard protocol with progressively increasing doses of 5, 10, 20, 30, and 40 γ/kg/min every 3 min. The peak dobutamine is defined by the achievement of the target heart rate (85 % of the maximum age-adjusted heart rate) or the maximal dosage of 40 μg/kg/min. After 3 min at peak, HG is performed at 50 % of the maximum effort for 1 min. Clinical symptoms, blood pressure, ECG, and regional wall motion are monitored by echocardiography at the beginning and at the end of the isometric effort. Subsequently, if target heart rate is not reached, the administration of atropine is required. If development of new or worsening wall motion abnormalities, significant arrhythmias, hypotension, severe hypertension, or intolerable symptoms occurs, the test is considered positive and interrupted.

HG appears a safe and feasible additional test to standard pharmacological stress protocol, which may be useful in daily clinical practice to improve diagnostic accuracy, to decrease drug dosage and study duration, and to avoid atropine administration with dobutamine, adenosine, or dipyridamole [32–36]. This may be particularly advantageous if we consider that atropine is contraindicated in some categories of patients (prostatic disease or glaucoma) and has been associated with potentially severe side effects. However, larger studies are warranted to confirm these data obtained in relatively small series.

17.3 Cold Pressor Stress Echocardiography

Cold pressor test (CPT) induces sympathetic tone activation with increase in myocardial oxygen demand also due to pain sensation. In normal conditions, catecholamine release results in endothelial-dependent (through β-adrenergic receptor stimulation) and endothelial-independent vasodilatation (mediated by α2-adrenergic

activity on smooth muscle cell layer). In addition, a flow-dependent vasodilatation secondary to endothelial increased nitric oxide release occurs.

In patients with coronary artery spasm due to endothelial dysfunction symptomatic for variant angina, an impairment of endothelial-dependent and flow-mediated vasodilatation or even a paradoxical vasoconstriction can be unmasked by CPT.

CPT has been proposed as a noninvasive diagnostic tool in a peculiar setting of patients with suspected variant angina associated with standard transthoracic echocardiography for the assessment of wall motion abnormalities [36].

After baseline measurement of blood pressure, 12-lead ECG and standard two-dimensional echocardiography are performed. Subsequently, patients immerse their right (or left) hand in cold water (3 °C). The CPT is stopped after 4 min. Blood pressure measurement and the 12-lead ECG are obtained immediately before withdrawing the hand from cold water. Continuous echocardiographic monitoring for assessing changes in regional wall motion is performed during CPT and the first 10 min after finishing the procedure. During the test, blood pressure measurements and 12-lead ECG are repeated every 2 min. In addition, flow mapping of the distal left anterior descending coronary artery (LAD) by transthoracic Doppler echocardiography can also be performed to assess noninvasively coronary flow reserve soon after CPT.

However, the sensitivity of the CPT alone in predicting variant angina is low. For this reason, a combination of hyperventilation test for 6 min (as previously described) immediately followed by CPT for 2 min has been introduced to improve diagnostic accuracy [37]. The combined test can induce coronary spasm, eliciting segmental wall motion abnormalities, which allows to diagnose vasospastic angina and to identify the involved coronary artery [21, 37].

Although the tests assessing myocardial perfusion have shown greater sensitivity in diagnosing coronary vasospastic angina [37], the combination of CPT with hyperventilation stress echocardiography can be a useful alternative as they show a higher specificity due to the ability to elicit mechanical dysfunction [20].

The evaluation of coronary flow reserve instead of wall motion abnormalities after CPT has been proposed as an alternative diagnostic tool for coronary artery spasm in patients with variant angina. Of note, despite endothelial dysfunction, ECG changes or clinical symptoms were rarely detected [38]. Moreover, noninvasive assessment of coronary flow reserve avoids any adverse effects related to angiography. In the guidelines for diagnosis of coronary spastic angina by the Japanese Circulation Society, non-invasive coronary spasm provocation testing with CPT is recommended (class IIb) in patients who are in stable conditions and suspected of having coronary vasospasm [16].

17.4 Squatting Stress Echocardiography

Squatting test is a type of stress echocardiography performed with the patient in squatting position. Patients are asked to squat for 2 min. The body weight is placed over the heels and the chest maintained in a nearly vertical position. Subjects are

instructed to maintain a normal breathing pattern, and blood pressure, heart rate, and echocardiogram are recorded. Patients are then asked to stand up and the above parameters are repeated.

Squatting determines compression of leg veins inducing augmented venous return to the right heart. In addition, when the subject assumes the squatting position, an increase in blood pressure due to femoral artery kinking can be observed. These hemodynamic effects lead to left ventricular enlargement and increased stroke volume. Owing to the ability to increase afterload and preload considered as the major determinants of myocardial oxygen consumption, squatting stress echocardiography has been proposed as a provocative test of ischemia and may induce wall motion abnormalities detectable by echocardiography in patients with significant CAD [39–41]. Experience is very limited to date.

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Grading of Ischemic Response

18

Quirino Ciampi, Ayana Arystan, and Eugenio Picano

The need for a dichotomy (yes/no) classification of the results of both provocative tests (positive or negative) and coronary angiography (disease present or absent) in conventional sensitivity/specificity analysis of test results has at least three important limitations [1]:

1. Coronary artery disease is not an all-or-nothing condition; a binary classification requires arbitrary threshold criteria and creates artificial distinctions in coronary artery disease, which in reality shows a continuous spectrum of severity.
2. Sensitivity and specificity values tend to be affected by the disease's distribution in the study population; a sample distribution with a high frequency of mild disease will be placed centrally near the threshold values, where scatter is more likely to lower sensitivity and specificity [2].
3. Percent diameter narrowing is not an adequate standard for quantifying stenosis severity in clinical studies [3]; in unselected populations, this anatomical parameter has a poor correlation with the coronary flow reserve. Thus, coronary artery disease is a complex phenomenon that cannot be described adequately by means of a simple normality versus disease paradigm; there are in fact significant differences as regards the degree and the extent of disease that carry important implications for both therapy and prognosis. A stress test should not only predict the presence or absence of coronary disease but should also stratify disease severity. The diagnosis of myocardial ischemia by stress echocardiography should be delimited by time and space coordinates of the circumferential (horizontal) extent of ischemia (x-axis), the transmural (vertical) depth of ischemia (y-axis), and the ischemia-free stress time (i.e., the time from the start of stress to the appearance of ischemia; z-axis) (Fig. 18.1).

The anatomical–functional degree of coronary artery disease is related to the area included in this three-axis system. From the theoretical point of view, poststress imaging (e.g., postexercise echocardiography) emphasizes the importance of the extent of asynergy. Time to ischemia is more informative in pharmacological tests in which

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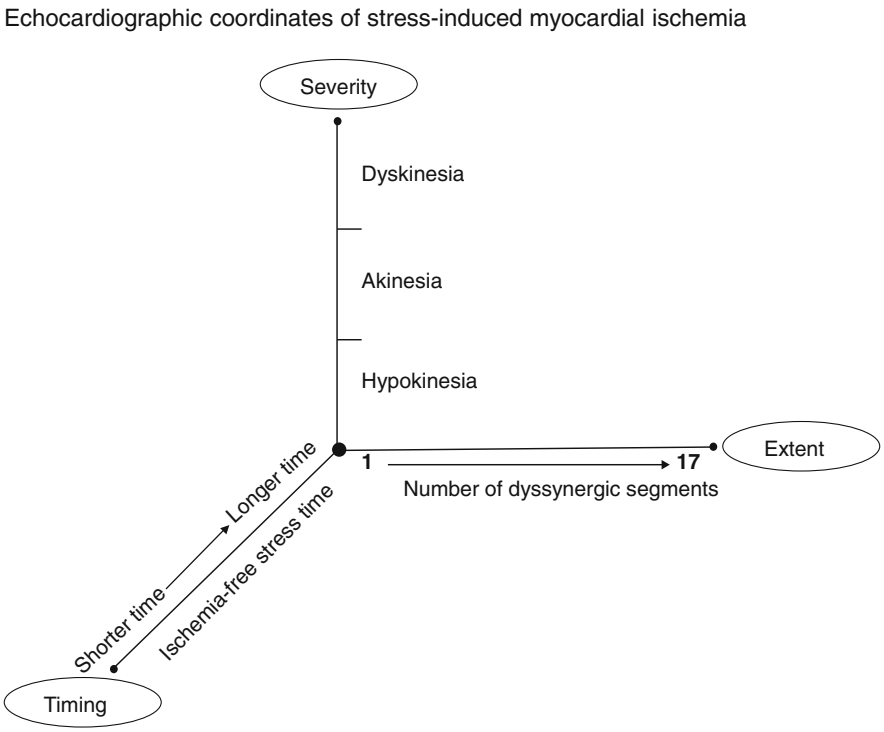

Fig. 18.1 Space and time coordinates of the ischemic response during stress echocardiography: *x-axis*, the number of segments in which the left ventricle is dyssynergic; *y-axis*, the severity of dyssynergy that is correlated to the degree of coronary flow impairment; *z-axis*, ischemia-free stress time

continuous monitoring of images during stress is obtained and the appearance of asynergy is the absolute end point; this usually makes it impossible to observe the effect of coronary stenoses that are less severe than the one that first provoked ischemia. Both parameters – time and space – can be usefully combined to describe the test's degree of positivity: the extent of dyssynergy reflects the extent of coronary artery disease (Fig. 18.2), whereas the time to ischemia is better related to the degree of stenosis in the ischemia-producing vessel. Another less common sign of disease severity is represented by slow and/or incomplete recovery after interruption of the stress and by the appearance of stress-induced arrhythmias. Other signs of disease severity, apart from short stress time and slow recovery (antidote resistance), include dyskinesis, heterozonal positivity (multiple coronary regions), and left ventricular dilatation.

18.1 Degree of Asynergy

The degree of subendocardial hypoperfusion and the transmural effect of ischemia are reflected in the severity of regional dyssynergy and hypokinesis indicating a milder and transmurally less extensive ischemia in comparison to akinesis and dyskinesis [4].

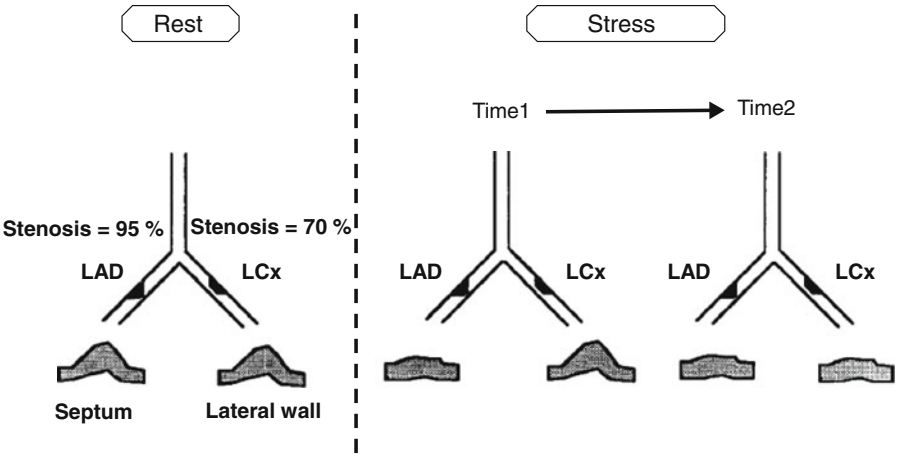

Fig. 18.2 Relationship between stress-induced asynergy and the extent of coronary artery disease. The extent of disease is best reflected by the extent of dyssynergy. A greater extent of coronary artery disease is mirrored by a greater extent of asynergy during stress. *LAD* left anterior descending artery, *LCx* left circumflex artery

18.2 Extent of Asynergy

The extension of the risk zone can be identified and quantified by evaluating the number of asynergic segments during stress. The wall motion score index in resting conditions and at peak stress represents an integrated estimation of spatial extent and of the severity of asynergy. Also, it is linearly correlated to the extent and severity of angiographically assessed coronary artery disease and to the perfusion defect simultaneously assessed with radionuclide scintigraphy [5–7] (Fig. 18.3). In patients with previous myocardial infarction, the appearance of homozonal asynergy during stress (in the site of necrosis) suggests that a critical residual stenosis is present in the infarct-related vessel [8, 9], whereas the presence of heterozonal asynergy identifies multivessel coronary artery disease [10–12]. However, a low wall motion score index or homozonal positivity cannot rule out multivessel coronary artery disease. This may be due to the test protocol employed in stress echocardiography, since the development of a new wall motion abnormality is an absolute end point of the test, chosen in order to prevent potential complications from severe or prolonged ischemia.

18.3 Ischemia-Free Stress Time

The most important diagnostic information extracted from the exercise test is the cardiac workload capable of inducing electrocardiographically [13] or echocardiographically [14] assessed myocardial ischemia. For a given extent and severity of induced ischemia, patients with more severe coronary artery disease and worse

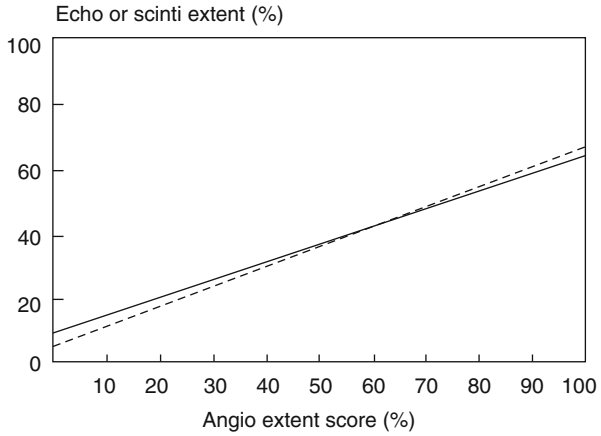

Fig. 18.3 Relationship between angiographically assessed coronary artery disease (*x-axis*) with dobutamine stress (*y-axis*) and the extent and severity of the perfusion defect during sestamibi scintigraphy or wall motion dysfunction during simultaneous echocardiographic imaging with dobutamine stress. *Solid line* scintigraphic score, *dashed line* echocardiographic score (From Marwick et al. [7], with permission)

prognosis are identified on the basis of exercise time, corresponding to the level of stress necessary to provoke ischemia.

The positive response on the basis of ischemia-free stress time (i.e., the time lag between the start of stress and the onset of echocardiographically detected ischemia) can also be stratified by exercise-independent tests. From the theoretical point of view, the step-by-step increase in heart rate induced by atrial pacing or the administration of scalar doses of a drug represents a graduated stress, similar to a multistage exercise test. The amount of stress capable of provoking myocardial ischemia (expressed as doses of drugs, heart rate, duration of exercise, or – for all stresses – ischemia-free stress time) is inversely related to the severity of coronary artery disease [15–22]. An early positivity with the lower dose of the drug indicates a more severe coronary artery disease from the anatomical [18, 19], functional [20–22], and prognostic points of view [23], as compared to late positivity with a higher dose. In single-vessel disease, severity of coronary stenosis and impairment in regional flow reserve are greater when the stress-induced dyssynergy appears earlier during the test (Fig. 18.4). In patients with a positive dipyridamole echocardiography study, regional coronary flow reserve (measured by dynamic positron emission tomography) correlated well with dipyridamole time, but not with the peak wall motion score index [21] (Fig. 18.5). For dobutamine and exercise or pacing, the shorter the ischemia-free stress time was, the more severe the underlying stenosis provoking ischemia was [17–20]. Patients with low-dose positivity are also at higher risk for subsequent cardiac events (Fig. 18.6).

Clearly, for proper recognition of the ischemia-free stress time, continuous echocardiographic monitoring is needed in order to obtain a cinematographic representation of ischemic stress. Poststress imaging cannot provide any information on the

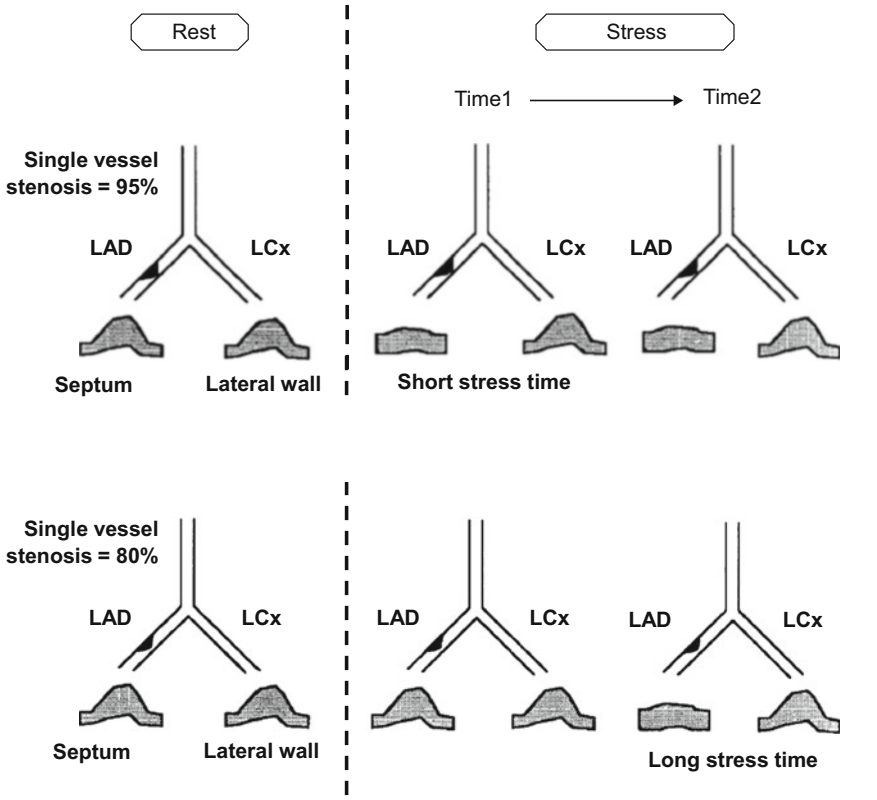

Fig. 18.4 Relationship between time of appearance of asynergy and the severity of coronary artery disease. The sensitivity of disease is best reflected by the timing of dyssynergy. Higher degrees of stenosis are mirrored by an earlier appearance of synergy during the test. *LAD* left anterior descending artery, *LCx* left circumflex artery

timing of asynergy during stress; the representation of ischemia in this case is photographic rather than cinematographic. In fact, two images are compared, one in basal conditions and the other after stress. The lack of the time coordinate reduces the overall diagnostic information provided by the stress test. The stress time is also a useful parameter to assess the effects of both antianginal therapy and revascularization procedures. These therapeutic procedures might determine a full negativity of a previously positive test, but when the test remains positive after the intervention, the potential beneficial effects can be assessed on the basis of a reduction in the peak wall motion score index and an increase in ischemia-free stress time. During both exercise and pharmacological stress, the echocardiographic evaluation of the wall motion score index and particularly of ischemia-free stress time allows an objective evaluation of either pharmacological [24–28] or mechanical [29–32] therapy. In addition, serial assessment of stress echocardiographic response on repeated testing allows one to separate angiographic progressors and nonprogressors

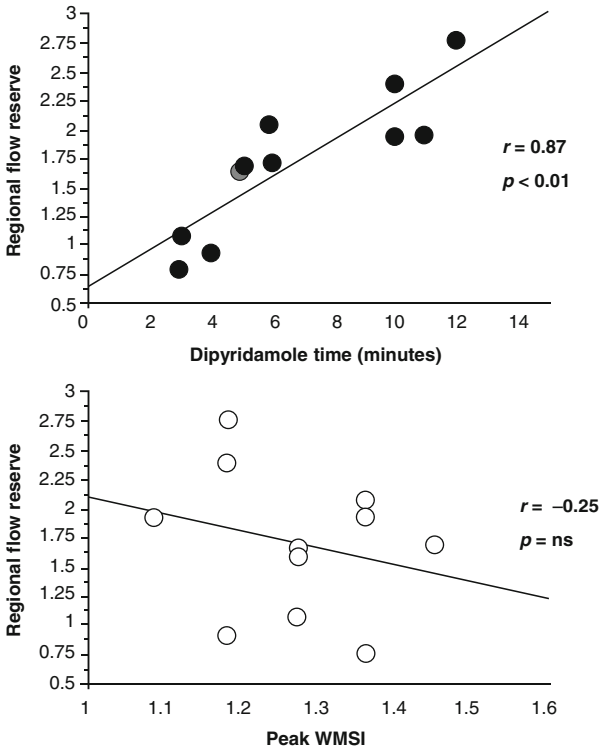

Fig. 18.5 Relationship between regional coronary flow reserve (*ordinates*) and either dipyridamole time (*abscissae*, *top*) or peak wall motion score index (*MWMSI*; *abscissae*, *bottom*) in patients with coronary artery disease and positive dipyridamole echocardiographic test. The relationship is significant only with dipyridamole time (From Picano et al. [21], with permission)

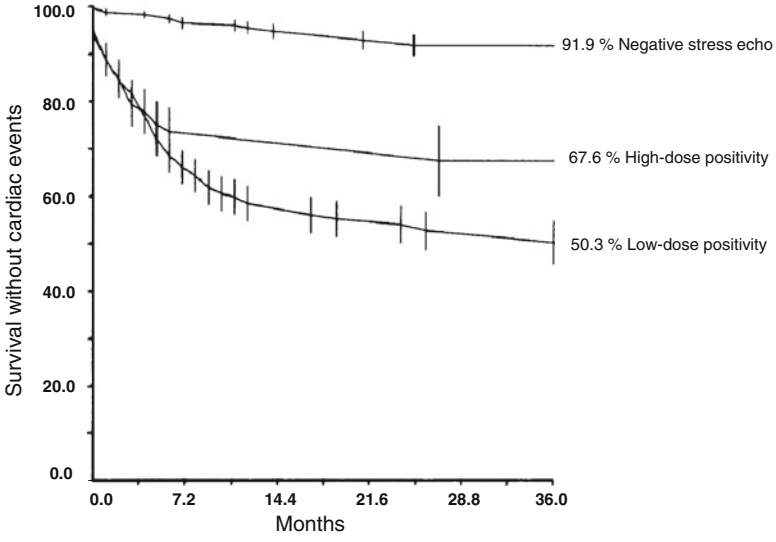

Fig. 18.6 Cumulative survival rates in patients free of cardiac events in group A (negative dipyridamole echocardiographic test), group B (positive high-dose echocardiographic test, i.e., with ischemia-free stress time longer than 8 min), and group C (positive low-dose dipyridamole echocardiographic test) (From Picano et al. [23], with permission)

efficiently, simply by taking into account the presence, timing, extent, and severity of stress-induced abnormalities of wall motion [33]. The prediction of angiographic progression is substantially more accurate with stress echocardiography than with exercise electrocardiography [34].

18.4 Slow or Incomplete Recovery

In 5–10 % of tests, the interruption of stress – cessation of exercise or, in the case of pharmacological tests, antidote administration – fails to reverse the induced ischemia. A longer recovery time (i.e., the time from the end of stress to the return to basal function) indicates more severe coronary artery disease. A possible explanation for a slow recovery may be the prolonged ischemia or greater severity of the coronary lesions underlying reperfusion. From the clinical point of view, this phenomenon is almost always associated with severe or extensive coronary artery disease [35].

18.5 False Friends of Stress-Induced Ischemia Severity: Arrhythmias and Hypotension

The administration of stress may induce arrhythmias for the stress per se or secondary to the induced ischemia. For example, adenosine and dipyridamole, albeit rarely, can provoke atrial standstill up to asystolia for the depressor effect of adenosine on the impulse formation and conduction [36]. Other stresses, such as dobutamine, have significant arrhythmogenic effects independently of ischemia [37–39] and can induce transient atrioventricular block for a neurally mediated vagal reflex [40]. These primary arrhythmic phenomena have no diagnostic value in the assessment of coronary artery disease; however, they may be useful ancillary markers to identify arrhythmic tendencies, which should be confirmed by other diagnostic evidence (such as Holter monitoring or the head-up tilting test). For instance, in patients with transient atrioventricular block during a negative dobutamine stress, the head-up tilting test is frequently positive [40].

The significance of stress-induced hypotension is different for exercise and pharmacological stress: during exercise, a fall in blood pressure implies the presence of acute cardiac insufficiency and is very often associated with advanced forms of coronary artery disease [13, 14]. In contrast, during pharmacological stress, hypotension can be induced without implying pump failure and is not related to the presence and severity of coronary artery disease. During dipyridamole, hypotension is probably caused by hypersensitivity to negative chronotropic effects of adenosine (hypotension and bradycardia) and/or to peripheral vasodilatory effects of adenosine (isolated hypotension). During dobutamine, the two main hypothesized ischemia-independent mechanisms are vasodepressor reflex triggered by left ventricular mechanoreceptor stimulation due to excessive inotropic stimulation [41] and the development of dynamic intraventricular pressure gradient mirrored by the

increased left ventricular outflow tract velocity [42–44]. While mild (20 mmHg) hypotension during dobutamine is frequent (20 %) and probably prognostically benign, profound (drop in systolic pressure >50 mmHg) hypotension during dobutamine is rare (3 % of cases) and has been associated with a worse prognosis for subsequent cardiac events [45, 46].

18.6 Beyond Regional Wall Motion: Coronary Flow and Left Ventricular Contractile Reserve

The classic model of stratification on the basis of three spatial and temporal coordinates shown in Fig. 18.1 has been expanded in recent years by the ability to include a further severity stratification on the basis of the type of positivity: reduction of coronary flow reserve (or perfusion changes) beyond wall motion abnormality. In the last 10 years, coronary flow reserve on the left anterior descending artery has become routine added information in the clinical setting of vasodilatory stress echocardiography [47]. In this way, the stress echocardiography response can be stratified on the basis of ischemic cascade, as occurs with other imaging techniques such as cardiovascular magnetic resonance [48]. In the absence of regional wall motion abnormalities, a reduced coronary flow reserve makes the wall motion negativity less prognostically benign [49, 50]. In presence of wall motion positivity, a reduced coronary flow reserve makes the wall motion positivity more prognostically malignant [51, 52]. This introduces a further, fourth dimension (type of positivity) in the coordinates of stress echocardiographic stratification. During exercise or dobutamine, the assessment of coronary flow reserve is not that simple, and the evaluation of left ventricular contractile reserve (as rest–stress variation in pressure–volume relationship described in Chap. 4) is technically easier and conceptually more appropriate. In patients with negative stress echo by wall motion criteria, a blunted contractile reserve (<2.0) identifies a higher risk subset [53].

Conclusion

The presence (or absence) of inducible wall motion abnormalities separates patients with different prognosis. A normal stress echocardiogram yields an annual risk of 0.4–0.9 %. Thus in patients with suspected coronary artery disease, a normal stress echocardiography implies excellent prognosis and coronary angiography can safely be avoided [54]. The criteria for moderate–severe ischemia involving >10 % of LV in stress echocardiographic, nuclear, and CMR imaging are somewhat technique specific and are listed in Table 22.2 [55]. Across the imaging modalities, they identify a threshold of critical mass of ischemic myocardium triggering a prognosis changing revascularization [56].

A positive stress echocardiography result is more prognostically malignant (Table 18.1), and a negative stress echocardiography result less prognostically benign (Table 18.2), if one considers simple variables in addition to regional wall motion. In patients with positive stress echocardiography results, the timing and extent of wall

Table 18.1 Stress echocardiographic risk titration of a positive test result

1-year risk (hard events)	Intermediate (1–3 % year)	High (>10 % year)
Dose/workload	High	Low
Resting EF	>50 %	<40 %
Anti-ischemic therapy	Off	On
Coronary territory	LCx/RCA	LAD
Peak WMSI	Low	High
Recovery	Fast	Slow
Positivity or baseline dyssynergy	Homozonal	Heterozonal
CFR	>2.0	<2.0

EF ejection fraction, *LAD* left anterior descending artery, *LCX* left circumflex, *RCA* right coronary artery, *WMSI* wall motion score index

Table 18.2 Stress echocardiographic risk titration of a negative test result

1-year risk (hard events)	Very low (<0.5 % year)	Low (1–3% year)
Stress	Maximal	Submaximal
Resting EF	>50 %	<40 %
Anti-ischemic therapy	Off	On
CFR	>2.0	<2.0
PVR	>2.0	<2.0

EF ejection fraction, *CFR* coronary flow reserve, *PVR* pressure volume relationship

motion abnormalities powerfully stratify the prognostic risk. In patients with a negative stress echocardiography result, a reduced coronary flow reserve with vasodilator stress or a blunted contractile response during exercise or dobutamine stresses help to identify the "wolf in sheep's clothes," in whom prognosis is less good, in spite of the falsely reassuring negativity of wall motion [57, 58].

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Diagnostic Results and Indications

19

Miguel Angel Garcia-Fernandez, Pedro Marcos-Alberca, and Eugenio Picano

The relationship between the data obtained from provocative tests and angiographically assessed coronary artery disease is usually expressed in terms of sensitivity and specificity, where sensitivity is the frequency of a positive test result in a population of patients with coronary artery disease and specificity is the frequency of a negative test result in a population of patients without disease. In a given population, sensitivity and specificity values are affected by a constellation of factors (some of which – more relevant to stress echocardiography – are summarized in Tables 19.1 and 19.2) related to the angiographic standard, patient population, stress methodology, and interpretation criteria. In the presence of more severe and extensive coronary artery disease, any stress echocardiography test will give higher sensitivity values [1]. For any given level of stenosis, angiographic coronary lesions of the complex type (i.e., with intraluminal filling defects and/or irregular margins suggestive of thrombus and/or ulcers) will give higher sensitivity values for vasodilator stresses [2], but not inotropic stresses [3]. Abundant coronary collateral circulation makes the myocardium more vulnerable to ischemia during vasodilator stresses [4], whereas exercise or inotropic stress results are independent of angiographically assessed collateral circulation [5]. All stresses yield better sensitivity results in populations with previous myocardial infarction and in patients studied while they are off antianginal therapy, which lowers the sensitivity of both physical and pharmacological stresses [6, 7]. The evaluation of patients with variant angina inflates sensitivity since stresses such as exercise or dobutamine may elicit vasospasm – and therefore ischemia – independently of the underlying organic stenosis. Stress-related factors are also important. Submaximal stresses sharply lower test sensitivity (to a greater extent than perfusion imaging sensitivity) [6]. During exercise, a peak stress acquisition yields better sensitivity than poststress imaging such as the one performed after treadmill exercise. The use of more aggressive test protocols leads to higher sensitivities; however, the user-friendliness of the test declines. For pharmacological tests, the best trade-off between accuracy and feasibility for primary diagnostic purposes is probably a high dose with atropine for dobutamine and an accelerated high dose for dipyridamole (Fig. 19.1).

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Table 19.1 Factors affecting stress echocardiography sensitivity

	Increases sensitivity	Decreases sensitivity
Previous myocardial infarction	Present	Absent
Antianginal therapy	Absent	Present
Stenosis severity	>75 %	50–75 %
Stenosis extent	Multivessel disease	Single-vessel disease
Stenosis morphology	Complex	Simple
Stenosis location	LAD	LCx
Stress intensity	Maximal	Submaximal
Variant (vasospastic) angina	Yes	No
Echocardiography interpretation criteria	Lack of hyperkinesia	Marked hypokinesia
Echocardiography reader	Expert	Beginner

LAD left anterior descending artery, *LCx* left circumflex artery

Table 19.2 Factors affecting stress echocardiography specificity

	Increases specificity	Decreases specificity
Resting wall motion abnormalities	Absent	Present
LVH, LBBB	Absent	Present
Stress intensity	Submaximal	Maximal
Variant (vasospastic) angina	No	Yes
Echocardiography interpretation criteria	Marked hypokinesia	Lack of hyperkinesia
Interpreting the basal third of the inferior wall	No	Yes
Echocardiography reader	Expert	Beginner

LBBB left bundle branch block, *LVH* left ventricular hypertrophy

The interpretation criteria also affect sensitivity. The lack of hyperkinesis will provide a higher sensitivity when compared with the more specific criterion of transient regional dyssynergy. An expert reading and high-quality two-dimensional (2D) imaging using a top-quality instrument will obviously improve the diagnostic accuracy. Digital acquisition capabilities do not increase accuracy compared to videotape recordings, but they probably do make the reading more reproducible. Specificity is also affected by many factors, some of which – not surprisingly – are the same as those affecting specificity. As a rule, several factors increasing sensitivity symmetrically lower specificity.

19.1 Stress Echocardiography Versus Other Diagnostic Tests

Given the many factors affecting the values of diagnostic accuracy, reliable information on the relative value of different tests can only be gained by studying an adequate number of patients in head-to-head comparisons under the same conditions. On the basis of these studies and meta-analyses, some conclusions on the relative value of various stress tests can be drawn.

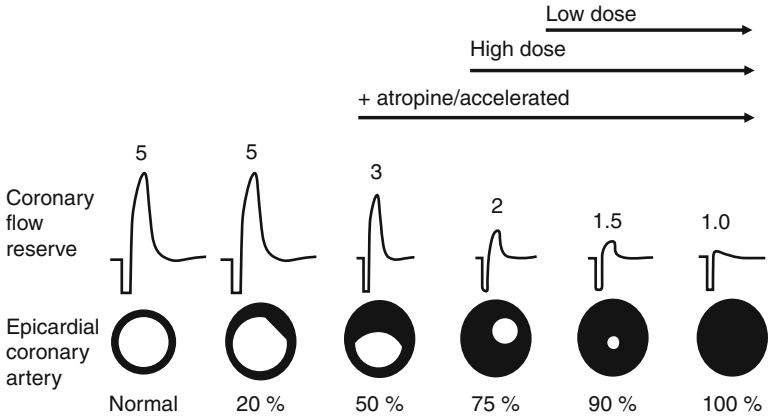


Fig. 19.1 Pharmacological test protocols for the detection of coronary artery disease (CAD). The various protocols can be ranked according to their different abilities to pick up different levels of CAD severity, the high-dose test protocol with atropine coadministration being the most sensitive, high-dose protocols (up to 40 μg kg^{-1} per min for dobutamine, up to 0.84 mg kg^{-1} for dipyridamole) of intermediate sensitivity, and low-dose protocols (up to 20 μg kg^{-1} per min for dobutamine, up to 0.56 mg kg^{-1} for dipyridamole) being the least sensitive

When compared to standard exercise electrocardiography testing, stress echocardiography has an advantage in terms of sensitivity and a particularly impressive advantage in terms of specificity [7]. Compared to nuclear perfusion imaging, stress echocardiography at least has similar accuracy, with a moderate sensitivity gap, especially in patients with single-vessel disease of mild severity (50–80 % stenosis) evaluated under antianginal therapy with submaximal stresses [6]; this sensitivity gap is virtually filled by state-of-the-art protocols (with atropine coadministration) and is more than balanced by a marked specificity gap in favor of stress echocardiography, which is particularly striking in populations with left ventricular hypertrophy, syndrome X, hypertension, and hypertrophic cardiomyopathy [8]. The sensitivity gap in favor of nuclear vs. echocardiography is slightly more pronounced with adenosine (often stopped at a submaximal level in order to limit side effects [8]) since it is less well tolerated subjectively than dipyridamole [9]. The extent and severity of the perfusion deficit by nuclear imaging are paralleled by the extent and severity of the wall motion dyssynergy during stress [8–10], and both perfusion and functional defects are correlated to the extent and severity of angiographically assessed coronary artery disease. Exercise, dipyridamole, and dobutamine stress echocardiography have similar overall accuracy [11, 12] comparable to stress perfusion scintigraphy [13]. Dipyridamole has a higher feasibility than dobutamine (Fig. 19.2). With dobutamine, the most frequent side effects are tachyarrhythmias and hypertension, whereas during dipyridamole infusion, bradyarrhythmias and hypotension are frequent. Dipyridamole has more often symptomatic, and dobutamine asymptomatic limiting side effects. Dipyridamole–atropine and dobutamine–atropine stress echocardiography have

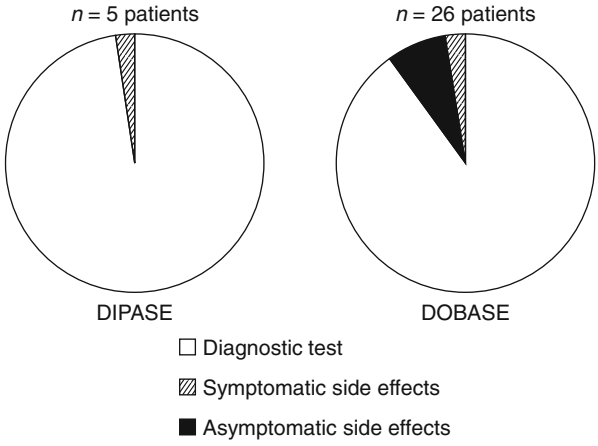


Fig. 19.2 Feasibility of dobutamine–atropine test (DOBASE, *right*) vs. dipyridamole–atropine (DIPASE, *left*). EPIC–EDIC study group (From Pingitore et al. [14], with permission)

similar sensitivity and specificity (Fig. 19.3) and a similar capability to stratify the ischemic response according to ischemia-free stress time and peak wall motion score index (Fig. 19.4) [14].

Dipyridamole and dobutamine stress echocardiography also have a comparable prognostic value [16] and similar accuracy for identification of myocardial viability [17]. As far as subjective tolerance is concerned, dipyridamole and dobutamine are similarly well tolerated, and both are significantly better tolerated than adenosine [18]. Some data are also available concerning the direct assessment of the relative intrinsic echocardiographic difficulty of the two tests, higher for dobutamine due to higher heart rate and contractility increase [19]. Another report semiquantitatively addressed the issue of image degradation during stress and described that image quality worsened significantly more frequently during dobutamine stress than with dipyridamole stress [20]. Also, for the recognition of myocardial viability, both tests in principle have a comparable diagnostic accuracy for predicting spontaneous or revascularization-induced functional recovery, with dipyridamole being slightly more specific and dobutamine slightly more sensitive. Dobutamine is the only one extensively validated and accepted by guidelines with this indication [15, 21, 22]. From the practical viewpoint, both tests should be used to optimize the diagnostic performance of the stress echocardiography laboratory – a policy that is justified for several reasons. Each patient referred for stress evaluation might suffer from relative or absolute contraindications to either stress modality. For instance, a patient with severe hypertension and/or a history of significant atrial or ventricular arrhythmias is more reasonably subjected to the dipyridamole stress test, which, unlike dobutamine, has no arrhythmogenic or hypertensive effect. In contrast, a patient with severe conduction disturbances or advanced asthmatic disease should undergo the dobutamine stress test, since adenosine has a negative chronotropic and dromotropic effect, as well as a documented bronchoconstrictor activity. Patients either taking xanthine medication or under the effect of caffeine contained in drinks (tea, coffee, cola) should undergo

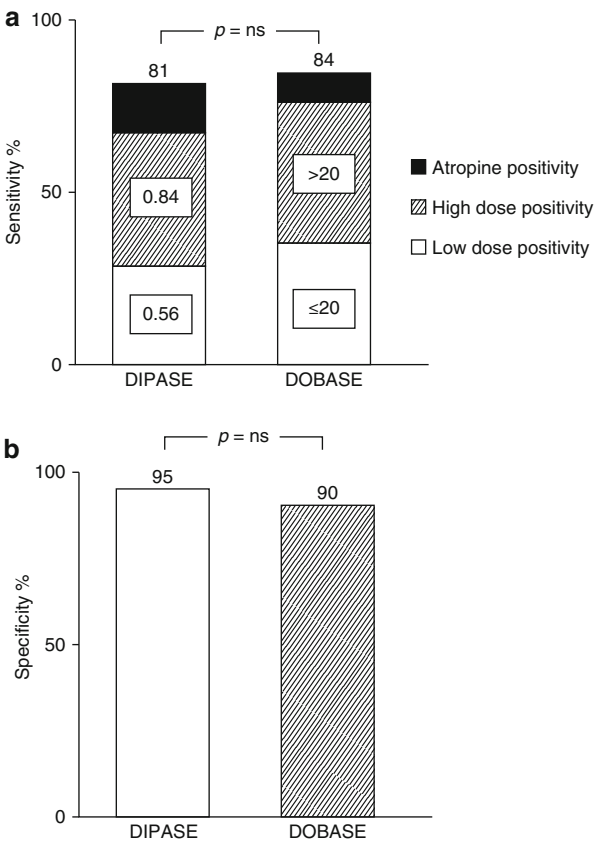


Fig. 19.3 (**a**) Sensitivity and (**b**) specificity of the dobutamine–atropine test (*DOBASE*) vs. dipyridamole–atropine (*DIPASE*). EPIC–EDIC study group. *ns* not significant (From Pingitore et al. [14], with permission)

the dobutamine test. Both dipyridamole and dobutamine have excellent overall tolerability and feasibility [22]. Nevertheless, submaximal nondiagnostic tests do occur in some patients because of side effects: less than 5 % of patients with dipyridamole infusion and about 10 % of patients with dobutamine infusion [16, 22]. Obviously, the negative predictive value for both diagnostic and prognostic standards is much lower when the peak dose is not achieved, as with a submaximal exercise stress test. Patients with a submaximal pharmacological stress should be switched over to the other stress. In addition, for the detection of minor, less extensive forms of coronary artery disease or of minor forms of myocardial viability, a combined pharmacological stress procedure may be needed. Dipyridamole and dobutamine are good options for the diagnosis of coronary artery disease, with dipyridamole having better feasibility and a more reassuring safety record [22]. The choice of one test over the other depends on patient characteristics, clinical issues, local drug cost, and the physician's preference. It is important for all stress echocardiography laboratories to become familiar with both stresses to achieve a flexible and versatile diagnostic approach that allows the best stress to be tailored to individual patient needs.

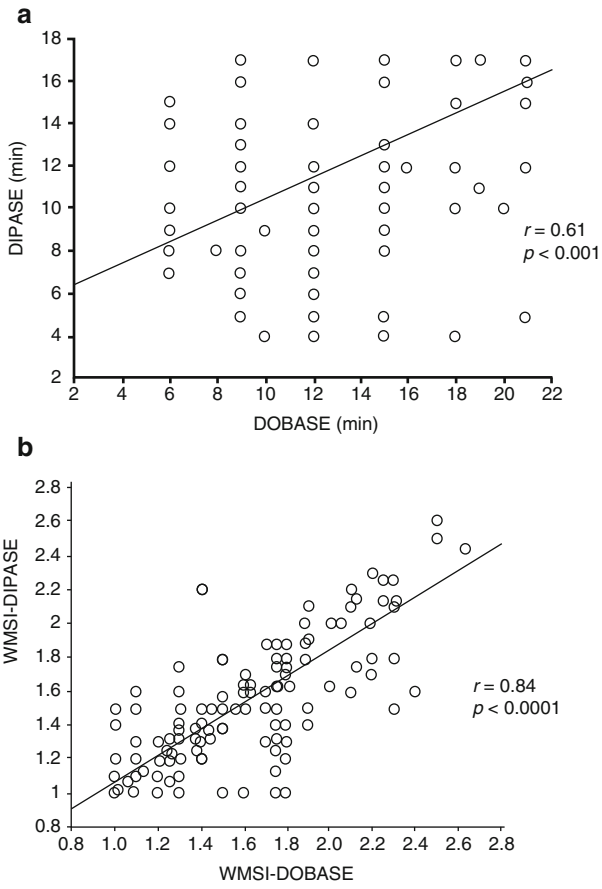


Fig. 19.4 Stratification of the stress echocardiography response in (**a**) the time domain and (**b**) the space domain. EPIC–EDIC study group. *DOBASE* dobutamine atropine test, *DIPASE* dipyridamole– atropine test, *WMSI* wall motion score index (From Pingitore et al. [14], with permission)

19.2 Novel Techniques Applied to Diagnosis with Stress Echocardiography

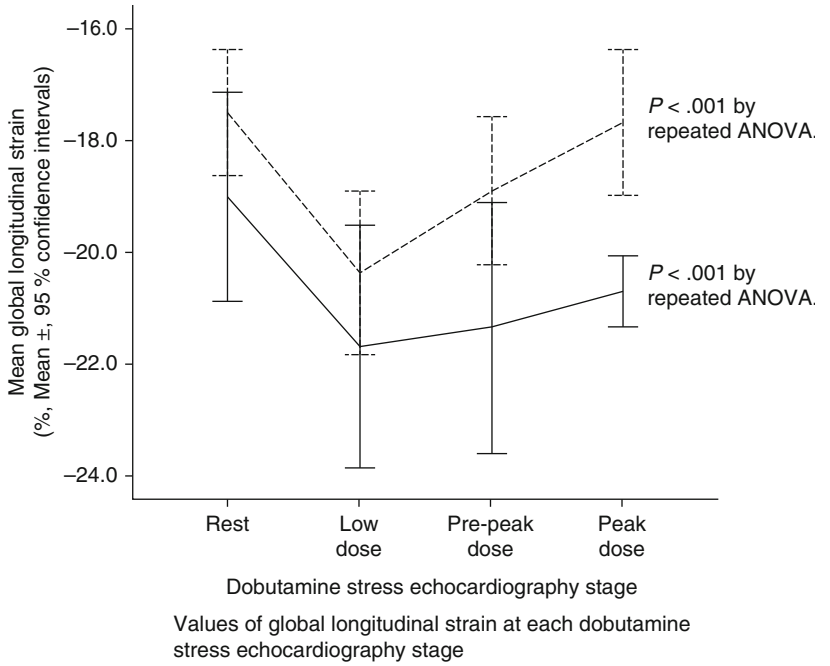
19.2.1 Cardiac Mechanics

In the last decade, we have contemplated the development and implementation of new echocardiographic dynamic imaging focused on sophisticated analysis of cardiac mechanics. Some became part of the clinical routine, whereas others remained limited to research and exploration of new clinical applications. Stress echocardiography with dobutamine has played an outstanding role in the development of myocardial dynamic imaging and its experimental validation. Although with limitations, cardiac mechanics evaluation during stress echocardiography has an increasing acceptance in clinical practice with a promising landscape of improvement and superior accuracy for the diagnosis of myocardial ischemia or the evaluation of myocardial viability [23].

Cardiac mechanics are evaluated throughout two different imaging techniques: (1) Doppler-based tissue velocity measurements, normally referred to as *tissue Doppler imaging* or *TDI*, and (2) *speckle tracking*, based on direct displacement measurements of myocardial "speckles," that means the backscatter of the myocardial fibers. Both types of measurements yield to the derivation of several parameters of myocardial function: myocardial velocity, strain rate, strain, rotation, twist, and torsion. Among them, strain and strain rate are underscored [24]. Strain (ε) describes myocardial deformation and it is defined as the fractional change in the length of a myocardial segment. Strain is unitless and is usually expressed as a percentage. Strain can have positive or negative values, which reflect lengthening or shortening, respectively; for example, a 1 cm string stretched to 1.2 cm would have 20 % positive strain. Strain rate (SR) is the rate of change in strain (first temporal derivative) reflecting instantaneous strain and is usually expressed as 1/sec or $\sec - 1$. Left ventricular regional function studied with echo-derived strain and strain rate has demonstrated excellent correlations with myocardial mechanics evaluated with sonomicrometry in experimental models of dobutamine-induced ischemia and in the clinical setting with tagged cardiac MRI as gold standard [25, 26]. Other variables, such as postsystolic shortening or time-to-peak SR, have also disclosed good results as markers of ischemia [27]. Opposite to TDI strain and SR calculated from myocardial velocities, 2D speckle tracking offers the superior advantage of its independence of the angle of US beam incidence resulting in more accurate, reproducible, and less vendor different strain and SR calculations (see also Chap. 23). Therefore, in recent years, speckle tracking stress echocardiography seems more reliable than TDI stress echocardiography and it has been more widely accepted in stress laboratories (Figs. 19.5 and 19.6) [28].

Cardiac mechanics analysis on dobutamine stress echocardiography has been evaluated in the diagnosis of coronary heart disease. By means of tissue Doppler imaging, the detection of regional postsystolic shortening and SR changes increases sensitivity from 81 to 82 % and specificity from 86 to 90 % [27]. Accuracy of both TDI and speckle tracking for the diagnosis of CAD is around 70 % [28]. Nonetheless, the combination of the wall motion score index (qualitative assessment of dyssynergy) and longitudinal strain derived from 2D speckle tracking (quantitative assessment of regional function) shows the best incremental increase in diagnostic accuracy of dobutamine stress echocardiography for CAD diagnosis, with a sensitivity of 100 %, specificity of 87.5 %, and accuracy of 96.3 % (Fig. 19.7) [29]. Strain and SR can detect myocardial dysfunction during intermediate doses of dobutamine stress, with minimal or any changes in regional wall motion abnormalities at this stage, allowing the diagnosis of CAD in early interrupted or not tolerated tests that otherwise would be labeled as inconclusive [30].

Low-dose dobutamine stress echocardiography to assess myocardial viability is also favored when quantitative analysis of regional function with strain and SR is added. Global longitudinal end-systolic strain and peak systolic SR at low-dose dobutamine had incremental value over wall motion analysis with a total accuracy when added to wall systolic motion index of 79 % (5 % of increment) and correlates with the index of microcirculatory resistance, a reliable measure of coronary microvascular dysfunction [31, 32].



Values of global longitudinal strain at each dobutamine stress echocardiography stage

	Rest	Low dose	Pre-peak dose	Peak dose
—— No significant CAD	–19.0 ± 2.8	–21.7 ± 3.3*	–21.3 ± 2.9*†	–20.7 ± 0.8†
--- Significant CAD	–17.5 ± 2.4	–20.4 ± 3.1*	–18.9 ± 2.8*	–17.7 ± 2.7

Fig. 19.5 Behavior of global longitudinal strain (resulting from pooling the longitudinal strain of myocardial segments in four-, two-, and three-chamber apical view) during dobutamine infusion in patients with and without significant CAD. Note the improvement on mechanics in low dose and the marked deterioration when significant CAD is demonstrated with coronary angiography (From Hanekom et al. [28], with permission)

Current development integrating cardiac mechanics and three-dimensional imaging offers a new and very promising perspective in the evaluation of regional contractile abnormalities during pharmacological stress [33].

19.2.2 Value of Contrast Agents on Stress Echocardiography

Contrast agents used in ultrasound consist of microbubbles of encapsulated high-molecular-weight gas (see also Table 24.1 in Chap. 24). When the ultrasound interacts with microbubbles, the backscatter that they produce results in intense echocardiographic signals, which are proportional to the blood volume. First application of contrast agents was LV cavity opacification, which enhances the endocardial boundaries allowing better assessment of regional contractility and hence more

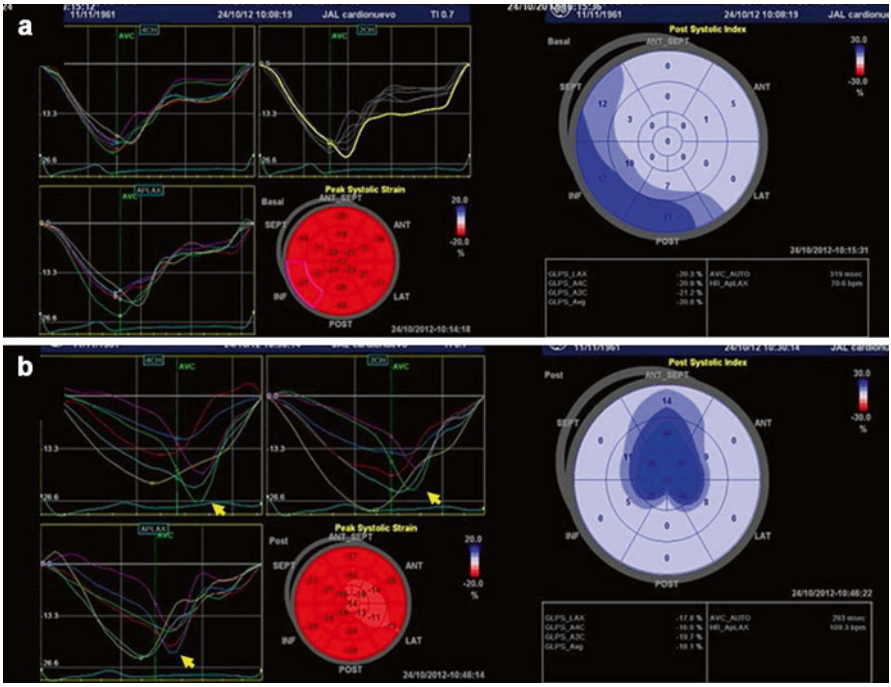


Fig. 19.6 Example of post-processing of 2D speckle tracking acquired during dobutamine stress echocardiography. Panel (**a**) shows parametric strain along the cardiac cycle (HR 70 bpm) in rest and Panel (**b**) at peak stress (HR 106 bpm) in apical 4C, 2C, and 3C. Red bull's eye represents longitudinal strain of the myocardial segments and blue bull's eye time-to-peak strain. Note the decrease of strain values of anteroapical segments at peak stress and the delay of the peak stress. Such delay agrees with the appearance of the reduced peak stress of ischemic segments after the electrical systole (postsystolic shortening; *yellow short arrow*) (Courtesy of Prof. J Lowenstein. Buenos Aires, Argentina)

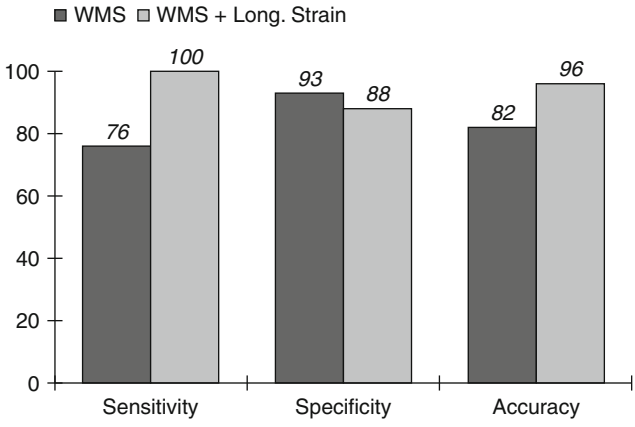


Fig. 19.7 Bar plot depicting the incremental value of global longitudinal strain and wall motion score (*WMS*) over WMS alone in the diagnosis of significant coronary heart disease (Adapted from Hanekom et al. [28])

accurate quantification of LV volume and ejection fraction. Later, the improvements in contrast agent technology and ultrasound techniques (i.e., flash imaging acquisition and parametric algorithms) have also made it possible to assess myocardial microcirculation and perfusion [34, 35].

Since the identification of regional contractile abnormalities is the cornerstone of the diagnosis of CAD with stress echocardiography, contrast agents allowed the extension of the technique in patients whose visualization of the endocardial boundary is poor, the so-called poor acoustic window, a condition present up to 30 % of patients submitted to the echo laboratory. Contrast agents in dobutamine stress echocardiography results in the improvement of the endocardial border resolution in 95 % of patients at peak stress, an important fact considering the natural image degradation implicit in dobutamine stress echocardiography due to tachycardia. As an expected consequence, LV opacification with contrast agents reduces also the interobserver variability. It is important to note that the most favored are those patients with the worse basal endocardial boundary visualization [36].

In addition to the reliable performance of the stress test in around 20 % of patients in whom basal echocardiogram would seem them not suitable for stress echocardiography, contrast agents have been evaluated in terms of accuracy for the diagnosis of CAD. The OPTIMIZE trial showed that the use of contrast agents in dobutamine stress echo increases the interpretation of wall motion with high confidence from 36 to 74 %. No study was considered uninterpretable with the use of contrast agent (8 % in unenhanced). The sensitivity and specificity for CAD in unenhanced dobutamine stress echocardiography studies that could be interpreted were 75 % and 51 %, respectively. With the use of a contrast agent, sensitivity and specificity increased to 80 % and 55 %, respectively. The increment in sensitivity, specificity, accuracy, and agreement is more remarkable in poor echocardiographic windows, achieving values similar to those obtained in confident unenhanced stress echocardiograms of patients with good window [37]. Overall concordance of agreement on the presence or absence of CAD with coronary angiography had the most significant impact with contrast agent use in studies with low confidence (68 % vs. 36 %). There was no impact of contrast agent use if all 17 segments were visualized. Besides, a significant impact of contrast agent enhancement was seen in patients with >2 nonvisualized segments (Fig. 19.8) [38]. Therefore, the decision to use contrast agents in stress testing is usually made at the start of the study, depending on image quality (low confidence interpretation and/or >2 nonvisualized segments). When image quality is good at baseline but degrades during stress (heart rate-dependent image degradation), there is usually time and opportunity to administer contrast medium during a pharmacologic stress test, i.e., at peak stress.

In recent years, the use of myocardial contrast enhancement to evaluate the myocardial perfusion has gained great attraction. The greatest potential of combining MCE with dobutamine stress echocardiography lies in the possibility of displacing perfusion techniques based on the use of isotopes and hence prevent patient to

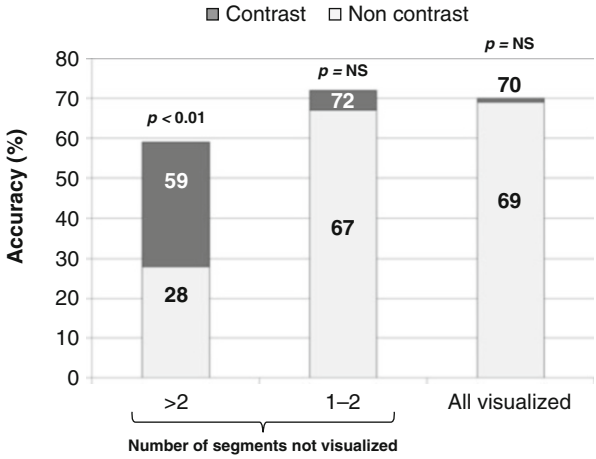


Fig. 19.8 Bar plot depicting the incremental accuracy on dobutamine stress echocardiography in the diagnosis of CAD with the use of contrast agents. Note the maximal weight when more than two segments (endocardial boundary) are not visualized

radiation exposure. Briefly, perfusion based on MCE consists of the following basic principles. First, when the entire myocardium is fully saturated during a continuous infusion of microbubbles, the signal intensity denotes the capillary blood volume. With a short flash of high acoustic power signal, there is destruction or depletion of microbubbles in the myocardium, and, under low intensity signal, replenishment of contrast within the myocardium afterward can be observed. Then, it takes ~5 s for complete replenishment of the myocardium. Any decrease in myocardial blood flow (MBF) prolongs replenishment time in proportion to the reduction in MBF. MBF with MCE can be quantified since the product of peak microbubble intensity (representative of myocardial blood volume) and their rate of appearance (representative of blood velocity) equal MBF. Dedicated software displays the MBF curves (or parametric) in basal condition and after pharmacological stress with dobutamine, dipyridamole, or adenosine side by side to highlight regions of decreased perfusion due to significant coronary stenosis; even MBF differences can be represented in an intuitive-colored *bull's eye* map of the 17 myocardial segments evaluated [34].

The main application of MCE is the diagnosis of CAD. Preliminary reports were enthusiastic, with a high diagnostic performance and a yield similar to technetium-based nuclear MPI (sensitivity 84 % vs. 82 %, specificity 56 % vs. 52 %, and agreement of 73 %) [39]. However, poor reproducibility among different laboratories became an important limitation for a wide acceptance of the technique. Compared with single-photon emission computed tomography, the most recent and consistent evidence points out a higher sensitivity for MCE dipyridamole stress echocardiography (75 % vs. 49 %) but at cost of notably lower specificity (52 % vs. 81 %) in the diagnosis of CAD using quantitative coronary angiography as standard technique [40].

We can conclude that the current state-of-the-art and the high training and expertise level in the performance of MCE stress echocardiography nowadays precludes its realization routinely [41].

19.2.3 Three-Dimensional Stress Echocardiography

It is not surprising how one of the most impressive advances in cardiac imaging, three-dimensional or 3D echocardiography, has been rapidly employed in stress echocardiography. Although with limitations due to less temporal resolution than 2D echocardiography (30–40 volume rate in the latest 3D implementations vs. 80–90 frame rate with 2D), 3D stress echocardiography can offer some advantages: a short time in the acquisition of images, post-processing of echo data sets with the possibility to display the images in novel ways (i.e., a grid of synchronized short axis or cut views from base to apex grouped by stages (basal, low dose, high dose, and recovery)) [42], and, even, futuristic projects of multimodal imaging with fusion of 3D echocardiographic images as a full volume of simultaneous segmental shortening, regional strain, or strain rate and the coronary tree obtained with noninvasive coronary angiography with multirow computed tomography. However, real-time 3D is more time-consuming to analyze losing some of the advantages in short-time acquisition opposite to 2D images [43].

The first approach to 3D with the introduction of matrix array transducers was the development of multiplane imaging (Fig. 19.9). It is a kind of fast acquisition that displays the four-, two-, and three-chamber apical view of the heart without applying movements over the transducer. In an analysis comparing 2D dobutamine stress echocardiography and 3D multiplane acquisition (three-apical plane), with 3D, total effective acquisition time was significantly shorter (55 vs. 137 s). Confidence on data was similar for both methods (2D: 98 % vs. 3D: 97 %). Overall sensitivity (93 %), specificity (75 %), and accuracy (89 %) were identical between both methods. On a segmental level, results were similar [44]. The shortest time of acquisition opens the door to its implementation in the most exigent scenario of exercise echocardiography, where maximal sensitivity is obtained when patients are examined at peak exercise or very immediately postexercise. Preliminary results were better using bicycle ergometer than treadmill, where sensitivity was lower [45, 46].

Other modalities of 3D examination were progressively developed and implemented. Hence, full-volume (pyramidal) acquisition has also been tested. Nonetheless, full volume had the limitation of lower temporal resolution (low volume rate). Some have added contrast agents to the technique of full-volume 3D stress echocardiography, but they have reported inconclusive results precluding a wide adoption of the technique. Although contrast-enhanced 3D dobutamine is feasible in the majority of patients, there was only a moderate concordance with the standard 2D protocol (69 % in a patient basis and 88 % in a segment basis). The limitations were due to difficulties in visualizing the anterolateral segments because of the relatively large imprint of the transducer and lower frame rates with 3D dobutamine stress echocardiography resulting in the erroneous diagnosis of dyssynchrony [47].

Fortunately, advances in 3D echocardiography are very fast. Last developments allow 3D examination with more and more volume rates, increasing the reliability and diagnostic accuracy of the test. Definitively, time acquisition is lower with 3D,

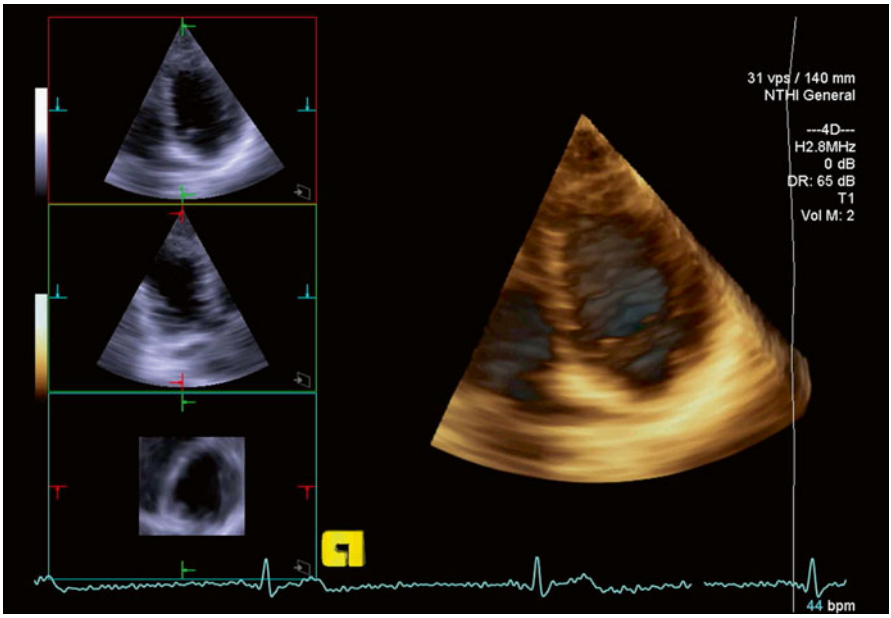


Fig. 19.9 Real-time 3D echocardiographic acquisition with one-beat technology (Siemens AG, Munich, Germany). *Right side* shows the full volume with coronal cut plane depicting the four chambers. *Left side* discloses simultaneous multiplane 2D views according to the cutting planes orientated across the pyramidal one-beat volume. *From the top to the bottom*: four-chamber apical view, two-chamber apical view, and cross-sectional mid-ventricular view. One-beat acquisition does not require iterative reconstruction with ECG gating avoiding step-stair artifacts due to respiration, premature beats, or atrial fibrillation, and it is able to achieve acceptable volume rate (around 30 vol./second)

and post-processing and analysis, thanks to software advances, have overcame previous limitations and the total time (acquisition plus processing/reading) is nowadays inferior to the 2D standard technique (total time 241 s for 2D and only 121 s for 3D, a 50 % of reduction). In patients who underwent coronary angiography, the overall accuracy of 3D dipyridamole stress echocardiography was similar to that of 2D (sensitivity, 80 % vs. 78 %; specificity, 87 % vs. 91 %) [48]. These results using the latest 3D technologies yielded similar results in other centers: sensitivity and specificity of 2D to detect CAD (with coronary angiography as reference) were 80 and 82 % and of 3D stress echocardiography were 82 and 64 %, respectively, whereas in the per segment analysis, the respective percentages were 88 and 64 % for 2D and 90 and 73 % for 3D [49]. Concordance of 3D and 2D stress echocardiography using ultimate technologies is excellent (Table 19.3).

It is reasonable to expect a more prominent role of real-time, perhaps contrast enhanced when acoustic window being limited, three-dimensional stress echocardiography in the still-to-come next statements of working groups on stress echocardiography of the cardiovascular imaging scientific associations.

Table 19.3 Concordance of LV wall motion semiquantitative evaluation of three-dimensional echocardiograms with standard 2D echocardiograms in a head-to-head comparison

Wall motion	Basal echo	Peak stress echo
3D-Normal/2D-Normal	68 %	71 %
3D-Abnormal-Ischemia/2D-Abnormal-Ischemia	21 %	20 %
3D-Abnormal-Ischemia/2D – Normal[a]	8 %	8 %
3D-Normal/2D-Abnormal-Ischemia[a]	3 %	1.5 %
Agreement (*kappa test*)	0.71	0.74

From Badano et al. [48], adapted
Kappa value denoted a high level of agreement of both techniques
[a]Values of discordant evaluation

19.3 Stress Echocardiography and the Effects of Medical Therapy

Patients may be undergoing various forms of antianginal therapy at the time of testing, both an advantage and a disadvantage for stress echocardiography testing. The disadvantage is that antianginal therapy reduces sensitivity, since stress-induced wall motion abnormalities are caused by the development of obligatory myocardial ischemia. The advantage is that the effect of therapy can be assessed using an objective, primary ischemic end point such as changes in stress-induced wall motion abnormalities. The presence of ischemia can be titrated on the basis of the ischemic-free stress time and the extent and severity of the induced dyssynergy. The various forms of stress are differently affected by various forms of therapy (Table 19.4). Antianginal therapy lowers the sensitivity of exercise echocardiography, as it does with vasodilator stress testing [21, 22]. The beneficial effect of therapy on dipyridamole time parallels variations in exercise time, providing the possibility of an exercise-independent assessment of efficacy of medical therapy (Fig. 19.10). Interestingly, the positive effects of β-blockers on dipyridamole stress are largely independent of the effect on heart rate, possibly involving a direct antisteal effect [15, 50]. Monotherapy with calcium antagonist and nitrates also protects the patient from dipyridamole-induced ischemia [15, 51]. Angiotensin-converting enzyme inhibitors have no effect on dipyridamole stress echocardiography results [52]. Aminophylline obviously blunts dipyridamole-induced ischemia, whereas concomitant oral dipyridamole therapy might potentiate it. The sensitivity of dobutamine is heavily affected by concomitant β-blocker therapy. Beta-blockers affect a rightward shift in the dose–response curve to dobutamine and sharply lower test sensitivity, unless atropine is used [53]. Calcium antagonists and/or nitrates only mildly reduce dobutamine stress sensitivity [22, 54], and they do so in a manner unrelated to changes induced in exercise tolerance [54]. Concomitant anti-ischemic therapy at the time of testing heavily modulates the prognostic value of pharmacological stress echocardiography. In the presence of concomitant anti-ischemic therapy, a positive test is prognostically more malignant and a negative test prognostically less benign. However, the decision to remove a patient from β-blocker therapy for stress testing should be made on an individual basis and should be done carefully to avoid a potential hemodynamic rebound effect, which can lead to accelerated angina or hypertension [1, 55].

Table 19.4 Effects of oral therapy on stress testing sensitivity

	Stress exercise	Dipyridamole	Dobutamine
β-Blockers	↓	↓	↓↓
Calcium channel blockers	↓	↓	↓↔
Nitrates	↓	↓	↓↔
ACE inhibitors	↔	↔	↔
Aminophylline	↓↔	↓↓	↔

ACE angiotensin-converting enzyme, ↓ decreased sensitivity, ↓↓ markedly decreased sensitivity, ↔ no effect on sensitivity, ↓ ↔ mild decrease in sensitivity

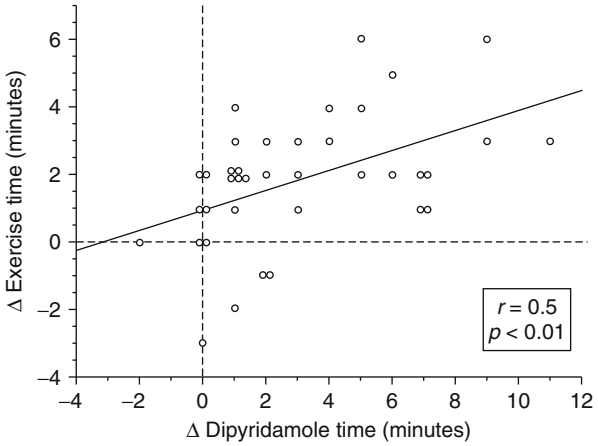


Fig. 19.10 Correlation between therapy-induced variations in dipyridamole time (i.e., the time from the onset of dipyridamole infusion to obvious dyssynergy) and exercise time (i.e., the time from the onset of exercise to 0.1 mV of ST-segment depression) in the 38 patients with positivity on both tests when off treatment. Δ variations (From Lattanzi et al. [21], with permission)

19.4 Contraindications to Stress Testing

The absolute and relative contraindications to stress testing are summarized in Table 19.5. Obviously, a poor acoustic window makes any form of stress echocardiography unfeasible. However, a difficult resting echocardiography greatly increases the probability of obtaining no interpretable study results during exercise and should be an indication for the less technically demanding pharmacological stress echocardiography to be used. Specific contraindications to dipyridamole (or adenosine) echocardiography include the presence of severe conduction disturbances, since adenosine can cause transient block at the AV node, and severe bronchopneumopathic disease requiring chronic xanthine therapy, since adenosine is a powerful bronchoconstrictor. Patients with resting systolic blood pressure under 100 mmHg generally should not receive dobutamine or dipyridamole. Dobutamine causes an increase in systolic blood pressure in the majority of patients but can also cause a significant decrease in systolic blood pressure in a substantial

Table 19.5 Absolute and relative contraindications to stress testing

	To all forms of stress testing		To stress echocardiography	To exercise stress	Dob	Dip	Atro
	Absolute	Relative					
Acute myocardial infarction (<2 days)	√						
Unstable angina not stabilized	√						
Uncontrolled cardiac arrhythmias	√						
Severe aortic stenosis	√						
Uncontrolled symptomatic heart failure	√						
Acute pulmonary embolism	√						
Acute myocarditis or pericarditis	√						
Acute aortic dissection	√						
Left main coronary stenosis		√					
Moderate aortic stenosis		√					
Electrolyte abnormalities		√					
Severe arterial hypertension (SAP >200; DAP 110 mmHg)		√					
Tachyarrhythmias or bradyarrhythmias		√					
High degree of atrioventricular block		√					
Poor acoustic window (obesity)			√				
Inability to exercise adequately				√			
Moderate hypertension, ventricular ectopy					√		
2nd–3rd-degree A–V block						√	
Relative hypotension					√	√	
Unstable carotid disease					√	√	√
Glaucoma, severe prostatic disease							√

SAP systolic arterial pressure, *DAP* diastolic arterial pressure

minority of patients. Dipyridamole usually causes a modest decrease in systolic blood pressure of 10–20 mmHg, but occasionally causes a more severe decrease. Adenosine is the preferred option because of its rapid half-life (<10 s) in patients with unstable carotid artery disease. Significant hypertension and prolonged hypotension should be avoided in these patients, making adenosine the agent of choice. Patients who do not achieve the target heart rate with dobutamine alone, or inducible ischemia with dipyridamole alone, are commonly administered atropine. Atropine use in this setting is a risk only for closed-angle glaucoma patients, a minority of patients with glaucoma. If eye pain occurs, the patient should call an ophthalmologist within the day [2]. Severe prostatic disease is also a contraindication to atropine use.

19.5 Indications for Stress Testing

Indications for stress echocardiography can also be grouped in very broad categories, which eventually could encompass the overwhelming majority of patients: diagnosis of coronary artery disease; prognosis and risk stratification in patients with established diagnosis, for instance, after myocardial infarction; assessment of preoperative risk; evaluation for cardiac etiology of exertional dyspnea; evaluation after revascularization; and localization of ischemia [15, 21]. As a rule, the less informative the exercise ECG test is, the stricter the indication to stress echocardiography is. Out of five patients, one is unable to exercise, one exercises submaximally, and one exercises maximally but the ECG is uninterpretable [22]. The three main specific indications for pharmacological stress echocardiography can be summarized as follows [22]:

1. Patients in whom the exercise stress test is contraindicated (e.g., patients with severe arterial hypertension)
2. Patients in whom the exercise stress test is not feasible (e.g., those with intermittent claudication)
3. Patients in whom the exercise stress test was nondiagnostic or gave ambiguous results: inability to achieve the target heart rate response, presence of chest pain in the absence of significant electrocardiographic changes, and a concomitance of conditions lowering the reliability of the ECG marker of ischemia (female sex, arterial hypertension, repolarization abnormalities on ECG under resting conditions or after hyperventilation, and the need to continue drugs such as digitalis or antiarrhythmics that potentially induce ST segment and T wave changes)

The published evidence in this field is rapidly growing and may possibly change some of the present indications in the near future. In more general terms, evaluation of the clinical utility of a diagnostic test is far more difficult than assessment of the efficacy of a therapeutic intervention, because the diagnostic test cannot have the same direct effect on patient survival or recovery. Furthermore, there are no double-blind, randomized studies to prove the usefulness of the technique in a given

situation [22]. As always, the appropriateness of the indication should be found in the point of balance between published evidence, personal experience, available resources, and common sense.

19.6 The Justified and Optimized Use of Stress Testing

Whatever the stress test used, some common rules in stress test indication and/or interpretation should be considered [22, 56].

1. All available information (clinical, stress, and imaging data) should be considered when interpreting the test. In the Bayesian analysis, the probability of the patient having the disease before the test is considered the a priori (pretest) likelihood, since it can be estimated by retrospective observations (Table 19.6). Bayes' theorem states that the probability of a patient having the disease after the test is performed will be the product of the disease probability before the test and the probability that the test provided a true result. After the test, the new value of the probability of the patient having the disease will be the posttest likelihood. For instance, a positive exercise electrocardiography test indicates a probability of coronary artery disease of 90 % in a patient with typical angina, 80 % in a patient with atypical chest pain, and 35 % in an asymptomatic subject. The clinician often makes this calculation intuitively, for instance, when he or she suspects a false result when a 30-year-old woman with atypical angina has an abnormal exercise test result (low pretest probability). The same abnormal response would be intuitively considered a true-positive result in a 60-year-old man with typical angina pectoris (high pretest probability) [56].

   Typical or definite angina pectoris can be defined as (1) substernal chest pain or discomfort that is (2) provoked by exertion or emotional stress and (3) relieved by rest and/or nitroglycerin. Atypical or probable angina can be defined as chest pain or discomfort that lacks one of the three characteristics of definite or typical angina pectoris.

Table 19.6 Pretest probability of coronary artery disease by age, gender, and symptoms

Age (years)	Gender	Typical/definite angina pectoris	Atypical/probable angina pectoris	Nonanginal chest pain	Asymptomatic
30–39	Men	Intermediate	Intermediate	Low	Very low
	Women	Intermediate	Very low	Very low	Very low
40–49	Men	High	Intermediate	Intermediate	Low
	Women	Intermediate	Low	Very low	Very low
50–59	Men	Intermediate	Intermediate	Intermediate	Low
	Women	Intermediate	Intermediate	Low	Very low
60–69	Men	Intermediate	Intermediate	Intermediate	Low
	Women	Intermediate	Intermediate	Intermediate	Low

Adapted from Gibbons et al. [55]

2. Most patients with a normal or near-normal resting ECG who are able to exercise adequately should undergo standard exercise treadmill testing rather than exercise or pharmacological imaging. Standard exercise ECG tests are currently underutilized in favor of more expensive imaging tests. However, in patients with normal ECG, the negative predictive value of exercise ECG is almost as good as that of a stress imaging test. Exercise ECG should be the first-line test in these patients. All forms of stress echocardiography (or stress imaging) testing are inappropriately applied as a first-line test in lieu of exercise ECG testing, for instance, when screening asymptomatic patients with low pretest likelihood of disease and/or when doing routine assessment of asymptomatic patients after revascularization [22].
3. The prescribing physician should decide which stress imaging study to order. Expertise with the various imaging modalities should be the most important factor determining selection of a specific modality in an individual patient [22]. If more than one technique is available in a given practice or institution, the technique that has been found to be most accurate should generally be the modality of choice [56].
4. Useless testing should be avoided. Every test has a cost and a risk. If the physician's decision will be the same whatever the result of the test, the test should not be ordered [55–60]. If the physician will in any case go to angiography in view of an anatomy-guided revascularization, the imaging test is useless. Compared with the treadmill exercise test, the cost of stress echocardiography is at least 2.1 times higher, stress single-photon emission computed tomography myocardial imaging is 5.7 times higher, and coronary angiography is 21.7 times higher [55]. In particular, in screening asymptomatic adults with low probability of cardiovascular disease, the potential benefit of identification of undiagnosed coronary heart disease should be balanced against the costs of screening (in dollars: 155 for stress ECG; 371 for stress echo; 709 for myocardial perfusion imaging) and the harms of screening which include death or major adverse events during exercise or pharmacological stress, radiation exposure with ionizing testing, false-positive results (leading to anxiety and additional unnecessary tests and treatments), disease labeling (with health insurance denials or increased insurance premium), and downstream harms due to follow-up testing and interventions. The summary of the recommendations of the American College of Physicians advice for high value care is that "clinicians should not screen for cardiac disease in asymptomatic, low risk adults with resting or stress electrocardiography, stress echo, or stress myocardial perfusion imaging" [61].
5. All other considerations being equal, tests involving radiation should be avoided when the desired information can be obtained with a non-ionizing test with comparable accuracy. If you perform a test that utilizes ionizing radiation, choose the one with the lowest dose and be aware of the many factors modulating the dose. The actual delivered dose should always be recorded and included in the patients' records [58]. Education, justification, and optimization are the cornerstone to enhancing the radiation safety of medical imaging. The continuously expanding repertoire of techniques that allow high-quality imaging with lower radiation exposure should be used when available to achieve safer imaging [57].

6. In spite of encouraging results and potential for further short-term technological refinements, no quantitative stress echo technique (including real-time 3D and 2D strain) is ready today for unrestricted clinical use [22, 23].

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Myocardial Viability

20

Luc A. Piérard and Eugenio Picano

20.1 Historical Background

When facing dangerous environmental situations, most animal species react with a sympathoadrenergic fight or flight activation; others, such as the opossum, react with a vagal sympatho-inhibitory discharge or the play dead reaction, which discourages possible predators. The myocardium reacts to dangerous situations with opossum-like behavior. In several altered myocardial states (ischemia, hibernation, stunning), when the local supply–demand balance of the cell is critically endangered, the cell minimizes expenditure of energy used for development of contractile force, accounting at rest for about 60 % of the high-energy phosphates produced by cell metabolism, and utilizes whatever is left for the maintenance of cellular integrity. The echocardiographic counterpart of this cellular strategy is the regional asynergy of viable segments [1]. Both viable and necrotic segments show a depressed resting function [2], but the segmental dysfunction of viable regions can be transiently improved or even normalized by proper inotropic stimulus. From the pathophysiological and experimental viewpoint, stunning and hibernation are sharply separated entities (Table 20.1). Between fully reversible ischemia and ischemia lasting more than 15–20 min, invariably associated with necrotic phenomena, there is a blurred transition zone. Within this gray zone, ischemia is too short to cause myocardial necrosis but long enough to induce myocardial stunning: a persistent contractile dysfunction lasting for hours, days, and even weeks after the restoration of flow [1].

The stunned myocardium differs from the "hibernated" myocardium (Table 20.1). In the hibernating myocardium, myocardial perfusion is chronically reduced (for months or years) but remains beyond the critical threshold indispensable to keep the tissue viable, albeit with depressed performance. While in the stunned myocardium a metabolic alteration causes an imbalance between energy supply and work produced [3], the hibernating myocardial cell adapts itself to a chronically reduced energy supply, and its survival is guaranteed by a reduced or abolished contractile function [4, 5]. Rahimtoola referred to the hibernating heart as a "smart heart" [6],

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Table 20.1 Altered myocardial states

	Stunned	Hibernated
Resting function	Depressed	Depressed
Flow	Normal/increased	Decreased/normal
Coronary anatomy	Any	Severe stenosis or occlusion
Duration	Hours to days	Days to months
Recovery	Spontaneous	After revascularization
Clinical significance	Prognostic	Therapeutic
Clinical models	Acute myocardial infarction	Ischemic cardiomyopathy

appropriately downregulating its biochemical and physiological activities as an act of self-preservation aimed at ensuring the long-term survival of the anatomical and physiological integrity of its constituent cardiac cells. Currently, hibernation is not viewed as a simple consequence of an oxygen deficit but as an adaptive response to maintain cardiomyocyte viability in the setting of reduced blood flow or severe reduction of flow reserve. Reduced calcium responsiveness and alterations in adrenergic receptor density have been proposed as mechanisms for decreased contractility. Morphologically, hibernating myocardium displays features of dedifferentiation, with loss of cardiomyocytes and myofibrils and small mitochondria and of degeneration with increased interstitial fibrosis [6].

Persistent but reversible post-ischemic dysfunction was initially an experimental observation described by Heyndrickx [1], later popularized with the successful term "myocardial stunning" by Braunwald in 1982 [2]. Conversely, myocardial hibernation was a clinical assumption – copyrighted by a cardiac surgeon, Rahimtoola – describing hearts with severely depressed resting preoperative function that spectacularly recover following revascularization [4]. While myocardial stunning might be referred to as a laboratory phenomenon [1] in search of a clinical manifestation, hibernation would seem to be a clinical condition in search of a good laboratory model [3]. Although their separation is clear-cut from the conceptual and pathophysiological viewpoint, stunning and hibernation are sometimes indistinguishable in the clinical setting. They can coexist in the same patient in space (with islands of hibernated and stunned tissue interspersed with necrotic and/or normal cells) and in time (with early phenomena of acute stunning progressively leading to chronic hibernation, as may occur after an acute myocardial infarction with critical residual stenosis of the infarct-related artery). What is clinically important is the distinction between asynergic viable and asynergic but necrotic segments (Table 20.2).

20.2 Pathophysiology Behind Viability Imaging

The clinical cardiologist can address the viability issue with a variety of imaging techniques, including nuclear, magnetic resonance, and echocardiographic methods. The markedly hypokinetic or akinetic regions, which are the target of our

diagnostic efforts to recognize myocardial viability, can have a continuous spectrum of damage, from mild to irreversible (Table 20.3). The different diagnostic probes sample different markers of the viability cascade. If a function is strictly essential to cell survival, e.g., cell membrane integrity, it will be lost only for advanced, close to irreversible degrees of damage (Fig. 20.1). Conversely, other functions such as functional response to inotropic stimulation indicate that the damage is limited and the segment is highly likely to recover. Hibernation has different depths similar to sleep stages that correspond to increasing levels of myocardial damage and decreasing chances of functional recovery upon revascularization (Table 20.3). The initial stages of dysfunction are probably caused by chronic stunning. These stages are characterized by normal resting perfusion but reduced flow reserve, mild myocyte alterations, maintained membrane integrity (allowing the transport of both thallium and glucose), preserved capacity to respond to an inotropic stimulus, and little or no tissue fibrosis. After revascularization, functional recovery will probably be rapid and complete. On the other hand, the more advanced stages of dysfunction are likely to correspond to chronic hibernation. They usually are associated with reduced rest perfusion, increased tissue fibrosis, more severe myocyte alterations (degeneration, apoptosis), and a decreased ability to respond to inotropic stimuli. Nonetheless, membrane function and glucose metabolism may remain preserved for a long period of time. After revascularization, functional recovery, if there is any, will probably be quite delayed and mostly incomplete. The possibility of recruiting the inotropic reserve might appear paradoxical in the presence of hibernation. The traditional

Table 20.2 Differentiation between viable and necrotic myocardium

	Viable	Necrotic
Myocyte	Normal to altered	Absent
Fibrosis	Normal	Increased
Coronary flow reserve	Usually present	Absent
Inotropic response	Usually present	Absent
Recovery	Usually present	Absent
Th, MIBI, FDG uptake	Yes	No
End-diastolic thickness	Normal	Normal to reduced
Microvascular integrity	Present	Absent

Th thallium scintigraphy, *MIBI* Tc 99m-sestamibi, *FDG* fluorodeoxyglucose

Table 20.3 Viability cascade

Levels of damage	DOB	Thallium, FDG	DE-CMR (%)	Chance of recovery	% Viable myocytes
Mild	+	+	25	High	>75
Moderate	+–	+	25–75	Moderate	25–75
Severe	–	–	>75	Low	<25

DE-CMR delayed enhancement cardiovascular magnetic resonance, *DOB* dobutamine, *FDG* fluorodeoxyglucose

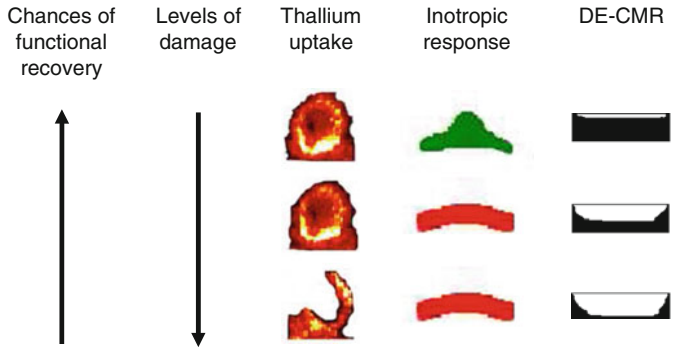

Fig. 20.1 The viability cascade. Higher degrees of cellular damage correspond to progressive loss of cellular functions. Mild damage is associated with preserved inotropic response and thallium uptake. Moderate damage can be identified as a reduced or loss of contractile response with preserved thallium uptake. Severe preterminal damage is expressed by loss of contractile response, no thallium uptake, and transmural scar

concept is that a decrease in resting coronary blood flow indicates that coronary vasodilating reserve is exhausted. However, hibernating segments have some vasodilatory reserve, which is mirrored by contractile reserve [7]. The hibernating myocardium acts like King Lear, the Shakespearean character: once rich and now poor in coronary supply for the presence of a severe flow-limiting coronary stenosis, precluding a normal myocardial function even at rest. However, even the most stunned or hibernating myocardium has some superfluous flow reserve, which can be recruited by the appropriate pharmacological stimulus: "Oh! Reason not the need: our basest beggars are in the poorest thing superfluous" (Shakespeare, King Lear, II, IV, 262–263). The increase in flow will lead to increased function [8], since the physiology of myocardium is that an "erectile" organ [9], and the augmentation of flow is paralleled – in the low flow range – by a parallel increase not only in stiffness but also in function, both in experimental animals and in humans [10]. As stated by Salisbury in the original description in 1960, quoting Webster's unabridged dictionary, "erection in physiology indicates a becoming or being hard and swollen by filling with blood," and myocardium fills these requirements. In a physiologic sense, vasodilation (primarily achieved with adenosine or secondarily with dobutamine) is a "Viagra test" of the viable but hibernating heart.

20.3 Nuclear and Magnetic Resonance Techniques for the Identification of Myocardial Viability

Nuclear medicine long had a monopoly on the diagnosis of myocardial viability. The viable myocardial cell does not move but still maintains a series of biochemical and metabolic activities that are critical for cell survival and are highly useful markers for the clinical identification of viability using nuclear techniques [11] (Fig. 20.2). The viable cells have a residual coronary flow, which can be

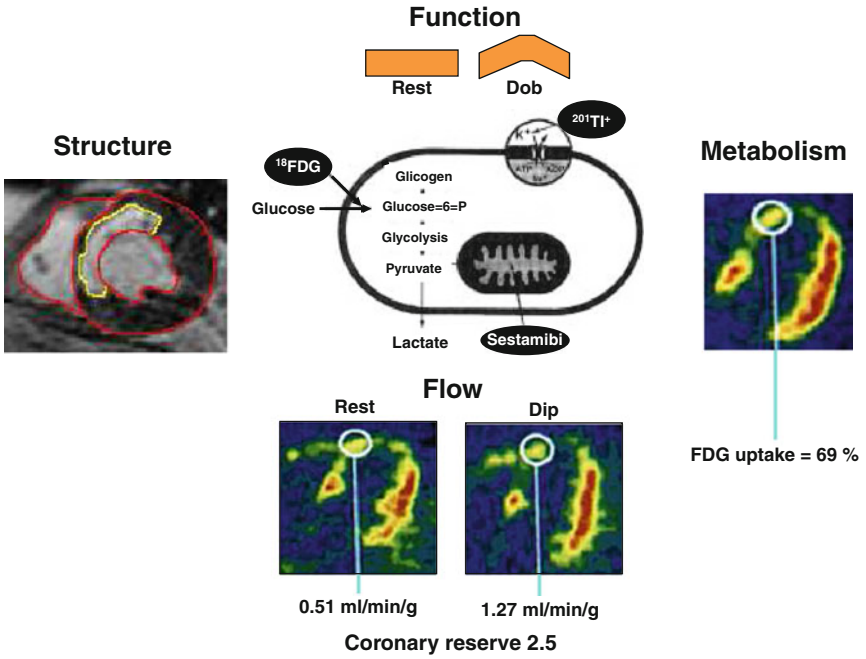

Fig. 20.2 Echocardiographic, nuclear, and magnetic resonance markers of myocardial viability. Cell viability can be identified by 201-thallium, a potassium analog requiring integrity of ionic pumps, by technetium sestamibi, which is trapped intracellularly, or by fluorodeoxyglucose (*FDG*) uptake, which images the glycolytic pathway (*central panel*). With echocardiography (*upper panel*), viability is imaged through its functional fruit of contractile reserve. With magnetic resonance (*left panel*), myocardial structure is imaged through the roots of the transmural extent of the scar, visualized with the delayed enhancement technique: scar tissue is *bright*

visualized with a flow tracer such as technetium sestamibi (gamma emitting and therefore detectable by a gamma camera) or rubidium (positron emitting and therefore detectable by positron emission tomography). The viable cell has membrane integrity and intact function of ionic pumps and is therefore capable of taking up 201-thallium, a potassium analog, and storing it intracellularly. The viable cell can also metabolize glucose, which can be traced with fluorodeoxyglucose, a positron-emitting glucose analog. It competes intracellularly for phosphorylation by means of cellular hexokinase. Phosphorylated fluorodeoxyglucose cannot be further metabolized and remains trapped with the cell as a viability marker. With a completely different approach, cardiovascular magnetic resonance (CMR) with a delayed gadolinium enhancement (DE) technique [12] directly visualizes myocardial scar as hyperenhanced areas in T1-weighted images. The imaging study is performed at rest (no stress required) and after several minutes from contrast medium injection, since the redistribution phase of the tissue (and not the first pass effect of the vessels) is the diagnostic target [12]. Summarizing the versatility of diagnostic markers of viability, we might say that

of the viability plant, DE-CMR evaluates the structural roots, contrast echocardiography (or scintigraphy) the lymph, and stress echocardiography the fruit (functional response). If the fruit is present, the roots (normal structure) and the lymph (microcirculatory integrity) must be present. If roots are destroyed (wall thickness <6 mm or delayed enhancement >50 % of wall thickness), the lymph and the fruit will generally be absent.

20.4 Resting Echocardiography

Echocardiography can provide a reasonably accurate detection of myocardial viability with several parameters derived from different techniques, i.e., resting echocardiography, contrast echocardiography, tissue characterization and myocardial velocity imaging, and pharmacological stress echocardiography (Table 20.4).

Each of these techniques detects a separate variable of the myocardial segments with resting dysfunction, i.e., connective tissue increase, microvascular integrity, intramural function, and contractile reserve. The echocardiographic appearance of a markedly thinned myocardial wall, with an end-diastolic thickness of less than 6 mm and obviously increased echocardiographic reflectivity [13], possibly with a thrombus adhering to the asynergic wall, is a poorly sensitive but highly specific marker of necrosis, because of the extensive replacement of myocytes with fibrous tissue determining thinning and increased wall brightness (Fig. 20.3) [14].

Table 20.4 Ultrasonic assessment of viable myocardium

	Rest 2D echocardiography	Pharmacological stress echocardiography	Contrast echocardiography	Myocardial velocity
Sign	Dyskinetic, thinned, hyperechoic region	Functional improvement	Contrast opacification	Preserved subendocardial strain
Physiological variable	Transmural extent of necrosis	Contractile reserve	Microvascular integrity	Sarcomere shortening
Advantages	Simple	Fast	Simultaneous flow–function assessment	No intervention needed
Limitations	Insensitive	Stress echocardiography know-how	Catheter for intracoronary injection, inadequate evidence for intravenous	Inadequate/ unsatisfactory evidence for clinical use
Clinical value	Mild	Excellent	Unsatisfactory	Unsatisfactory

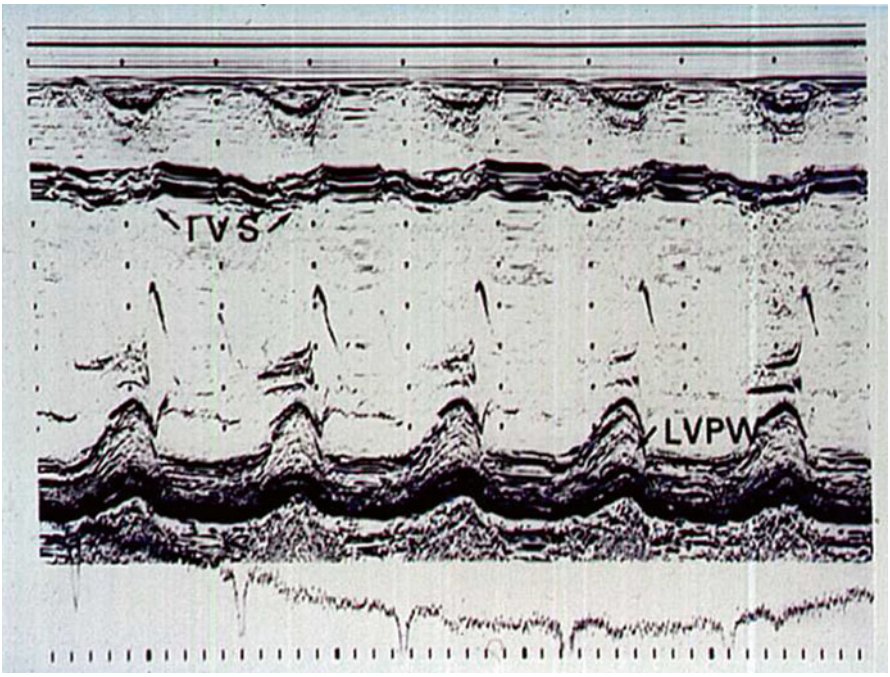

Fig. 20.3 *M*-mode resting echocardiogram of a previous old anteroseptal myocardial infarction, suggesting no residual viability. The posterior wall shows normal thickness, texture, motion, and thickening, whereas the necrotic septum is thinned and hyperechoic, with no active systolic thickening. There is a slight passive systolic movement due to tethering from adjacent normally contracting myocardium. *IVS* interventricular septum, *LVPW* posterior (inferolateral) wall of left ventricle

20.5 Myocardial Contrast Echocardiography

Microvascular integrity is a prerequisite for myocardial viability detection by contrast echocardiography. Viability is associated with the presence of collateral blood flow within the infarct bed, and this preserved flow can be detected with intracoronary [15–18] and – less accurately – with intravenous contrast echocardiography [19–21]. Echocontrast negativity is invariably associated with no response to dobutamine and no functional recovery, whereas echocontrast positivity can be found with and without dobutamine-induced response [18]. The combination of inotropic response and echocontrast information may be useful to titrate the sensitivity of damage, with mild degree of damage (echocontrast with dobutamine response) associated with prompt recovery; moderate degree (echocontrast with no dobutamine response) associated with possible, but unlikely recovery; and severe degree (no echocontrast and no dobutamine response) virtually never associated with recovery, the specific marker of irreversible microvascular and myocyte damage. In the viability cascade (Table 20.3), the loss of microvascular integrity corresponds to

levels of damage very close to irreversibility. If there is no lymph in the plant of viability, it is useless to look for the fruit of inotropic reserve. It is also true that lymph (microcirculatory integrity) can be present, without the fruit of functional integrity: the myocardial region can show contrast echocardiography positivity, with no improvement after revascularization.

20.6 Tissue Characterization and Myocardial Velocity Imaging

The myocardial wall has an echoreflectivity that is not stable during the cardiac cycle, showing a physiological systolic-to-diastolic cyclic variation. Myocardial echodensity decreases with contraction. This quantitative parameter can be translated into the more familiar gray-level codification: the image of a normal wall is darker during end systole and brighter during end diastole. The systolo-diastolic excursion of echodensity is due, in a very complex way, to wall thickening and intramural function. After a few minutes of ischemia, systolo-diastolic variation is abolished but is promptly restored in the case of effective reperfusion for the preserved intramural function, when regional wall motion is still compromised. The usefulness of this index has been demonstrated in the research and clinical settings [22, 23]. Necrotic regions do not show cyclic gray-level variation, which is preserved in asynergic but viable segments. With a conceptually similar approach, in myocardial infarction, transmural extension of scar distribution in the infarct zone is proportionally related to the reduction in systolic function measured by the radial transmural velocity gradient or strain rate imaging or peak radial strain using the speckle tracking technique [24–26].

20.7 Dobutamine Stress Echocardiography

Ten years before the description by Rahimtoola of hibernated myocardium [4], several clinical and experimental studies had recognized the inotropic reserve as a marker of reversible myocardial dysfunction after revascularization during cardiac catheterization (ante litteram hibernation). Regional wall motion was evaluated at ventriculography, and the inotropic stimulus was either post-extrasystolic beat or adrenaline [27–29]. After many years, the same mechanism was employed for the recognition of myocardial viability through pharmacological stress echocardiography. Asynergic, but viable myocardium preserves a contractile reserve, which may be evoked by an appropriate stimulus (Prince Charming's kiss) awakening the seemingly dead myocardium. The recovery of function may take place either through a primary inotropic stimulus (determining a secondary increase in flow to meet the augmented metabolic demands) or through a primary vasodilatory stimulus (determining the increment of regional function) [10]. The prototype of an inotropic stress for viability assessment is low-dose dobutamine [30], originally proposed by Luc Pierard in 1990 and today the reference standard for the

recognition of viability by stress echocardiography. Dobutamine is usually employed as an ischemic stress at a dosage of 5–40 μg kg^{-1} per min. The viability assessment is usually performed at a dose of 5–15 μg kg^{-1} per min. In fact, the effects on myocardial receptors can be obtained at a very low dose of dobutamine, which does not elicit major increases in either heart rate or blood pressure, with the consequent modification of regional function by extrinsic mechanisms.

Following the pioneering observation by Pierard et al. [30], several groups have confirmed that low-dose dobutamine can identify viable myocardium both early after an acute myocardial infarction (stunning) [31–35] and in chronic coronary artery disease (hibernation) [36–46]. Dobutamine-induced functional recovery correlates well with other, more complex imaging techniques, including fluorodeoxyglucose uptake with positron emission tomography (PET) or SPECT and thallium scintigraphy. In a population of asynergic segments, thallium uptake occurs more frequently than a dobutamine-induced response [40–42]. Thallium demonstrates the ability of the myocardium to take up a cation by an active process that takes place at the cell membrane level. Stress echocardiography assesses the ability of the cardiac muscle to increase its contraction in response to an inotropic stimulus, which requires the functional integrity of the cell's contractile machinery. These different cellular functions are not all simultaneously and equally present in the viable myocardium but are hierarchically ranked according to a sequence outlining a viability cascade (Fig. 20.1), conceptually similar to the well-known ischemic cascade. In the viability cascade, a preserved inotropic response to dobutamine expresses a mild level of damage, which will usually allow prompt restoration of function following revascularization (Table 20.3). For presumably more severe levels of damage, a segment can be unresponsive to inotropic stress and still be capable of taking up a significant amount of thallium [36]. This is likely to correspond to a more advanced form of cellular damage, in which only those cellular functions that are strictly essential to cell survival (such as membrane integrity) are preserved. From the pooled analysis of available studies using functional recovery following revascularization as a gold standard [42], thallium has a sensitivity superior to stress echocardiography but a lower specificity, with similar overall accuracy [11, 39–43] (Fig. 20.4). Thus, a significant number of myocardial segments with baseline systolic dysfunction will lack inotropic reserve during dobutamine administration in spite of preserved thallium uptake. Only a minority of these dobutamine-nonresponsive and thallium-uptaker segments are destined to recover following revascularization [11, 39].

In general, there is an excellent correlation between PET and dobutamine echocardiography results [47, 48]. The increased sensitivity of PET compared with dobutamine echocardiography occurs at the expense of lower specificity regarding the recovery of function. In quantitative terms, contractile reserve evidenced by a positive dobutamine response requires at least 50 % viable myocytes in a given segment, whereas scintigraphic methods also identify segments with less viable myocytes [47]. Minor levels of viability, characterized by scintigraphic positivity and dobutamine echocardiography negativity, are often unable to translate into functional recovery but may contribute to an improvement in exercise capacity after

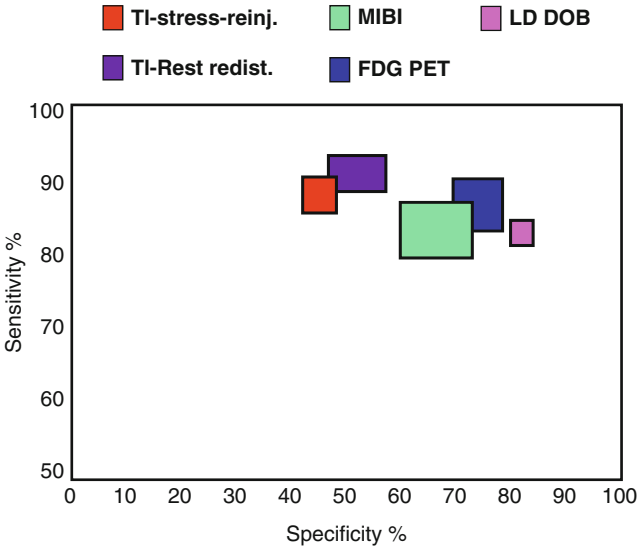

Fig. 20.4 Sensitivity and specificity of nuclear techniques and dobutamine echocardiography in predicting functional recovery (From a meta-analysis conducted by Bax et al. [42]) Low-dose dobutamine echocardiography has a clearly better specificity and a slightly lower sensitivity than nuclear techniques

revascularization, which is better correlated to the extent of viability by PET than to the extent of viability by dobutamine echocardiography [48]. It should be remembered that the relative contribution of the inner wall to total thickening largely exceeds that of the outer muscle. If the endocardial half of the myocardial segment is necrotic, the myocardium can remain asynergic at rest after revascularization, but the salvaged epicardial half can recover contractile reserve elicited during exercise [49]. When compared to DE-CMR, dobutamine stress echocardiography has similar overall accuracy, although for regions with less than 25 % scar, it is possible that dobutamine may provide a higher positive predictive value than DE-CMR [50, 51]. Both dobutamine echocardiography and DE-CMR require intravenous access, but the latter does not require infusion of pharmacological stress agent. Thus, DE-CMR is safer, requires less intensive monitoring, and is also somewhat easier to interpret. However, it is more expensive, less widely available, and cannot be performed at bedside. In poorly echogenic patients, the dobutamine test can be coupled with CMR [52]. An advantage of dobutamine echocardiography is its ability to distinguish between presumably stunned myocardium and presumably hibernating myocardium using both low and high doses of dobutamine. Sustained improvement corresponds in the setting of acute coronary syndrome to stunned myocardium – improvement of contractility in dyssynergic segments until peak dose without deterioration – than can recover its function progressively without revascularization. In the setting of chronic coronary artery disease, sustained improvement implies the presence of non-transmural necrosis and preserved coronary flow reserve. A

biphasic response – initial improvement of contractility at low-dose dobutamine followed by subsequent worsening at high-dose dobutamine – implies viable but jeopardized myocardium with blunted flow reserve. Timely revascularization is required in this condition. Too early follow-up echocardiography may result in underestimation of the extent of possible functional improvement which can continue to progress.

20.8 Alternative Stress Echocardiography Methods

Dobutamine is widely used to assess myocardial viability in both acute and chronic postinfarction patients. However, it does have limitations:

1. In a certain number of patients, even at low doses, it induces myocardial ischemia, which obscures the recognition of viability. Such percentages have been reported to be especially consistent in patients with chronic coronary artery disease evaluated before bypass surgery [37]. This occurs if the resting heart rate is too high, precluding the early phase of contractile reserve. Experimental study showed that ivabradine, a specific bradycardic agent, induces a decrease in heart rate and enhances the inotropic stimulation. However, for some patients, a more selective stress is needed for viability that will not immediately induce ischemia.
2. Concomitant β-blocker therapy blunts the inotropic response to low-dose dobutamine. Although good results have been reported in populations largely on β-blocker therapy [21], β-blockers may conceivably alter the ability to detect contractile reserve at low-dose testing [35]. This problem becomes clinically relevant since patients with acute myocardial infarction or chronic coronary artery disease are largely on chronic β-blocker therapy, and withdrawal may be impractical and possibly dangerous.
3. Even in the ideal conditions of selected patients without inducible ischemia and off therapy, dobutamine has a suboptimal sensitivity for predicting recovery. If a segment shows improved wall motion with dobutamine, it is likely to be viable and move better with revascularization, but viability is still possible even if wall motion does not improve with dobutamine.

These limitations have led to the identification of alternative stresses to evoke an inotropic response in viable segments. Enoximone is a phosphodiesterase inhibitor increasing cyclic adenosine monophosphate (cAMP) concentration independently of β-receptor activation [53]. Dipyridamole evokes a vasodilation through A2-adenosine receptor stimulation, although a flow-independent effect due to direct stimulation of A1-myocyte adenosine receptors has also been suggested [54]. These stresses have a lower ischemic potential than low-dose dobutamine and are unaffected by β-blocker therapy. Low-dose dipyridamole stress (0.28 mg kg^{-1} over 4 min) for viability has a diagnostic accuracy comparable to that of dobutamine for predicting spontaneous and revascularization-induced

functional recovery [55]. In addition, low-dose dipyridamole can be used in combination with low-dose dobutamine for recruiting inotropic reserve [56] in segments which are thallium-uptakers, nonresponders to dobutamine, and destined to recover following revascularization [57]. It has an impressive prognostic value in identifying patients with severe left ventricular dysfunction who can benefit more from revascularization [58]. Also, low-level exercise can recruit a contractile reserve in viable myocardium through production of endogenous catecholamines and with an accuracy comparable to low-dose dobutamine [59]. An exercise test with continuous monitoring of regional function can also identify a biphasic response [60].

20.9 The Clinical Value of Myocardial Viability: Critical or Luxury Information?

The recognition of myocardial viability is associated with a higher incidence of unstable angina in patients evaluated early after an acute myocardial infarction [54].

If patients with severe resting dysfunction are considered, myocardial viability is associated with a better survival rate, both in medically treated patients after acute myocardial infarction (Fig. 20.5) [60–63] and in patients with chronic coronary artery disease submitted to revascularization procedures [64–67] (Fig. 20.6). The quest for myocardial viability is per se prognostically and therapeutically critical in patients with ischemic cardiomyopathy (Table 20.5), with the clinical picture dominated by heart failure symptoms (Fig. 20.7), the coronary anatomy suitable for revascularization, and no spontaneous or inducible ischemia. The indication for revascularization is stronger in those patients with severe left ventricular dysfunction but with preserved myocardial viability and suitable coronary anatomy. When viability is restricted to only certain coronary areas, selective revascularization (usually with angioplasty) can be performed, targeted at stenotic coronary arteries feeding asynergic, yet viable regions. In patients with markedly reduced resting function (ejection fraction <35 %) and chronic coronary artery disease, the stress echocardiography documentation of myocardial viability is associated with a much lower mortality rate in revascularized patients than in medically treated patients [68]. The absence of viable myocardium downstream from a critical coronary artery stenosis in the absence of inducible ischemia substantially weakens the indication for revascularization and directs the clinical decision toward medical therapy or, if possible, cardiac transplantation.

These conclusions apply to the recognition of myocardial viability by virtually all methods, including thallium-perfusion imaging, fluorodeoxyglucose metabolic imaging, or dobutamine echocardiography, with no measurable performance difference for predicting revascularization benefit between the three testing techniques [68]. In patients with viability, there is a direct relationship between severity of left ventricular dysfunction and magnitude of benefit with revascularization [68].

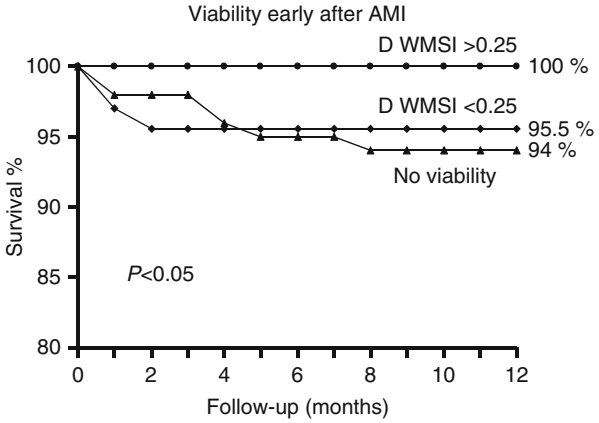

Fig. 20.5 Kaplan–Meier survival curves (considering only death as an end point) in patients with absence (no viability) and presence (viability) of myocardial viability. Patients with myocardial viability are separated on the basis of the number of segments showing improvement by the use of an arbitrary cutoff value for the difference between rest *WMSI* (wall motion score index) and low-dose dobutamine WMSI ($\Delta WMSI$) set at 0.25. Absence of myocardial viability is associated with greater incidence of cardiac death ($p<0.05$). Survival in patients with little myocardial viability is comparable to patients without myocardial viability (Adapted from Picano et al, [64])

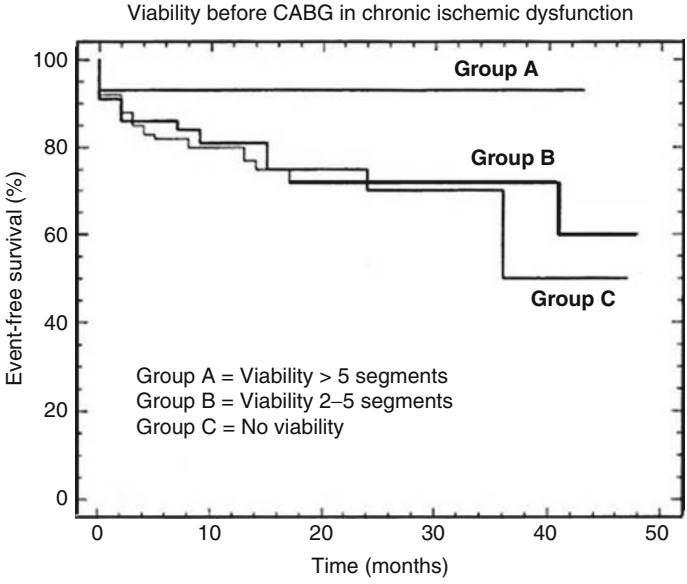

Fig. 20.6 Kaplan–Meier curves showing survival free of cardiac events (including death, nonfatal MI, unstable AP requiring hospitalization, and hospitalization for heart failure) in *groups A* (viability in more than five segments), *B* (viability in fewer than five segments), and *C* (no viability) patients. Event-free survival was significantly better in *group A* than in *group B* or *group C*, both being $p<0.05$ (Adapted from Meluzin et al, [65])

Table 20.5 Clinical relevance of myocardial viability

	Luxury information	Critical information
Global left ventricular function	Preserved	Impaired
Typical history	Single recent infarction	Multiple previous infarctions
Prognostic significance of viability	Predicts angina	Predicts death
Prevailing pathophysiological substrate	Stunned	Hibernated
Method of choice	Stress for ischemia and viability (high-dose pharmacological stress echocardiography)	Selective assessment of viability (low-dose pharmacological stress echocardiography)

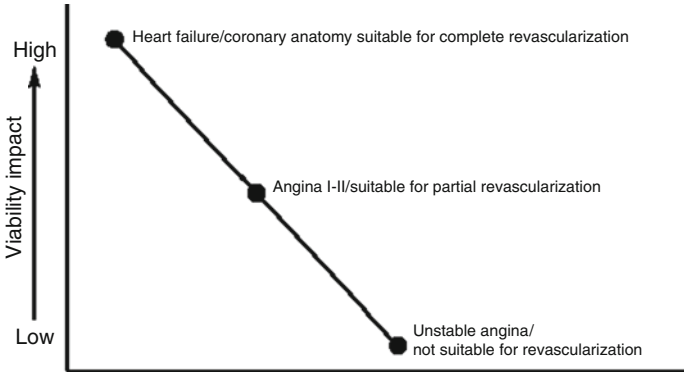

Fig. 20.7 Clinical and angiographic variables modulating the clinical impact of viability testing, which is higher in patients with heart failure symptoms, with little or no anginal symptoms, and with coronary anatomy suitable for complete revascularization

20.10 The Prognostic Value of Myocardial Viability: A Moonlight Serenade

Viability information is like a moon in the sky of prognosis: in the daytime of a preserved global left ventricular function (ejection fraction >35 %), the sun shines, and the moon – even if present in the sky – gives no additional prognostic light. The prognosis is linked to the clouds of ischemia, which obscure the sun of preserved resting function. In these good ventricles, with ejection fraction greater than 35 %, the documentation of ischemia should dictate a revascularization oriented by the results of physiological testing. In the prognostic night light of a reduced left ventricular function (ejection fraction <35 %), the adverse prognostic effects of ischemia are magnified, and ischemia, per se, warrants revascularization. For any given level of inducible ischemia, the prognosis worsens with

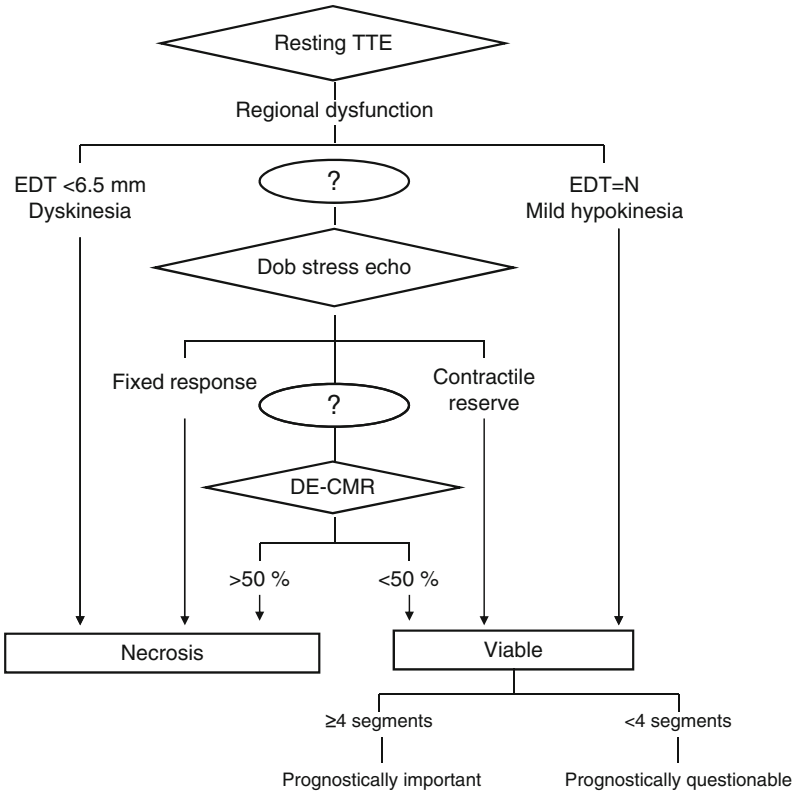

Fig. 20.8 Algorithm for the diagnosis of myocardial viability. A sequential application of resting echocardiography, dobutamine echocardiography, and delayed enhancement cardiac magnetic resonance provides a very accurate diagnosis of myocardial viability at very reasonable cost and without the long-term risks due to radiation burden of scintigraphy and positron emission tomography. *EDT* end-diastolic thickness, *DE-CMR* delayed enhancement cardiac magnetic resonance, *TTE* transthoracic echocardiography

the worsening of the left ventricular function. The documentation of a large amount of viable myocardium reduces the risk of revascularization, and viability-oriented revascularization determines a survival advantage in comparison to medically treated patients. It is important, however, that the "viability moonlight" can direct the cardiologist only when a "full moon" is present, i.e., a considerable amount of viable myocardium. Similar to ischemia, viability response should also be titrated. Viability is not a binary, dichotomous response, but it is a continuous response that should be stratified in different shades of gray. The prognostic protection conferred by viability is only detected when it exceeds a critical threshold of at least four segments or 20 % of the total left ventricle [11, 68]. The beneficial impact of viability on survival is observed both in revascularized and medically treated patients (Fig. 20.8).

20.11 Myocardial Viability in Context

At present various problems increase the difficulty of clinical assessment of myocardial viability and clinical decision making based on the recognition of myocardial viability. We evaluate diagnostic tests in terms of their capacity to predict functional recovery, and this is the best available gold standard. However, we now know that not all segments destined to recover do so early after revascularization. Moreover, some partially viable segments do not recover at all. In addition, functional improvement can occur during inotropic stimulation in the absence of salvageable myocardium:

- *Not all segments destined to recover do so in days or weeks*. Functional recovery is frequently used for comparison in studies evaluating different techniques to assess myocardial viability. It is the gold standard against which the sensitivity and specificity of the various techniques are assessed. In fact, recovery of ventricular function depends on many factors, including quality of the revascularization procedure, perioperative ischemia, and recurrence of obstruction in native or graft vessels. The time course of recovery can be extremely variable, since recovery of ventricular function depends on the quality and completeness of the revascularization procedure and the severity of histological abnormalities: the higher the dedifferentiation of myocytes, the longer the time needed for recovery. In the later stages of hibernation, intracellular glycogen accumulates and myofibrillar units drop out, offering a morphological substrate to the reduced or absent inotropic response to low-dose dobutamine infusion. Therefore, the time course of recovery can be highly variable; a too early assessment may underestimate the incidence and degree of functional improvement.
- *Viability can be present without late functional improvement*. Even if tissue is viable preoperatively, the revascularization is complete, and the follow-up is appropriately long, the myocardium can remain asynergic, and still the restoration of flow can produce beneficial clinical effects [69]. In fact, systolic thickening occurs largely as a result of subendocardial thickening. The presence of viable myocardium in the outer layers of the ventricular wall may induce greater thickening during inotropic stimulation for transmural tethering. Perfusion may actually improve in a large amount of viable myocardium, outside the subendocardial layer, and this may not necessarily translate into an improved resting function. However, the beneficial effects may extend above and beyond functional recovery [70]; viable, well-perfused tissue may exert an antiremodeling effect, contributing to maintaining left ventricular shape and size by preventing infarct expansion and subsequent heart failure. In patients with acute myocardial infarction and ischemic cardiomyopathy, a substantial amount of viable myocardium prevents ongoing left ventricular remodeling after revascularization and is associated with persistent improvement of symptoms and better outcome [71–73]. Exercise capacity may improve, and substrate for arrhythmias may change with a possible antiarrhythmic effect of improved perfusion, without functional recovery.

- *Functional improvement can occur during inotropic stress without viability*. An inotropic stress can induce improvement in an asynergic region even in the absence of significant viability; this occurs because of transmural or horizontal tethering in non-transmural infarctions [63]. This effect is more prominent when the inotropic stimulus is also exerted in normal myocardium and when it is of a moderate to marked degree. This may explain the declining specificity associated with increasing doses of dobutamine. In spite of these theoretical, pathophysiological, and clinical limitations, pharmacological stress echocardiography can now be considered the technique of choice for the recognition of myocardial viability. Its major advantage is the simultaneous insight it provides into resting function, which determines the overall clinical relevance of the viability issue, and into myocardial ischemia, which integrates the prognostic impact of viability and can be assessed at high doses of the drug. The accuracy is high and comparable to scintigraphy and CMR techniques (Table 20.5), but the cost is lower [74], and, similarly to CMR, there is no radiation dose and biological burden increasing long-term cancer risk [75–77]. This is especially important in patients with heart disease who undergo multiple imaging tests with high and cumulative radiation exposure [78] of which neither the cardiologist [79] nor the patient [80] are fully aware. No new technologies (including contrast echocardiography or myocardial velocity imaging) can be proposed for a clinically oriented use today [81–83] (Table 20.6).

However, our time-honored imaging-guided indication to revascularization can be challenged by prospective, randomized trials when modern medical therapy is used for stable ischemic CAD patients with reduced ejection fraction. The results of the STICH (Surgical Treatment for Ischemic Heart Failure) trial proved that myocardial viability (assessed with either dobutamine echo or SPECT) had a significantly lower mortality rate than did patients with nonviable myocardium improves prognosis in patients with left ventricular dysfunction and stable coronary artery disease, independently of the treatment (medical therapy or coronary artery revascularization) [84] (Fig. 20.9). These data counter the prevailing wisdom that viability is per se an indication to revascularization but agree with extensive evidence that modern medical therapy, in particular with beta-blockers, improves left ventricular function in patients with myocardial viability [85–87]. Although the STICH trial was prospective and randomized, there were several limitations: viability was defined as a yes or no phenomenon, no difference was made between sustained improvement and biphasic response, and the number of patients without viability was very low.

20.12 Clinical Guidelines

The currently accepted appropriate indications for clinically driven testing of myocardial viability are summarized in Table 20.7. The results of testing for myocardial viability have been interpreted differently in the guidelines. The

Table 20.6 Methods to assess myocardial viability

	Relative cost	Radiation dose (mSv)	Cancer risk per exam	Accuracy
Stress echocardiography	1	0	0	++
DE-CMR	5.5	0	0	++
MIBI scintigraphy	3.5	10	1 in 1,000	++
Thallium scintigraphy	3.5	20	1 in 500	++
PET-FDG	14	5	1 in 2,000	++

CXr chest radiograph, *DE-CMR* delayed enhancement, *MIBI* Tc 99m-sestamibi, *PET-FDG* positron emission tomography fluorodeoxyglucose

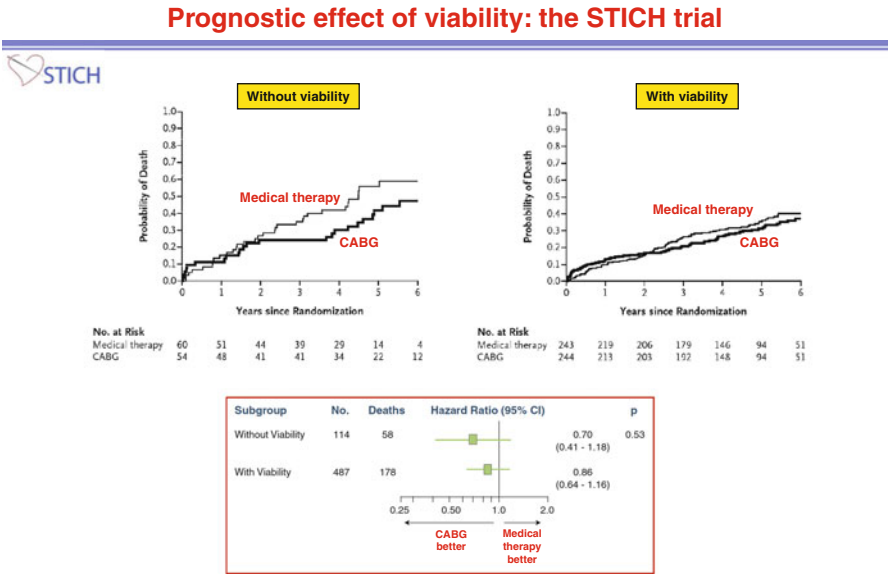

Fig. 20.9 STICH trial results. The probability of death is shown according to myocardial viability status and treatment (Adapted from Bonow et al. [84], STICH trial investigators)

ESC recommendations (class III) are that patients without angina and without viable myocardium should not have CABG [88]. The ACCF/AHA guidelines recommend that CABG might be considered in patients with ischemic heart disease, severe LV systolic dysfunction, and operable coronary anatomy whether or not viable myocardium is present (class II B) [89]. It would thus appear that the ACCF/AHA guidelines most closely reflect the results of STICH, and the assessment of myocardial viability or reversible ischemia by imaging does not appear to be helpful in determining which patients will improve more after CABG [90].

Table 20.7 Most frequent indications to viability testing in CAD patients with HF

	COR	LOE	Ref
Noninvasive imaging to detect myocardial ischemia and viability is reasonable in HF and CAD	II a	C	ACCF/AHA 2013
Viability assessment is reasonable before revascularization in HF patients with CAD	II a	B	ACCF/AHA 2013

Adapted from Yancy et al. [89]
CAD coronary artery disease, *HF* heart failure

Table of Contents Video Companion

See stress echo primer, cases number 6 by Daniele Rovai, MD, Pisa, Italy (viability by dipyridamole with intracoronary contrast echocardiography); case number 8 by prof. Albert Varga, Szeged, Hungary (biphasic response with dobutamine and dipyridamole); and case number 12 (viability test with dobutamine) by Maria Joao Andrade, Carnaxide-Lisbon, Portugal.

See also, in the section Nuovo Cinema Paradiso remastered, the short movie: Myocardial viability, a moonlight serenade (By Prof. Albert Varga, Szeged, Hungary).

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Diagnostic Flowcharts

21

Rocio Toro, Eugenio Picano, and Jose L. Zamorano

Diagnosis of coronary artery disease (CAD) is still mainly clinical; however, an additional test helps to confirm the diagnosis and risk stratification of the underlying disease because early and accurate diagnostic testing is critically linked to an optimal management of CAD. Noninvasive cardiac imaging has become a central tool for the evaluation of CAD. The diagnosis of CAD may also be supported by a functional testing exercise ECG or an imaging stress test. These tests provide important information about the causal relationship between ischemia and the occurrence of the patient's symptoms. Emerging techniques for noninvasive assessment of myocardial perfusion and coronary angiography include cardiac computed tomography, cardiac magnetic resonance imaging, and positron emission tomography [1]. Guidelines usually recommend pathways that are meant to optimize the diagnostic process (minimizing the number of false-positive and false-negative tests). Based on the pretest probability of the patient, the guidelines suggest different stress testing approaches [2–5]. The first step in choosing a noninvasive stress test must consider patient characteristics and their availability. The choice of one test over another is based on improving symptoms and quality of life and minimizing negative cardiovascular events. However, the fact that a test provides more information does not mean that it is the most appropriate test. The information derived from the chosen test must be useful to improve the patient care, so the first step should be based on the patient's features, comorbidities, and quality of life. Some general principles should be considered. First, no single test or strategy has been proven to be overall superior [5]. Second, all published research consistently demonstrates that stress testing with radionuclide scintigraphy and echocardiography provides more information than exercise electrocardiography alone [1–4]. Third, regardless of which test is used, a normal test result should never be considered a guarantee that the patient does not have coronary artery disease or is not at risk of cardiovascular episodes [3]. The rational diagnostic approach can be divided into successive steps, progressing from a clinical picture to an exercise electrocardiography then to an imaging stress test. In highly selected cases, testing for coronary vasospasm can also be considered.

E. Picano, *Stress Echocardiography*, DOI 10.1007/978-3-319-20958-6_21

21.1 Step 1: Clinical Picture

After a clinical history and evaluation of the patient, a 12-lead ECG during or immediately after an episode of chest pain, a resting echocardiography, and cardiac markers, the risk stratification is performed. All this steps will help to estimates the pretest probability. High-risk patients are candidates warranting a coronary angiography; moreover, in certain situations such as ischemia after myocardial infarction, mechanical, or arrhythmic complications, patients with unstable angina not responding to the maximal therapy or patients with malignant arrhythmias should be referred directly for a coronary angiography [6] (Table 21.1). Coronary angiography is the gold standard test for epicardial ischemia but not useful for microvascular dysfunction. It is important to note that coronary angiography is appropriate only when the information derived from the procedure will significantly influence patient management and if the risks and benefits of the procedure have been carefully considered and understood by the patient. Before any testing is considered, one must assess the general health, comorbidities, and quality of life of the patient [6] (Table 21.1).

The guidelines from the American College of Cardiology and of the American Heart Association consistently indicate exercise electrocardiography as the appropriate first test in patients with intermediate risk, interpretable ECG, and at least moderate physical functioning. In patients who are able to perform daily activities, exercise tests are preferred because of their superior capacity to detect ischemia [3]. The exercise testing for assessment of patients who show while resting ECG preexcitation (Wolff-Parkinson-White) syndrome, electronically paced ventricular rhythm, 1 mm or more of resting ST, complete left bundle branch block, or any

Table 21.1 First step option depending on the clinical picture

Coronary angiography	EET	Stress imaging (exercise rather than pharmacological when possible)
High pretest probabilities	*Intermediate pretest probabilities*	*Intermediate pretest probabilities*
Complicated myocardial infarction	After uncomplicated myocardial infarction	Significant ECG abnormalities at baseline Electronically paced ventricular rhythm
Unstable coronary syndromes after maximal therapy	Stable chest pain syndrome with intermediate pretest probabilities	≤1 mm ST-segment depression on resting ECG
Aborted sudden death etc.	Capability to exercise	Severe exercise limitations
	No contraindications to exercise testing	Left ventricular dysfunction (<50 %) critically viable
	Interpretable ECG	Intermediate severity coronary lesions to assess functional situation

Modified and adapted from the guidelines developed by the American College of Cardiology, the American Heart Association, the American College of Physicians, and the American Society of Internal Medicine [1–4]
EET exercise electrocardiography, *ECG* electrocardiography

interventricular conduction defect with a QRS duration greater than 120 ms should be avoided [2]. Imaging stress tests are the first option considered for these and also for those who have severe exercise limitations or left ventricle dysfunction with critical viability [7].

21.2 Step 2: Exercise Electrocardiography Stress Test

The main purpose of stress testing with or without imaging is to identify high-risk patients who may benefit from early coronary angiography and consideration for revascularization to improve their prognosis [8]. The goal of exercise testing is to achieve high levels of exercise, which in the setting of a negative ECG generally and reliably excludes obstructive CAD, or to document the extent and severity of ECG changes and angina at a given workload so as to predict the likelihood of underlying significant or severe CAD [6]. Diagnostic accuracy is improved when consideration is given to additional non-ECG factors, such as exercise duration, chronotropic incompetence, angina, ventricular arrhythmias, heart rate recovery, and hemodynamic response to exercise, or when combination scores such as those of the Duke treadmill or Lauer scores are applied. The advantages of exercise ECG testing are its ability to test functional capacity, which is a powerful predictor of mortality, widespread availability, safety, ease of administration, and relatively low cost. The interpretation of the results of an exercise test as positive or negative on the basis of electrocardiographic changes alone is a simplification to be avoided. Other important information includes a patient's symptoms and exercise capacity and the hemodynamic changes (e.g., in blood pressure and heart rate) that occur in response to exercise. The risk of a fatal event (myocardial infarction or death), which is assumed in this test is about 1 in 2,500 [9]. A negative exercise electrocardiography test is associated with 99.3 % survival at 5-year follow-up in patients with normal resting function. Survival is only slightly lower in patients with previous myocardial infarction [10]. Therefore, in a patient capable of adequate physical effort and with an interpretable ECG, exercise electrocardiography should be the first step in the diagnostic sequence, and in the case of negativity for both electrocardiographic criteria and chest pain at a maximal load, it should also be the latter (Fig. 21.1).

The exercise electrocardiography test can also show a high-risk response (Fig. 21.1), including at least one of the following signs [11]:

1. Early positivity (with an exercise time of less than 4 min)
2. Prolonged positivity with slow recovery (>8 min)
3. Marked positivity (>3 mm of ST-segment depression or ST-segment elevation in the absence of resting Q waves)
4. Global ST-segment changes
5. Associated hypotension, which may indicate either left main or advanced triple vessel coronary artery disease versus underlying left ventricular dysfunction
6. Reproducible malignant arrhythmias

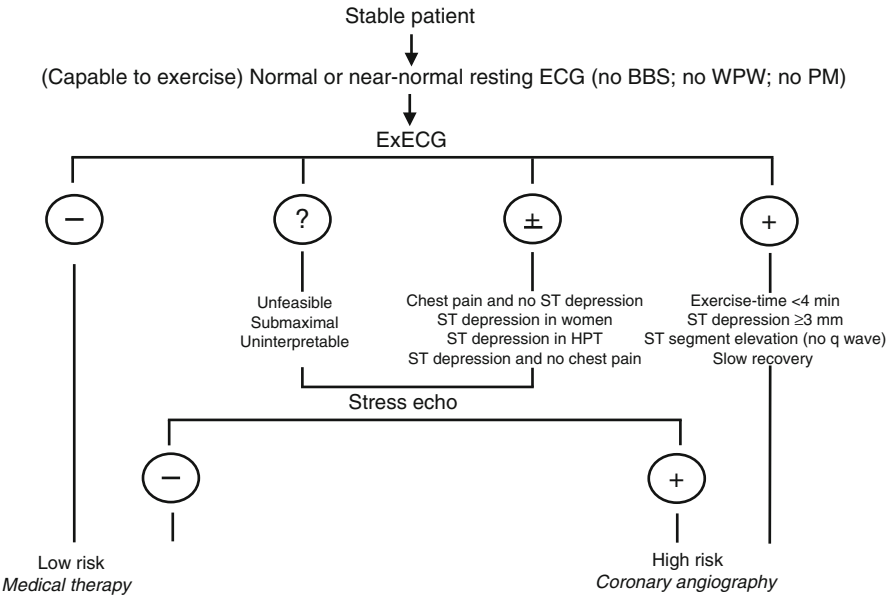

Fig. 21.1 Chain of decisions in stable patients with suspected coronary artery disease (CAD) based on pretest probabilities. *HPT* hypertensives, *LBBB* left bundle branch block, *PM* pacemaker, *WPW* Wolff-Parkinson-White

In patients with these or other markers of adverse prognosis, angiography is warranted without any further imaging testing (Fig. 21.1).

21.3 Step 3: Stress Imaging Testing

This option is recommended as the first component in the chain of decision depending on the presence of a stress imaging expertise and its availability. Patients with low and intermediate pretest probability stress imaging such as echocardiography, cardiac resonance or nuclear imaging is preferred if available. Stress echocardiography is an established method for the diagnosis and prognostic stratification of CAD. Recently, data have emerged supporting the prognostic capabilities of stress echocardiography in patients with various levels of systolic dysfunction, diastolic abnormalities, and valvular heart disease [12]. Related to CAD, stress echocardiography is the test of choice when feasible and consistent protocols with vital sign control are required to conduct an adequate risk stratification and diagnosis [7]. Maximal, symptom-limited stress must be the target. Exercise stress echocardiography, more physiological, is the first option, whenever possible. However, one fifth does not reach the required stress level. For patients who are not able to exercise or for the assessment of myocardial viability, pharmacological stress echocardiography with sympathomimetics (i.e., dobutamine) or vasodilators (i.e., dipyridamole, adenosine) is preferred. Physical stress imaging has a slight superior sensitivity and

Table 21.2 Stress echocardiography indications depending on the patient features

Patient characteristics	Exercise	Dipyridamole	Dobutamine
Under theophylline therapy	**1**	3	**1**
Positive EET at≤6 min of exercise in hypertensives, women, baseline ECG changes	**1**	2	2
Relative hypotension	**1**	3	3
2nd- to 3rd-degree AV block	**1**	3	2
Malignant ventricular ectopy	**1**	**1**	3
Evaluation of antiischemic therapy efficacy	**1**	**1**	2
Well-controlled hypertension	2	**1**	2
Severe hypertension	3	**1**	3
Suboptimal acoustic window	3	**1**	2
Inability to exercise	3	**1**	**1**
Contraindication to exercise	3	**1**	**1**
Asthmatic patient	2	3	**1**
Unstable carotid disease	2	2	2
Permanent pacemaker	Pacemaker stress echocardiography		

1 **Especially indicated,** *2* **relatively contraindicated,** *3* **contraindicated**
EET exercise electrocardiography, *ECG* electrocardiography, *AV* atrioventricular

specificity than pharmacological; but vasodilator stress echocardiography has a higher specificity than inotropic stress echocardiography. This technique is safe, versatile, non-ionizing, and inexpensive and can be rapidly performed in experienced hands but needs a considerable learning curve. However, according to its disadvantages, is remarkable the imaging quality dependence, relatively interobserver variability in the interpretation and reduced sensitivity for multivessel disease [13]. Exercise electrocardiography positivity at an intermediate to high load, as well as negativity at a submaximal workload, or negativity in the presence of chest pain, warrants a stress echocardiography test. The latter should establish the diagnosis of ischemia with a higher reliability and should define its extent and severity. Furthermore, it is important to choose the right stress echocardiography test for the right patient. Table 21.2 and Fig. 21.2 summarize the relative indications and contraindications to each of the major stresses – according to the evidence, which is more extensively discussed on Chap. 19.

As previously reported, exercise echocardiography is the best choice when feasible in patients with intermediate pretest probability. Additionally, it should be the first-line test in patients with conditions making ECG uninterpretable, such as left bundle branch block or Wolff-Parkinson-White syndrome or baseline ST segment abnormalities [14] (Fig. 21.2). Instead of pharmacological stress echocardiography, it may be wise to choose exercise echocardiography also in patients with an ambiguous positive result during an exercise electrocardiographic test at a workload of

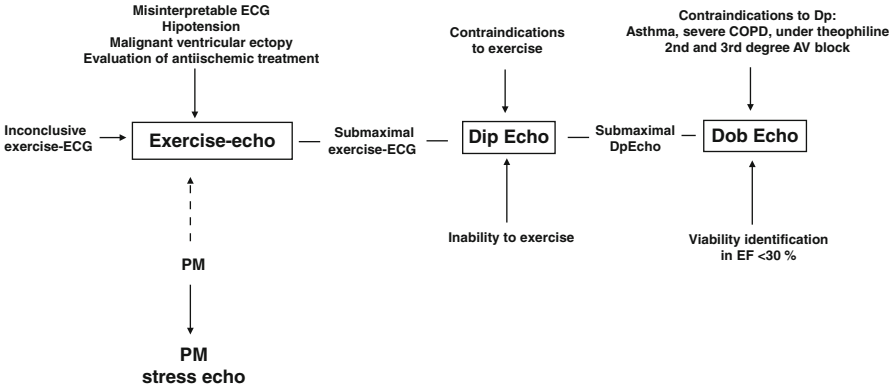

Fig. 21.2 Type of stress echocardiography (exercise, dipyridamole, dobutamine, or pacemaker stress echocardiography) according to several clinical, resting electrocardiography, resting echocardiography, and exercise electrocardiography test variables

Table 21.3 Stress echocardiography risk stratification

Risk	Low (2 % year)	High (20 % year)
Dose/workload	High	Low
Resting EF	>50 %	<40 %
Anti-ischemic therapy	Off	On
Coronary territory	LCx/RCA	LAD
Peak WMSI	Low	High
Recovery	Fast	Slow
Positivity on baseline dysynergy	Homozonal	Heterozonal
ESV increase at peak stress	No	Yes

EF ejection fraction, *WMSI* wall motion score index, *ESV* end-systolic volume, *LCx* left circumflex, *RCA* right coronary artery, *LAD* left anterior descending

6 min or less. This kind of patient (typically, a middle-aged hypertensive woman with ST-segment depression at a peak rate pressure product below 20,000) can have either angiographically normal or severely diseased coronary arteries. Unnecessary testing should be avoided in daily practice [15]. Stress echocardiography test negativity reasonably permits avoiding a coronary angiography, thereby leading to an excellent outcome. Patients with positive stress echocardiograms can be further stratified into intermediate (1–3 % year) or high risk (>3 % year) for major events, and as a result, coronary angiography is warranted (Fig. 21.1). However, as discussed in (see also Chap. 17), the extent and severity of ischemia with the hemodynamic response to exercise, recovery of inducible wall motion abnormalities, stress-induced ECG findings, exercise capacity, patient's symptoms with stress, baseline echocardiographic parameters, anti-ischemic therapy, and clinical risk factors will complete the prognosis assessment picture (Table 21.3).

The accuracy of stress echocardiography for the detection of significant coronary artery stenosis is between 80 and 90 %, which is greater than that of exercise electrocardiographic testing and comparable to that of nuclear stress imaging [16]. On

the other hand, nuclear perfusion imaging can still be a viable alternative in four basic situations, which can be related to the institution, the patient, or the stress used. As with all stress imaging techniques, SPECT perfusion also provides a more sensitive prediction of the presence of CAD than the exercise ECG. Transient ischemic dilatation and reduced post-stress ejection fraction are important non-perfusion predictors of severe CAD. Pharmacological stress testing with perfusion scintigraphy is indicated in patients who are unable to exercise adequately or may be used as an alternative to exercise stress, or when the results obtained with stress imaging are not clearly positive. These situations can be minimized but not totally eliminated, and therefore access to a high-quality nuclear laboratory remains an important resource for the clinical cardiologist (Chap. 38). Ischemia evaluation by cardiac magnetic resonance has shown to be a cost-effective choice with both diagnostic and prognostic accuracy and, therefore, is an alternative to stress echocardiography (Chap. 40). Cardiac magnetic resonance has high temporal and spatial resolution, relatively few contraindications, and absence of ionizing radiation [6].

21.4 Step 4: Testing for Vasospasm

Coronary spam is frequently overlooked. The hallmarks of variant angina include recurrent and spontaneous angina episodes associated with transient ST-segment elevation and relative exercise tolerance. The diagnosis must also be considered in patients with recurrent rest angina associated with syncope or even cardiac arrest [6, 17]. Most episodes happen at midnight and early morning, when the vague tone has increased but while patients have good functional capacity. They can also be influenced negatively by beta-blockers, circadian, and circannual variation. Additionally, some environmental factors such as smoking, metabolic abnormalities, and alcohol consumption might also be pathogenic contributors. Furthermore, certain therapies such as the chemotherapeutic agent 5-fluorouracil, sumatriptan, or ergometrine or bromocriptine can trigger an angina episode [18]. In all these cases, the diagnosis (and the treatment) is easy (and potentially lifesaving) only if one thinks of it in terms of clinical scenarios far from the classic cardiological stage.

This entity has been considered classically low risk, but ultimately, contemporary reports indicate its link with arrhythmias, sudden death arrest, and coronary acute events, with an even worse prognosis than coronary stenosis. Vasospastic origin should be considered when the chest pain is permanent and after a negative maximal exercise stress testing (only approximately half of the patients elevate ST-segment) or imaging stress (see Chap. 16). Noninvasive evaluation includes a 12-lead electrocardiogram, Holter monitoring, exercise testing, and hyperventilation testing [19]. In properly selected patients, vasospasm testing (either with ergometrine or hyperventilation) can be performed safely and practically outside the cardiac catheterization laboratory. Testing for vasospasm is the only way to make a diagnosis that can be overlooked by conventional testing, imaging stress, and even coronary angiography [20]. Vasospasm testing is the last resort if chest pain is present and a coronary origin is sought. Angiography is recommended for this segment of the population, and either ergonovine or acetylcholine has a comparable

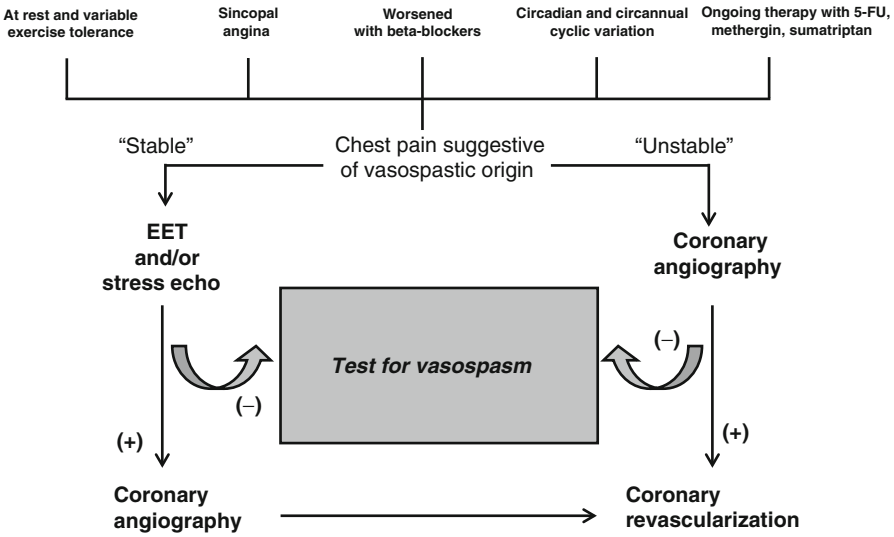

Fig. 21.3 Indications for coronary vasospasm testing in stress echocardiography laboratory. *EET* exercise electrocardiography testing, *5-FU* 5-fluorouracil

diagnosis result. The suspicion of spasm should be raised if coronary arteries are normal or nearly normal, although spasm may coexist with severe organic stenosis (Fig. 21.3).

The diagnosis (and the treatment) is easy (and potentially lifesaving) only if clinical scenarios far from the classic cardiological stage are considered. In properly selected patients, vasospasm testing (either with ergonovine or hyperventilation) can be performed safely and practically outside the cardiac catheterization laboratory [20]. Testing for vasospasm is the only way to make a diagnosis, which can be missed by conventional testing, imaging stress, and even coronary angiography. The single most important factor affecting the frequency with which variant angina is recognized depends on the physician's awareness of its existence.

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Prognosis

22

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According to Maseri, "Identification of patients with known ischemic heart disease who are at low risk is important, first, because it is reassuring for the patient; second, because in such a group the prognostic accuracy of any diagnostic test becomes very low; third, because it is difficult to demonstrate that even the most aggressive treatments can increase life expectancy when the latter is not reduced appreciably" [1].

Echocardiography is the most useful technique for the identification of these patients. In fact, resting left ventricular function, myocardial viability, and stress-induced ischemia showed their prognostic impact in the pre-echocardiographic era, when evaluated by different tools, i.e., radioisotopic techniques for ventricular function [2], fluorodeoxyglucose uptake for viability [3], and exercise electrocardiography [4] and myocardial scintigraphy [5] for inducible ischemia. Only echocardiography allowed all these pieces of information – previously scattered among several diagnostic techniques – to be put together in a synoptic way.

22.1 Left Ventricular Function

The risk increases hyperbolically with the reduction in ventricular systolic function [2], with relatively moderate increments of mortality for values of ejection fraction between 50 and 30 % and with marked increments below 30 % [6] (Fig. 22.1). In the steep segment of the curve, a reduction of 10 % of ejection fraction (from 30 to 20 %) results in an 8–16 % increase in mortality at 6 months; in the flat part of the curve, the same reduction in ejection fraction (from 60 to 50 %) leads to an undetectable, nonsignificant increase in mortality, from 1 to 1.5 %.

The asynergic regions might be viable and therefore may potentially recover to normal function. The more dysfunctional myocardium there is, the more important the search for viability will be (see Chap. 20).

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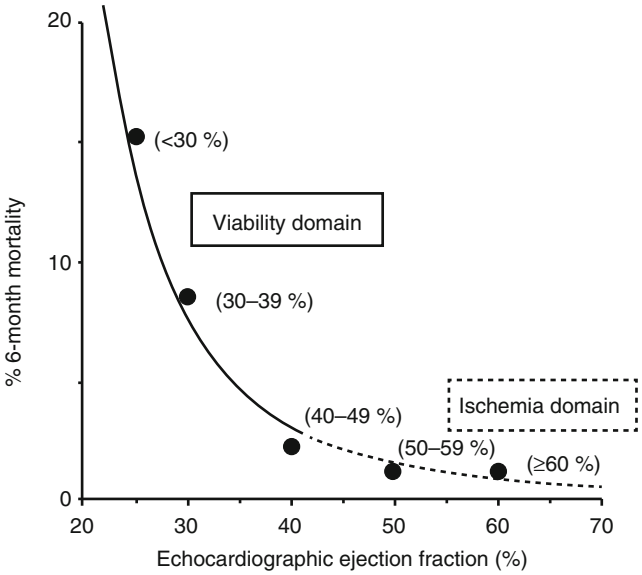

Fig. 22.1 Hyperbolic curve relating 6-month mortality and values of ejection fraction in patients recovering from an acute myocardial infarction. Beyond 40 %, even large increases in ejection fraction determine only a mild decrease in mortality; this is the "flat" arm of the curve, where the impact of viability is probably minimal. Below 40 %, even small changes in ejection fraction determine marked changes in mortality; this is the "steep" arm of the curve, where the impact of viability is probably critical to survival (Redrawn and modified from Volpi et al. [6], with permission)

22.2 Myocardial Viability

In patients with good ventricles (dashed line in Fig. 22.1), viability is basically neutral for survival, and cardiac death can be predicted only on the basis of the extent and severity of induced ischemia [7]. However, myocardial viability detected with low-dose dobutamine tends to be associated with unstable angina and nonfatal reinfarction (Fig. 22.2).

In patients with coronary artery disease and severe chronic left ventricular dysfunction (solid line in Fig. 22.1), the presence of myocardial viability is associated with a better survival rate both in revascularized and medically treated patients [8–13] (Fig. 22.3). The survival benefit is also apparent in patients with both ischemic and nonischemic dilated cardiomyopathy treated with beta-blockers [14]. Also, in patients with severe left ventricular dysfunction evaluated early after an acute myocardial infarction, myocardial viability is associated with better survival both in revascularized and in medically treated patients [15, 16].

22.3 Inducible Ischemia

Tests provoking ischemia, such as exercise electrocardiography and stress scintigraphy, yield more accurate prognostic information when the result is stratified in the space and/or time domain. The ischemic workload, i.e., the stress time necessary to

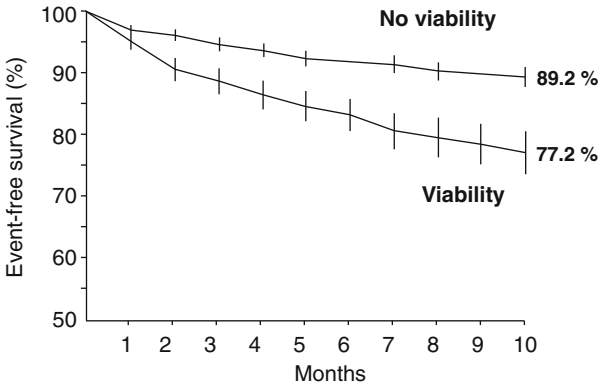

Fig. 22.2 Cumulative survival rates free of spontaneously occurring events (including death, reinfarction, and unstable angina) in patients with absence (*top curve*) and presence (*bottom curve*) of myocardial viability, recognized as functional improvement in a segment with rest wall motion abnormalities after low-dose dobutamine. The presence of myocardial viability is associated with a greater incidence of events ($p < 0.05$) (From Sicari et al. [7], with permission)

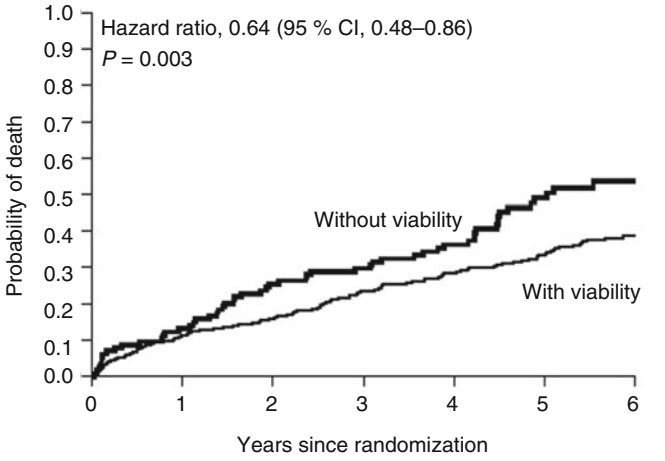

Fig. 22.3 Myocardial viability is associated with better survival in both revascularized and medically treated patients with coronary artery disease and left ventricular dysfunction (Adapted from Bonow R et al., STICH trial investigators [12])

induce a diagnostic modification, is the most useful prognostic information during exercise electrocardiography [4]. The severity and extension of the perfusion defect are the most important information with stress scintigraphy [5]. Stress echocardiography provides information both in the time (ischemic load) and space domain (extension and severity of asynergy) [17]. The timing, extent, and severity of the induced wall motion abnormality are the main determinants of the prognostic impact of stress echocardiography positivity (see also Table 18.1). As for rest

function, the presence of inducible ischemia increases the risk hyperbolically with the progression of severity. The shorter the ischemia-free stress time and the higher the wall motion score index are, the lower is the survival rate (Fig. 22.4).

The prognostic effects of inducible ischemia are additive to resting left ventricular function (Fig. 22.5).

However, prognosis is not destiny, and the natural history may be dramatically changed by revascularization interventions guided by the results of physiological testing. Indeed, in patients with positive stress echocardiography, ischemia-guided revascularization reduces the risk of death by a factor of 11, while, importantly, the risk is three times higher in patients with negative tests and anatomy-guided revascularization [18–21] (Fig. 22.6).

For pharmacological stress echocardiography, effectiveness studies (Table 22.1) have also been performed with large-scale, multicenter, prospective, observational design. The Echo Persantine International Cooperative (EPIC) and Echo Dobutamine International Cooperative (EDIC) trials recruited thousands of patients, enrolled mostly by primary care cardiology centers employing stress echocardiography in their daily work for diagnostic, not academic purposes. As this large and simple clinical trial studies were designed, produced, and interpreted by cardiologists working in primary care centers, most likely dealing with real patients, real doctors, and real problems, they seem more likely to provide data directly relevant to clinical practice [22].

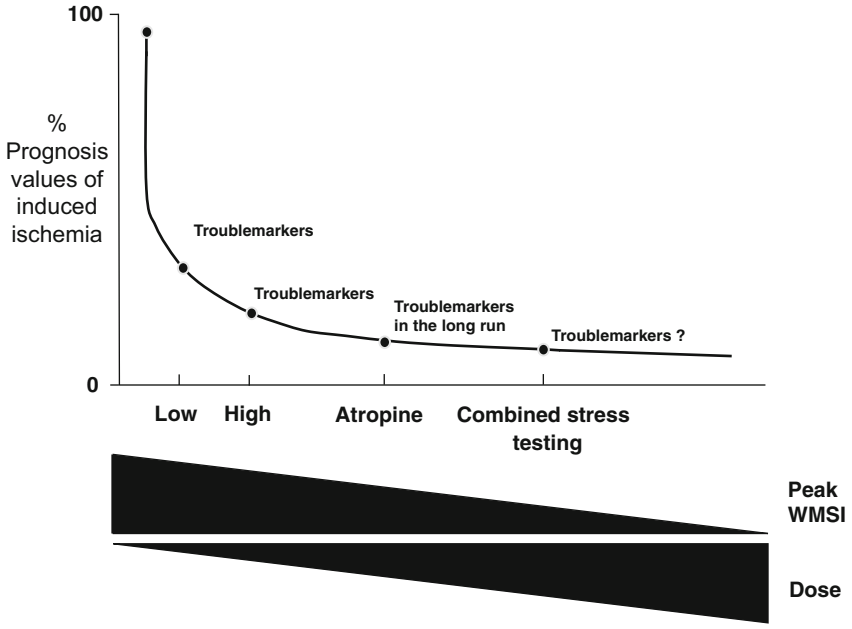

Fig. 22.4 Prognostic impact of inducible ischemia rises hyperbolically with increasing values of peak wall motion score index (WMSI) and decreasing doses necessary to evoke ischemia. The higher the wall motion score index, the lower the ischemic dose and the worse the prognosis

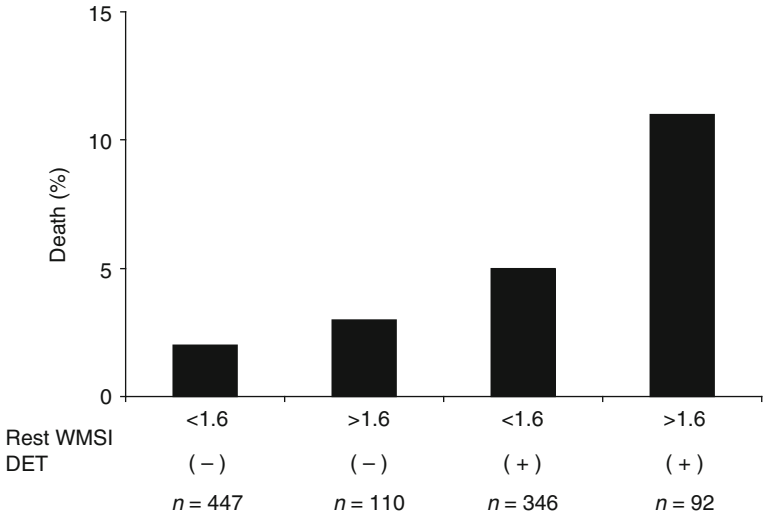

Fig. 22.5 Combined effect of resting function and inducible ischemia (with stress echocardiography) on the incidence of mortality in early postinfarction (10 days after acute myocardial infarction). Follow-up, 14.6 ± 10.2 months. *WMSI* wall motion score index, *DET* dipyridamole echocardiography test. EPIC update ($n = 995$) (EPIC data, adapted from Picano et al. [16], with permission)

22.4 Pathophysiological Heterogeneity of Different Events

In the assessment of risk stratification, disparate events such as coronary revascularization, recurrence of angina, nonfatal reinfarctions, and cardiac death are often pooled together for statistical reasons. Nevertheless, they have very heterogeneous pathophysiological mechanisms and a different clinical meaning. Studies on large populations, with an adequate number of events, have pointed out that the broad definition of the term "predictor of risk" relates to widely different kinds of risk. Early after myocardial infarction, myocardial viability identifies patients at higher risk for subsequent unstable angina [7], but at lower risk of cardiac death [15, 16], since the negative impact on events related to residual ischemic instability is offset by the beneficial impact on functional recovery. Resting function is an excellent predictor of cardiac death, but it does not predict recurrence of angina, which is less frequent in conditions of more extensive dysfunction. On the other hand, inducible ischemia effectively predicts recurrence of angina (with a relative risk of 3:1) and cardiac death (with a relative risk of 4:1), but it only weakly predicts nonfatal reinfarction marginally (relative risk 2:1) [23]. These data might appear contradictory in the light of the classical theory of the progressive worsening of ischemic plaque as a cause of angina, moving from angina at rest to myocardial infarction with total occlusion. In fact, from a pathophysiological standpoint, angina and reinfarction are qualitatively different events. As for reinfarction, the occlusion of a critical, ischemia-producing plaque is asymptomatic in 50 % of patients; it is often an angiographic, not a clinical event (Fig. 22.7). The occlusion of a critical coronary stenosis

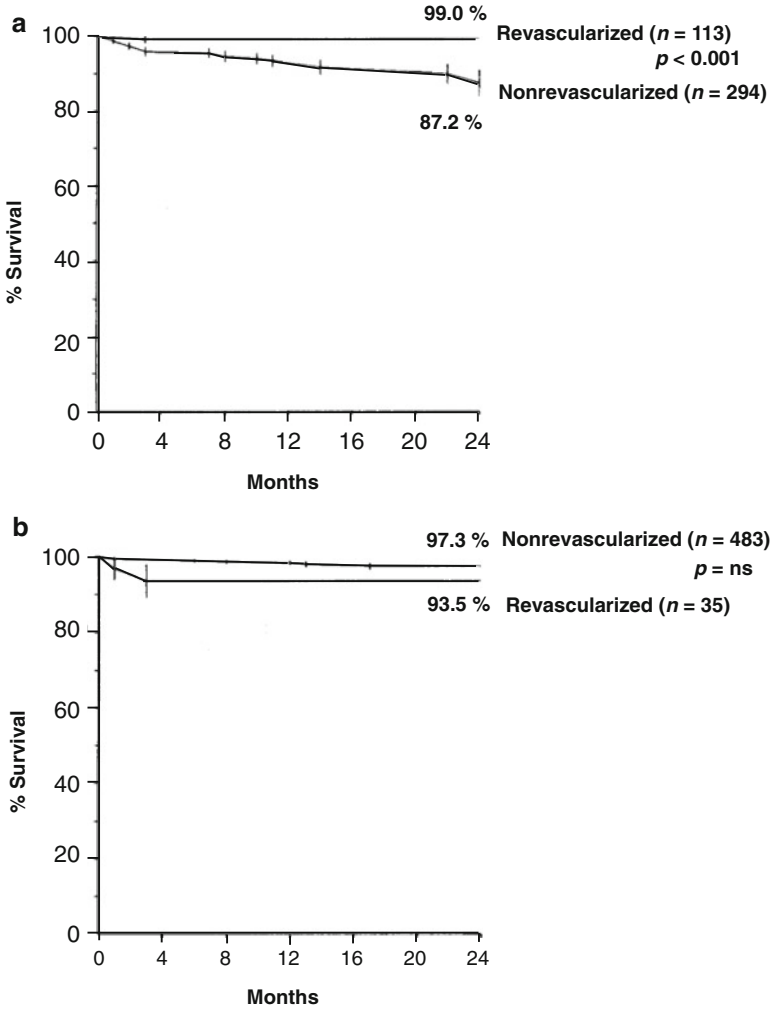

Fig. 22.6 Effect of revascularization on mortality. (**a**) Highly positive results (with an 11-fold reduction in mortality) in patients with ischemia during stress echocardiography. (**b**) Counterproductive effect (with threefold increase in mortality) in patients undergoing revascularization in spite of a negative stress echocardiography test (EPIC data from Picano et al. [16], with permission)

Table 22.1 Single-center versus large-scale design in prognostic studies

Design	Small	Large scale
Enrollment sites	Single center	Multicenter
Patient sample size	Tens (hundreds)	Thousands
Main events considered	Revascularization	Cardiac death
Recruiting centers	Tertiary care	Primary care
Echocardiography reading	Centralized	Peripheral (quality controlled)
Domain of application	Virtual reality	True life

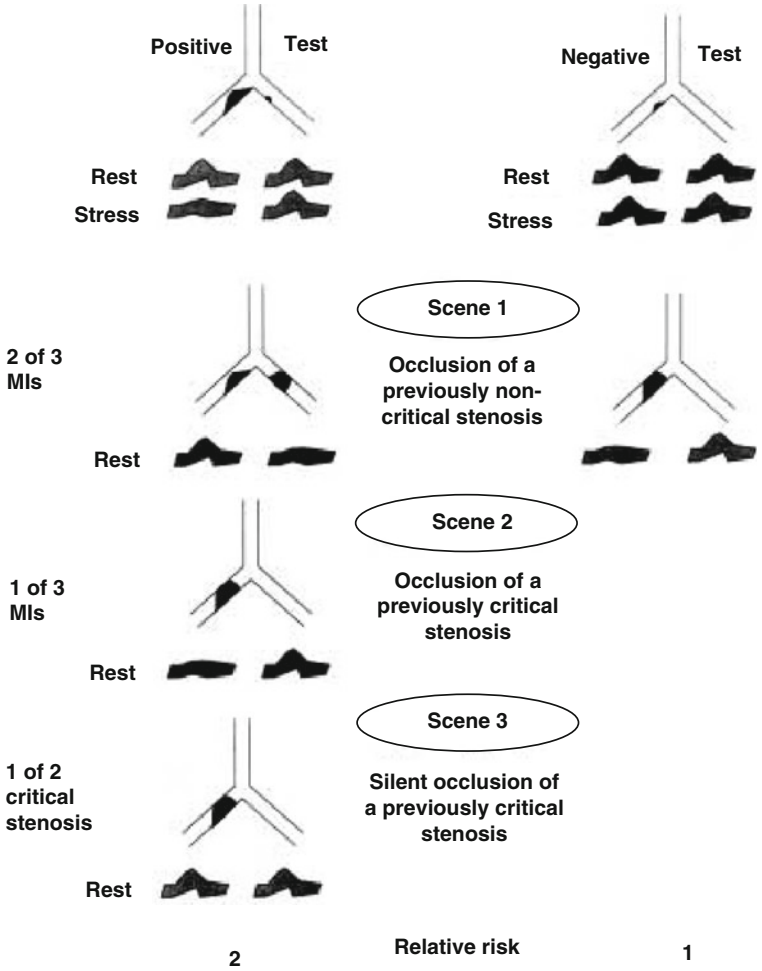

Fig. 22.7 Possible mechanisms of reinfarction. According to this theoretical model, the stress echocardiography positivity of the index test is associated with more extensive coronary artery disease, with critical stenosis in the coronary artery feeding the myocardial region with stress-induced dyssynergy (*left upper panel*); coronary artery disease is more often noncritical in patients with test negativity (*right upper panel*). In keeping with angiographic data, two out of three infarctions are linked to the occlusion of a previously noncritical stenosis incapable of provoking ischemia during stress; in the patient with a positive test (scenario 1, *left panel*), a coronary stenosis different from the ischemia-producing stenosis can become occluded, with the infarction paradoxically occurring in a region different from the area at risk identified during stress. Also, in the patient with a negative stress echocardiography test, the coronary occlusion will provoke the infarction in an area with no inducible ischemia during stress (scenario 1, *right panel*). The second possibility (occurring in one third of infarctions) is the occlusion of a coronary artery with a previously critical stenosis capable of provoking ischemia during stress; this clinical and pathological pattern occurs more frequently in patients with a previously positive stress (scenario 2, *left panel*). Another possible outcome of the critical ischemia-producing coronary stenosis is occlusion without clinical signs of myocardial infarction or regional dysfunction (scenario 3, *left panel*); the myocardium region fed by the occluded coronary keeps contracting normally

is the mechanism underlying 15 % of infarctions; in this subgroup, the predictive power of the test might be very high, but it is diluted by the remaining 85 % of reinfarctions, which occur at previously noncritical stenoses (i.e., transparent to any stress testing). In agreement with pathophysiological premises, the event reinfarction (which in 80 % occurs independently of stenosis significance) is predicted by stress echocardiography, with a relative risk of 2.0. The ratio of fatal to nonfatal reinfarction is higher in the presence of a positive stress. Induced ischemia (imaged as the area at risk showing transient dyssynergy by stress echocardiography) inconsistently identifies the site of future infarction, although most infarctions occurring within 1 year of stress testing are in the area identified as ischemic during stress testing. When the prediction of site of infarction is the reference, stress echocardiography results are wrong in four out of ten cases (infarction occurring in a patient with a previously negative test), right in four cases (infarction occurring in the area identified as ischemic during previous stress), and right for the wrong reason in the remaining two cases (infarcted zone different from the ischemic zone identified as at risk during stress) [24]. These discrepancies cannot be considered surprising if one considers that plaque rupture, inflammation, and embolization are largely independent of plaque size, which limits coronary flow reserve and determines stress echocardiographic results. Vulnerable plaques are often angiographically invisible, and a significant number of disruption episodes that precipitate infarction occur in coronary arteries that were normal or mildly stenotic on a previous angiogram [25]. The recognition of these vulnerable but hemodynamically subcritical plaques is out of reach even for third-generation (atropine) stress echocardiographic testing [24].

22.5 Practical Implications

Clinical evaluation will readily identify patients at high risk: patients with complicated acute myocardial infarction (with arrhythmic, mechanical, or ischemic complications), patients with unstable angina refractory to maximal medical therapy, and patients with ischemic modification during angina suggestive of extensive multivessel coronary disease. In these situations, a good cardiologist needs little help. For most patients, on the other hand, even the best clinician will need instrumental support for an adequate risk stratification (Fig. 22.8). Resting echocardiography helps to identify patients with severe baseline dysfunction who are at high risk and in whom the search for myocardial viability becomes critical. Exercise electrocardiography is the next stress test. It is less sensitive and feasible than stress echocardiography, but the negative predictive value of a maximal test is high and the combination of a maximal exercise electrocardiographic test with a good echocardiographic function identifies a large group of patients at low risk, with an annual death rate of 1–2 % [25]. It is very difficult for any imaging test to add further information to this subset [26–28]. Markedly positive exercise electrocardiography test results identify a group at high risk in which an imaging test might be redundant and hazardous. This subset of patients must be treated aggressively. In the rest of the patients with moderate-to-high workload positivity or equivocal or submaximal

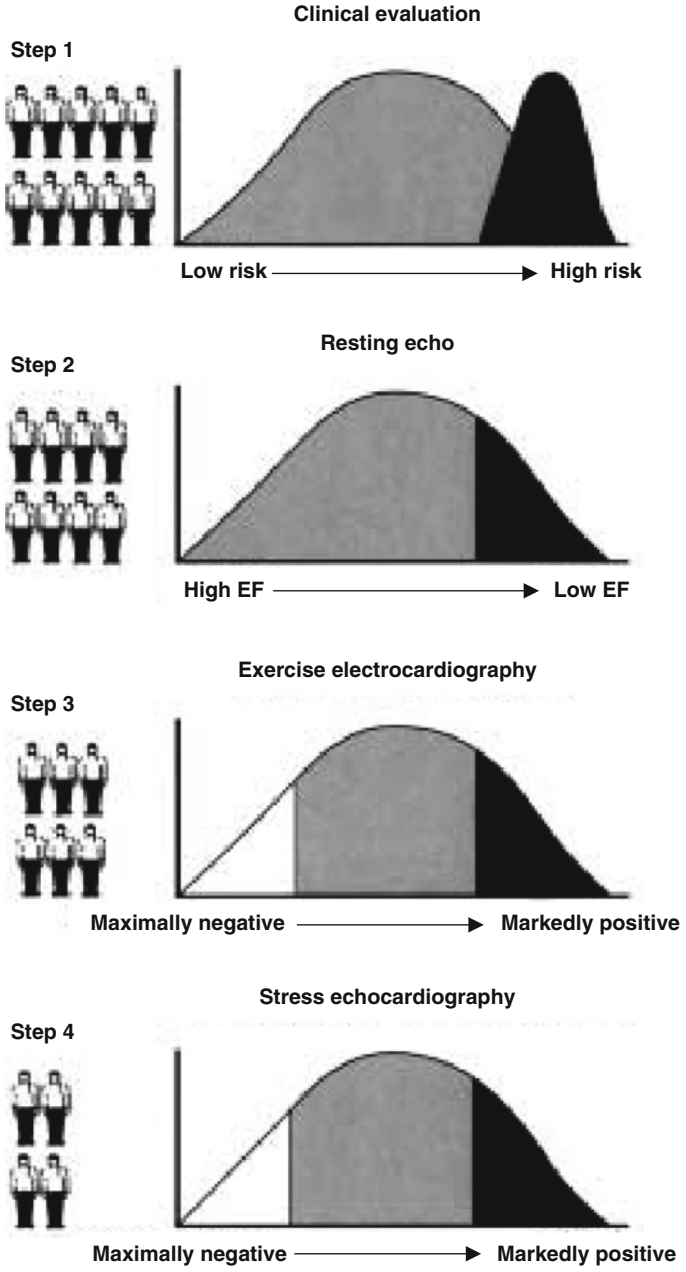

Fig. 22.8 The four-step prognostic algorithm, starting from clinical evaluation (*step 1*) and moving to resting echocardiography (*step 2*), exercise electrocardiography (*step 3*), and, when necessary, stress echocardiography (*step 4*). *Black* high risk, *gray shading* intermediate risk, *white* low risk, *EF* ejection fraction

results, the combined information provided by rest and pharmacological stress echocardiography results in an integrated view of the most important prognostic determinants (resting function and ischemia) that identify different subsets of patients, with an annual death risk ranging from about 1 % (good resting function, no inducible ischemia) up to 20 % (severe rest dysfunction, extensive inducible ischemia at low dose). A high-risk response points to the need for more invasive procedures. In the early postinfarction phase, revascularization increases the risk of death if undertaken in patients without inducible ischemia on the basis of an anatomical indication, whereas it markedly reduces this risk in patients with inducible ischemia. In patients with poor prognosis, a coronary angiography is warranted in view of a revascularization. As a rule, the steeper the decline of annual survival in the medically treated control group, the greater the benefits of revascularization [1].

22.6 Comparison of Invasive and Noninvasive Approaches

In the field of prognostic stratification, in the absence of carefully controlled studies, any chosen strategy currently reflects a philosophy rather than a scientifically based method [27]. The invasive philosophy considers coronary angiography as the only essential tool; the noninvasive strategy uses a noninvasive test to indicate access to catheterization in clinically stable patients. In the invasive approach, stress echocardiography is considered as a possible candidate to break open the vicious circle of chest pain: coronary angiography revascularization; in the noninvasive approach, it is considered capable of offering insight into the main determinants of survival, i.e., function, viability, and ischemia. The noninvasive strategy can be preferred by necessity when there is restricted access to cardiac catheterization facilities, but it remains a questionable choice in the presence of unrestricted access to coronary angiography. When there is access to the invasive procedure, the question arises as to whether all patients should be catheterized and all stenoses revascularized ("angiography in all, and dilate what you can") or whether a simple stress test procedure is preferable, avoiding the further risks and discomfort of any additional procedure ("a noninvasive stress test, and back home safely") [29–31]. Risk stratification can be carried out aggressively (and expensively) or in a low-profile, less expensive manner with noninvasive testing first and medical therapy in all patients with negative stress. Only then can the noninvasive stratification strategy centered on stress echocardiography be accepted as a way of saving resources, and above all of providing patients with better treatment. Observational studies have suggested that the noninvasive method not only saves money but may actually result in a longer survival time [18, 28]. Randomized trials show a worse outcome in patients with anatomy-guided revascularization when compared to those with ischemia-guided revascularization [32–35]. In patients with chronic stable angina, the anatomy-driven revascularization will not increase life expectancy and/or quality of life [36], although this may change in the era of drug-eluting stents. Nevertheless, only 9 % of patients with recent myocardial infarction undergo stress testing before coronary intervention [29], but more than 40 % of patients undergo angioplasty after

receiving thrombolytic therapy [30]. In spite of accumulating evidence and recommendations of guidelines, the risk stratification strategy is often the result of a costly philosophical opinion rather than an evidence-based behavior.

22.7 Risk Stratification in Clinical Guidelines

The criteria for moderate-severe ischemia involving >10 % of LV in stress echocardiographic, nuclear, and CMR imaging are somewhat technique specific and are listed in Table 22.2 [37]. Across the imaging modalities, they identify a threshold of critical mass of ischemic myocardium triggering a prognosis-changing revascularization [38] (Fig. 22.9). In symptomatic patients with suspected CAD, a strategy of initial CTA compared to functional testing with stress echo did not improve clinical outcomes and was associated with higher radiation exposure [39].

Of note, this approach neglects the possible contribution of several ancillary markers of ischemia which may help in severity stratification, such as severe mitral

Table 22.2 Definition of risk for various test modalities

Definition	Low risk	Intermediate risk	High risk
CV mortality	<1 %/year	1–3 %/year	>3 %/year
SE	Negative	1–2 segments	≥3 segments
SPECT	Negative	1–10 % of LV	>10 % of LV
Stress CMR			
Functional	Negative	1–2 segments	≥3 segments
Perfusion	Negative	1–10 % of LV	>10 % of LV
CTA	Normal coronary arteries or plaques only	CAD without high-risk pattern	3VD, or left main, or proximal LAD stenosis

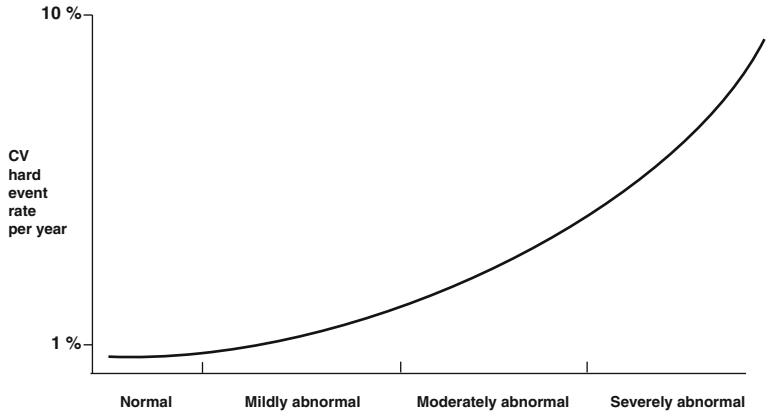

Fig. 22.9 The increase in risk rises hyperbolically with the extent of ischemia during stress imaging (Adapted from Ref. [37])

insufficiency, LV dilation, or B-lines during stress. However, these ancillary signs are rare and incompletely validated, although helpful, when present, to tailor the risk profile in the individual patient. The high-risk pattern during stress corresponds to the eligibility criteria to enter the ISCHEMIA (International Study of Comparative Health Effectiveness With Medical and Invasive Approaches) trial, sponsored by NIH/NHLBI. The primary aim of the ISCHEMIA trial is to test the hypothesis that among patients with moderate-severe ischemia on stress imaging, a routine early invasive strategy with coronary angiography followed by optimal revascularization plus optimal medical therapy is superior to an initial conservative strategy of optimal medical therapy alone, with angiography and revascularization reserved only for those who fail to respond to medical therapy. The results of the trial should be available in 2018.

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Part III

New Technologies and New Diagnostic Targets

New Ultrasound Technologies for Quantitative Assessment of Left Ventricular Function

23

Thomas H. Marwick and Eugenio Picano

Stress echocardiography is an established and mainstream method for the diagnosis and risk stratification of patients with known or suspected coronary artery disease [1, 2]. While the overall accuracy of stress echocardiography techniques is high, these methods are inherently limited by the subjective, eyeballing nature of image interpretation [3] and the learning curve [4] with relatively wide interinstitutional variability [5], unless conservative reading criteria are developed a priori through consensus [6]. In addition, the diagnosis is based on visual assessment of systolic thickening and endocardial motion, estimating radial function, which is theoretically less sensitive to ischemia than longitudinal and circumferential function [7]. Electrical activation disturbances (such as left bundle branch block or right ventricular pacing), hemodynamic conditions (such as right ventricular overload), or extracardiac factors (such as cardiac surgery or constrictive physiology) may affect wall motion independently of ischemia, making the analysis dependent on evaluation of systolic thickening alone [8]. Tachycardia and an increase in blood pressure may mimic ischemia, inducing a reduction of wall motion and thickening [9] – this is usually global but may be regional. Conversely, ventricular unloading (e.g., caused by mitral insufficiency) may mask ischemic wall motion abnormalities because of hyperkinesis and low wall stress [10]. Our current approach to subjective wall scoring is to evaluate contraction on a transmural basis, without the ability to assess subendocardial function, which is more sensitive to ischemia than the subepicardial layer [8]. Furthermore, the current application of stress echocardiography is certainly "intelligent" (full of useful clinical information), but the results cannot be easily reduced to a "beautiful" graphical display, understandable at a glance also by a non-imaging specialist. The development of an objective, quantitative method for wall motion analysis during stress testing would overcome these limitations, translating the inducible wall motion abnormality from an opinion into a number (Table 23.1).

This would improve accuracy, shorten the learning curve, and improve communication of stress echocardiography results with clinicians, ultimately strengthening the current clinical and scientific role of the technique. In addition, the quantitative

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Table 23.1 Present reality and future promises in stress echocardiography

	What we have	What we need
Regional function	Thickening, motion	Strain
Ventricular function	Radial	Longitudinal and circumferential
Segmental function	Transmural	Subendocardial
Graphical display	"Intelligent"	"Beautiful"
Operator dependence	High	Low
Learning curve	Long	Steep
Diagnostic gold standard	Expert opinion	Automatic number

assessment of the time course of left ventricular contraction would allow a more comprehensive assessment of the complex physiology of the left ventricular function, which is incompletely described with a simple assessment of the radial transmural function through endocardial motion and thickening at a single end-diastolic and end-systolic time point during the cardiac cycle.

Strenuous efforts have been made in the last 30 years by bioengineers, industry, and researchers to reach the ambitious, yet elusive, target of quantitative assessment of ventricular function. Different waves of new ultrasound technologies such as *M*-mode for longitudinal function assessment with mitral annular plane systolic excursion (MAPSE), anatomical *M*-mode, tissue characterization, color kinesis (CK), tissue Doppler echocardiography (TDE), tissue Doppler strain rate imaging (TDSRI), two-dimensional speckle tracking imaging (2D-STE), and real-time three-dimensional echocardiography (RT3D) have been proposed to overcome the limitations of conventional echocardiography [11]. Each approach can be broadly assigned to five technological generations of ultrasound imaging: *M*-mode, 2D, speckle tracking, tissue Doppler, and 3D (Table 23.2). Many quantitative echocardiographic techniques for regional and global contractility assessment have had promising starts, but none of them has been incorporated to date into standard practice.

23.1 Spatial and Temporal Heterogeneity of Left Ventricular Contraction

The contraction of the heart is a complex phenomenon involving a deformation (strain) along three coordinates: radial thickening (centripetal squeeze), longitudinal (base-to-apex shortening), and circumferential shortening (related to torsional twist) (Fig. 23.1). Strain is a unitless quantity, and typical values of end-systolic radial, longitudinal, and circumferential deformation for normal volunteers are approximately 0.35, −0.18, and −0.20, respectively, in the midventricle, with good agreement between cardiovascular magnetic resonance (CMR) tissue tracking and quantitative echocardiographic techniques [11]. The complexity of this movement is further magnified by the physiological spatial and temporal heterogeneity observed in humans among different left ventricular segments both in resting conditions [12–14] and during stress [15, 16]. The left ventricular rotation as viewed from

Table 23.2 The five main approaches to quantification

	M-mode	2D	2D speckle	Doppler	RT3D
Biosignal	Mitral annulus	Grayscale *B*-mode	Myocardial deformation	Tissue Doppler	Segmental volume
Variable	Annulus motion	Endocardial motion	Strain	Myocardial velocity	Regional EF
Main function	Longitudinal	Radial (circumferential)	Longitudinal (circumferential)	Longitudinal	Composite
Angle dependence	No	No	No	Yes	No
Eyeballing feedback	+++	+++	+++	–	+++
Graphical display	Sober	Elegant	Elegant	Complex	Intuitive
All segments	±	++	++	–	+++
First generation	MAPSE	Centerline	2D speckle	TDI	Offline 3D
Second generation	Anatomical *M*-mode	Color kinesis	3D speckle	SRI	RT3D
Imaging/analysis time	Seconds	A few minutes	A few minutes	Several minutes	A few minutes

RT3D real-time three-dimensional echocardiography, *MAPSE* mitral annular plane systolic excursion, *TDE* tissue Doppler echocardiography, *SRI* strain rate imaging

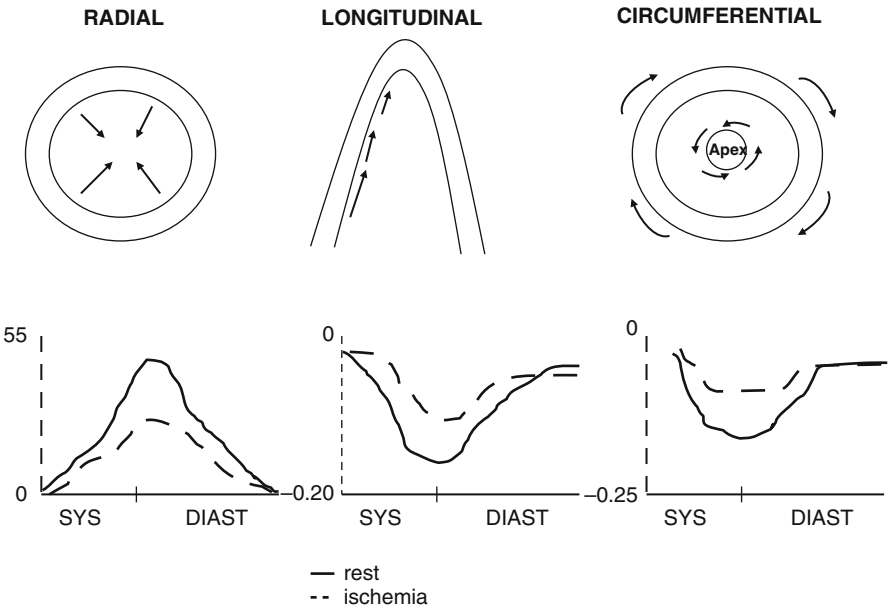


Fig. 23.1 A schematic representation of the three coordinates of left ventricular contraction: radial, longitudinal, and circumferential (*upper panels*). Note the physiological heterogeneity of left ventricular contraction (expressed by the *length of arrows*). Radial thickening is higher in the anterior and septal than in the inferior and lateral segments. Longitudinal shortening is highest in basal and lowest in apical segments. Circumferential shortening is highest (*clockwise*) in basal, counterclockwise in apical segments (*right panel*). All three can be altered in stress-induced ischemia (*lower panels*), which provokes both a reduction and a delay (dyssynchrony) of contraction in involved segments

the apex is clockwise in basal segments and counterclockwise in apical segments, creating the torsion or twisting motion. Toward the end of systole, a negative torsion velocity or untwisting begins, possibly as a result of the release of elastic energy accumulated in systole [11]. Systolic rotation, as a component of torsion, winds the heart muscle like a spring, setting up recoil for early diastole. Within each segment, there is also a clear vertical (transmural) gradient, with the subendocardial layers contributing to the majority of systolic thickening (radial function) [17], longitudinal shortening [18], and segmental twisting [19]. This physiology can be assessed experimentally but is difficult to apply all of these measurements clinically. At present, global longitudinal strain is the most feasible measurement, but regional strain – especially radial strain – has limited reproducibility.

The complex 3D deformation of the heart during the cardiac cycle may not be adequately captured by investigating only radial, transmural function with regional wall thickening and motion. The presence of stress-induced ischemia reduces (and may abolish) all three components of deformation – radial [20], longitudinal [21], and circumferential [22] (Fig. 23.1, lower panel) – but not all of them simultaneously and symmetrically. Experimentally, a reduction in overall systolic thickening (which is an index of radial function) is not the most sensitive mechanical

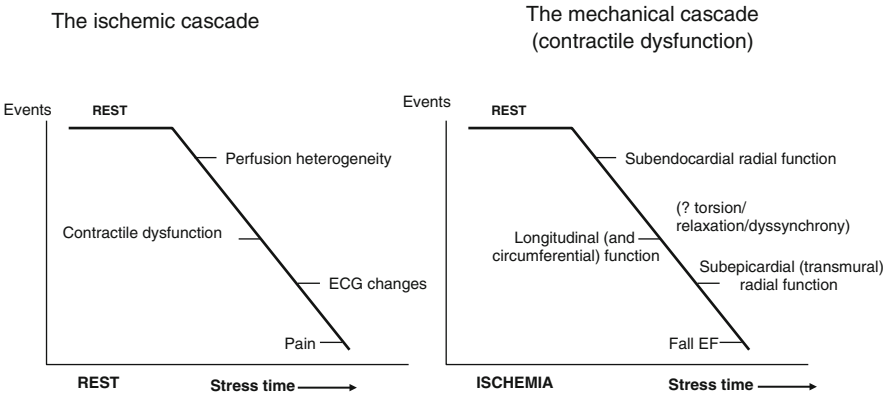


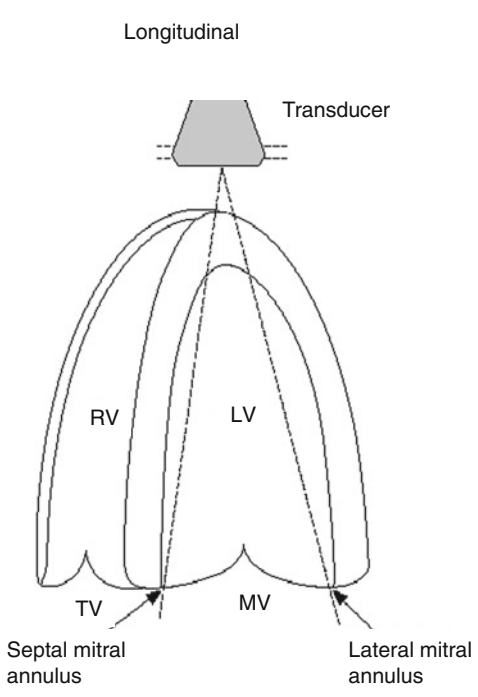
Fig. 23.2 On the *left*, the ischemic cascade, with a well-defined sequence of events, where perfusion heterogeneity is an earlier marker than regional contractile dysfunction, classically evaluated on the basis of segmental wall thickening. On the *right*, the mechanical cascade shown in its increasingly recognized complexity and heterogeneity. Segmental function indices (displayed on the *right* side of the cascade) tend to appear earlier than global function indices, with subendocardial dysfunction being earlier and more profound than subepicardial dysfunction. Among global indices, longitudinal (and probably circumferential) indices occur before radial indices. Ejection fraction reduction can appear only downstream in the cascade, since at initial stages the early depression of longitudinal function can be masked by normal, compensatory supernormal radial function

manifestation of local ischemia: subendocardial fibers that support ventricular long-axis function are more sensitive to ischemia than the circumferential ones responsible for normal radial myocardial thickening (Fig. 23.2) [23]. This is also true in early heart failure, where there is an initial phase when the reduced longitudinal function is compensated by supernormal radial function, yielding a normal ejection fraction [24, 25]. This correlates only weakly with percent systolic thickening and more closely with circumferential strain [26]. As discussed above, segmental to systolic thickening and motion can be normal at an initial stage when the subendocardial function is already markedly impaired.

In clinical echocardiography, we usually rely on ejection fraction (an index of global function) and percent systolic thickening (an index of regional function). Regional ejection fraction can be viewed as a composite measure of the local contribution to ejection, determined by the increased motion and deformation (circumferentially and longitudinally) of the endocardium. The regional ejection fraction increases significantly from base to apex, and remarkably, in normal hearts the regions with the highest ejection fraction show the least wall thickening [26]. On simple pathophysiological grounds, we might achieve better diagnostic sensitivity for more subtle, initial myocardial disease if we also assess longitudinal function, for the global assessment, and subendocardial function, for regional segmental assessment. In the ischemic or cardiomyopathy cascade, left ventricular dysfunction might be sampled upstream of the classical, conventional markers of global and regional dysfunction used in standard conventional echocardiography [24]. The different technologies proposed for quantitative assessment of left ventricular function focus on different aspects of this functional heterogeneity (Table 23.2).

23.2 *M*-mode Echocardiography and Longitudinal Function

The assessment of longitudinal function can be obtained not only with last-generation technology, but also – and probably with even greater reproducibility – by simple *M*-mode echocardiography, measuring the mitral annulus systolic amplitude excursion (Table 23.2). Mitral ring echoes are of high amplitude and can be recorded in the large majority of patients [25]. The technical basis, *M*-mode echocardiography, is simple and widely available. The printed records can be measured directly, thus avoiding the requirement for consensus and establishing clear unities (Fig. 23.3). Values greater than 25 mm are normal and below 20 mm are clearly abnormal. Use of different sites around the atrioventricular ring may allow the effect of induced ischemia to be localized, although not to the same extent as with the standard method. The technique detects the physiological heterogeneity of longitudinal function of the normal heart [14], the ischemia-induced alterations in longitudinal function during stress [27, 28], and the early changes in left ventricular function during cardiomyopathy [23, 24], with an accuracy similar to more trendy



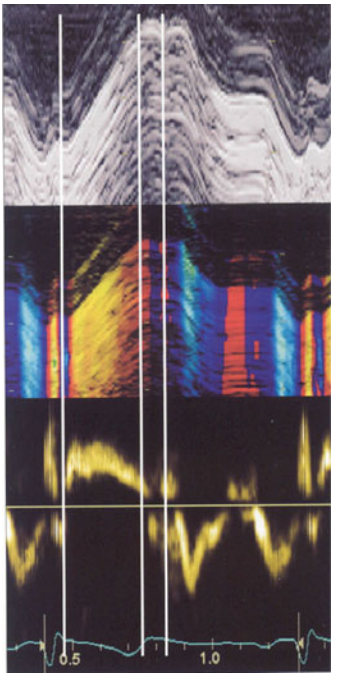


Fig. 23.3 The downward motion of the base of the ventricle toward the transducer can be imaged with mitral annular plane systolic excursion (*left*). On the *right*, the synchronous assessment of longitudinal function by *M*-mode (*upper panel*), tissue Doppler (*middle panel*), and strain rate imaging (*lower panel*) (Adapted and modified from [7, 14])

techniques such as TD or TDSE. No colors, no 3D reconstruction, and no fancy tracings support the interpretation. As a result, the technique suffers from the widespread perception that it is in some ways out of date. Yet, according to Derek Gibson [29], older techniques should be continuously kept under review, since reintegrating them into the mainstream often brings surprising dividends.

Specifically regarding stress applications, stress ventricular long axis demonstrates the mechanical behavior of the subendocardial layer of the myocardium [30]. The myocardial fibers of this layer are longitudinal in orientation. They originate from the ventricular apex and insert around the circumference of the mitral and tricuspid valve rings. In systole, as they contract they bring the insertion site (mitral and tricuspid annulus) toward their origin (the apex), and in diastole they move in the opposite direction, bringing the annuli back toward the atria in early diastole and again in late diastole, during atrial contraction. Having the ability to record the long-axis function from the valve annulus movement (fibrous landmark) makes the technique highly reproducible. The same principle can be used for studying the free wall function of the right ventricle, which cannot be assessed by other stress techniques. During stress, the normal ventricle increases the amplitude and velocity and long-axis function, whereas in the presence of a coronary artery stenosis, the amplitude is reduced, the time to peak delayed, and some degree of incoordination appears during stress. Disturbances of the anterior and septal segments of the mitral annulus represent left anterior descending coronary artery disease. The left segments represent the circumflex artery disease, and the posterior and right ventricular free walls represent the right coronary disease. The technique has also proved useful outside coronary artery disease, for instance, in children with Mustard repair for great vessel transposition. In these patients, the right ventricular long-axis contractile reserve of the systemic right ventricle mirrors the exercise capacity [31].

There is little doubt that this simple approach has suffered from the misperception that it is in some way out of date. Nonetheless, there are some problems. Although the use of different sites around the atrioventricular ring may allow the effect of induced ischemia to be localized, annular displacement is a function of the response in the entire wall. As four of the six walls have a different coronary supply to the apical and basal segments, ischemia in one zone may be obscured by hyperkinesis in another. In addition, the time course of contraction is at least as important (probably more so) as displacement in the recognition of ischemia.

23.3 Anatomical *M*-mode

The *M*-mode format is undoubtedly well suited to assess left ventricular regional function for several reasons. First, it objectively displays the motion of myocardial segments; second, it simultaneously evaluates endocardial excursion and myocardial thickening, the true marker of myocardial contraction; and third, it facilitates measurements of wall motion and thickening for quantitative analysis of function. Yet despite all these advantages, the conventional *M*-mode technique is not used in clinical stress echocardiography because its application is restricted to a limited

portion of the left ventricular myocardium, namely, the anterior septum and the posterior wall in the parasternal long- and short-axis view. Only these two walls, in fact, can be orthogonally cut by the ultrasound beam for correct *M*-mode representation of their motion. Anatomical *M*-mode is a postprocessing technique of 2D echocardiographic images designed to overcome the limitations of the conventional *M*-mode methodology (Table 23.2). A line of *M*-mode analysis can be freely oriented within the 2D sector angle regardless of the direction of the ultrasound beam. In this way, all myocardial segments can be reconstructed and displayed in *M*-mode format and their motion and thickening quantified [30]. At present, with the very high velocity of data processing and 2D frame rates provided by the current digital echocardiography scanners, the *M*-mode reconstruction can be obtained in real time, with a high degree of temporal resolution, and can be applied to multiple myocardial segments simultaneously. Specifically, the anatomical *M*-mode approach has been employed to characterize function in lateral and apical segments, which are off axis with the standard *M*-mode approach [31]. The amount and the time to peak systolic thickening are also different in normal individuals among the six myocardial segments studied in the short-axis view, with an earlier systolic peak of the inferior and anterior septum and the anterior wall. In the stress echocardiography setting, anatomical *M*-mode has been shown to precisely quantify the degree of myocardial ischemia [32], making it easier to measure the endocardial excursion and identify the pattern of wall motion abnormalities and incoordination [16]. However, the penetration of this technology has been limited for several reasons. Firstly, the same advantages but also the same limitations of *M*-mode apply to the technique, and one needs to visualize the wall endocardium and epicardium in systole and diastole to measure systolic thickening. Secondly, the frame rate is best in the axial rather than in the perpendicular line of view (250 fps, as in conventional *M*-mode) and in transverse views (100 fps), leading to poorer resolution, for instance, in the lateral wall in the apical four-chamber approach and particularly during stress when heart rate increases. Thirdly, the display of the technique is not so different from the old, standard, not so exciting display of the ultrasound image.

23.4 Tissue Characterization

Interest in ultrasound tissue characterization during stress echocardiography stems from experimental studies showing that transient myocardial ischemia is associated with an increased myocardial reflectivity and a blunting of the physiologic systolic–diastolic variation [33], whose amplitude mirrors the subendocardial function. In accordance with the experimental background, an increased myocardial echodensity – detectable by simple videodensitometric analysis of conventionally acquired images – has been observed in several models of transient acute myocardial ischemia, induced with angioplasty, ergonovine, dipyridamole, exercise, or pacing [34, 35]. The regional gray-level amplitude increased, and the blunting of cyclic gray-level (or backscatter) changes is detected well before the regional dyssynergy. The cyclic variation is of great potential interest as an ancillary marker of myocardial

ischemia, since it is affected symmetrically with regional wall thickening and, compared to wall motion analysis, is less operator dependent and therefore more quantitative. Cyclic variation is independent of motion abnormalities, which may impair the evaluation of regional wall motion in certain conditions, such as left bundle branch block or postcardiac surgery [36]. Cyclic variation can also be preserved in dyssynergic but viable myocardium, offering a clue to the identification of viable segments in ischemic cardiomyopathy [37].

In spite of the promising experimental and initial clinical results, the technique never gained clinical relevance for several reasons. First, the cyclic variation can only be observed in some myocardial regions orthogonal to ultrasound beam such as the septum and inferolateral (formerly called posterior) in the parasternal short axis. Second, the technique is exquisitely sensitive to artifacts, and great care is needed in image acquisition and analysis to obtain stable data. Third, tissue characterization data change monotonously in the same way – with increased echodensity and blunting of cyclic variation – in a variety of conditions, from ischemia to fibrous conditions to hypertrophy [33], and are profoundly affected by heart rate changes, making it difficult to assess these parameters fruitfully during stresses associated with tachycardia.

23.5 Color Kinesis

CK is a method that evolved from acoustic quantification, which uses ultrasonic integrated backscatter to track endocardial motion in real time and to create an image with an improved signal-to-noise ratio [38]. CK offers an objective and automated assessment not only of global function as acoustic quantification does, but also regional function. Employing a user-defined threshold, pixel transitions between blood and tissue are detected in real time based on differences in backscatter or signal strength, allowing the automatic detection and tracking of the endocardial boundary in real time on a frame-by-frame basis, and then color encoded. Each color represents a distinct time interval within the ejection period (33 ms). The thickness of the color bands represents the degree of endocardial wall motion during that systolic interval. The end-systolic frame, therefore, provides an integrated snapshot of both the magnitude and timing of systolic wall motion [39] (Table 23.2). Qualitatively, hypokinetic segments are depicted by a thinning of the color band in the affected region (Fig. 24.10 in Chap. 24). In contrast to other more time-consuming methods, analysis of CK images takes less than 2 min per echocardiographic view.

CK has been effectively used to detect regional wall motion abnormalities at rest and during stress, both in standard images and on contrast-enhanced images, allowing a simultaneous assessment of function and perfusion [40]. While both tissue Doppler imaging and CK provide quantitative information on the magnitude of regional wall motion, CK can also explore apical function (where tissue Doppler velocities are too low) and add information regarding the timing of endocardial motion in both systole and diastole and may also have a role in the assessment of regional diastolic function. Regional left ventricular delayed outward wall motion

or diastolic stunning after exercise-induced ischemia can last 1 h after stress, when normal regional systolic function was completely restored [41]. However, the image quality is significantly degraded during increased heart rate, and – as always – an optimal signal is required since the image quality affects the quality of data. The method's overall accuracy and intertechnique variability are comparable to the standard conventional grayscale image interpretation by expert readings. The method shows a modest degree of interbeat variability due to cardiac translation and respirophasic changes in image quality. Its sensitivity to careful adjustments in the lateral and time gain compensations to obtain accurate endocardial tracking makes it highly dependent on the technician's experience. There are no clear advantages over the standard black-and-white format and grayscale reading – except for the more attractive display.

23.6 Tissue Doppler Imaging

Tissue Doppler imaging color maps the tissue velocities rather than the blood velocities and is mainly used in the cardiac muscle. Myocardial velocities are considerably lower (0–30 cm s^{-1}) than blood velocities, but the amplitude of the echocardiography signal is approximately 40 dB larger than that of the blood flow. The signal processing is similar to color flow imaging, but the clutter filter is bypassed, so the signal component from the relatively slow moving myocardial tissue is not removed. The imaging parameters are optimized differently, and the PRF is lower in tissue Doppler imaging than in color flow imaging due to the lower velocities in the tissue compared to the blood. Color tissue Doppler imaging is therefore a new cardiac ultrasound technique, which in its current high frame rate format (>120 frames s^{-1}) can resolve all mean myocardial velocities along its scan lines [42]. The technique evaluates longitudinal function, rather than radial function as anatomical *M*-mode. The functional impairment induced by infarction and ischemia is mirrored in a reduction of peak velocity of S (systolic) wave in the involved wall, although basal segments are also affected by global contractility changes. Peak systolic velocity brings back in the clinical arena the important variable of the long-axis function, which is also expressed by the good old MAPSE. It is a potentially sensitive marker of ischemia, since the long axis is mostly affected by subendocardial ischemia (Table 23.2).

In addition to the physiological insight into longitudinal function of the left ventricle, the advantage of tissue Doppler would be the display, quantification, and regionality [43]. Experimental results were encouraging, proving that tissue Doppler imaging permits subtle segmental assessment of myocardial function during the cardiac cycle, is accurate compared to reference methods such as sonomicrometry [44], and is sensitive to inotropic stimulation and ischemic challenge [45]. Clinical studies show the feasibility of the TDSE, but the reproducibility of the method has been suboptimal [46], the accuracy no better than expert eye reading [47, 48], and the regional assessment is difficult in medial regions and impossible in apical regions [49].

Clinical data made clear to physiologists and bioengineers that the interrogation of regional myocardial velocities alone has major drawbacks. Firstly, as with any Doppler-derived method, the velocities measured are angle dependent, limiting this technique to the apical views. Angle issues may be circumvented by narrowing the sector and imaging single walls. Image collection is duplicated as TDE images are collected in addition to standard *B*-mode images. These issues make TDE challenging and time-consuming, thus reducing its wider application. In addition, the longitudinal systolic wall motion at the apex is minimal, and therefore myocardial velocities are too low and variable to reliably detect apical wall motion abnormalities. Because of the physiologic base-to-apex gradient, there is a need for different regional cutoff values, which can be implemented into the software of the echocardiography machine. Tissue Doppler is further limited by cardiac translation and rotation, which may cause the myocardial segment interrogated to move away from the Doppler sample volume [50]. In order to reduce the effects of translation, strain rate imaging, or in other words, rate or speed of deformation, has been developed by estimating spatial gradients in myocardial velocities.

23.7 Strain Rate Imaging

Strain and strain imaging techniques can be derived from color-coded TDI. Strain and strain rate (rate of shortening) imaging measures the rate of myocardial deformation and has the advantage of differentiating between active and passive myocardial motion [51]. Strain and strain rate are less tethering and translation dependent than tissue Doppler imaging and provide better assessment of myocardial contraction with almost homogeneous values within the different segments. This is particularly important in regions with extensive infarction and scar formation, where passive motion occurs. From strain rate curves, local strain can be extracted. Longitudinal strain can be measured in all left ventricular segments using the apical views. However, radial and circumferential strains can only be assessed in some segments, e.g., radial strain in the posterior wall and circumferential strain in the lateral wall using a parasternal short-axis view (Table 23.2). Experimental studies show that parameters derived from strain rate imaging can be helpful in identifying and quantifying ischemia-induced myocardial abnormalities and in identifying viable myocardium, whose strain rate is normalized in stunned areas following inotropic challenge with dobutamine or dipyridamole [52, 53]. These studies also suggest that indices of deformation (strain and strain rate) are better than those of displacement (myocardial velocity) in the evaluation of regional myocardial function, as they might avoid the limitations of velocity (overall heart motion, influence of adjacent segments, etc.). Unfortunately, clinical studies did not confirm the clear advantage suggested by experimental studies and show comparable values of strain rate and tissue velocity imaging for diagnosis of coronary artery disease and myocardial viability and comparable accuracy compared to expert reader eyeballing interpretation [54, 55]. Only the sophisticated analysis of strain and strain rate values, plus postsystolic shortening (which is not always pathologic under stress), plus time to

onset of regional relaxation together, has been shown to be accurate markers of ischemia [56]. The combination of strain and anatomical *M*-mode might be a promising alternative technique with prognostic value [57, 58]. The combination allows the expression of strain rate as magnitude (color-coded images instead of complex and less robust wave forms), location (apex–base direction), and timing.

The major limitation of TDSE, as for TDE, is that peak amplitudes, and to some extent phase (timing), of velocity and strain variables are influenced by the angle of the incident beam with the myocardial wall. This restricts imaging to the apical projections wherein the operator attempts to align the myocardial wall parallel to the ultrasound beam; however, this is not always possible. The technique is heavily dependent on the sonographer's expertise, has a limited reproducibility even in expert hands, loses stability with high heart rates and degraded image quality, and is unable to image apical segments (5 out of the total 17 of the left ventricle) [59]. Even in the ideal condition of patient selection, technology, and expertise, the accuracy is comparable to expert reader eyeballing interpretations [54]. In more general terms, the relatively unsatisfactory discriminating power of TDSE and TDE may stem from the very basic biophysical roots of the technique. In fact, the word "tissue Doppler" is a misnomer, since it gives the impression that only myocardial tissues are studied. The appropriate term would be "low-velocity Doppler" [50]. Any movement in the low-velocity range will be detected by tissue Doppler, and myocardial tissue movement is just one of them. In the cardiac motion there are translational, rotational, and deformational movements. Moreover, many tissues near the heart move – due to transmitted cardiac motion, vessel pulsation, respiratory motion, and involuntary muscle movements – and these interact with cardiac motion further and cause false Doppler shifts [50]. Velocity is a vector quantity, and so Doppler interrogation at one point will determine the velocity of the resultant of all these movements projected in the line of the Doppler beam with angle corrections. Similarly, at a particular point there are movements in several axes, and we can never predict the sum resultant vector. Even if known, the resultant is accurately recorded only if it is in line with the Doppler beam because of the inherent problems of directional bias.

23.8 Speckle Tracking and Velocity Vector Imaging

Two-dimensional speckle tracking (also used in velocity vector imaging) is based on 2D grayscale imaging, which is angle independent, differently from TDI and SRI. Thus, they can be used in any projection and without paying much attention to the orientation of the heart in the imaging sector. Speckles are natural acoustic markers, seen as small and bright elements in conventional grayscale ultrasound images. A speckle is a unique acoustic pattern resulting from the interaction of ultrasound energy with tissue. These unique patterns can be tracked automatically over periods of the cardiac cycle, thus providing information about motion and displacement of that particular region of the myocardium. The distance between selected speckles is measured simultaneously from multiple regions of interest and

is a direct measure of myocardial deformation, used to derive strain that occurs during the cardiac cycle. Radial strain (thickening of the myocardium during the inward motion of the left ventricle), longitudinal strain (percentage decrease in length of the myocardium during systole as the base moves toward the apex), and circumferential strain (change in length along the circumferential perimeter) can be assessed. In addition to measuring strain and strain rate, speckle tracking also assesses the rotation, twist, and torsion of the heart. Rotation is defined as the movement of the heart in relation to an axis through the middle of the left ventricular cavity from the apex to the base. Twist is the difference between the rotation of the apex and the base. Torsion is defined as the twist normalized to the length of the left ventricular cavity (i.e., twist divided by the ventricular distance between the apex and base). Speckle-derived strain has obvious advantages in stress imaging. *B*-mode images can be collected as in usual clinical practice; therefore, there is no duplication of image acquisition. The technique eliminates the angle dependency of Doppler-based modalities. Other advantages of 2D, non-Doppler-derived strain imaging include high reproducibility and the fact that it is an automated tracking method (especially important for inexperienced observers).

It evaluates the longitudinal and circumferential, and to a lesser extent radial, dynamics of the left ventricle, differently from TDI and SRI, which mainly assesses longitudinal function [59, 60]. Speckle-derived strain has been validated experimentally with excellent results, especially for the sensitivity and reproducibility of longitudinal strain [61]. The first clinical studies (Fig. 23.4) showed a high feasibility and good accuracy especially of longitudinal strain [62], with excellent reproducibility [63] but lack of incremental diagnostic value over conventional eyeballing wall motion analysis [64].

Some disadvantages are the lower frame rate in comparison with TDI, influenced by image quality, examination of strain rather than strain rate, and reduced combination with contrast echocardiography for enhancement of border detection [64]. As additional limitations, speckle-derived methods measure systolic strain, but not

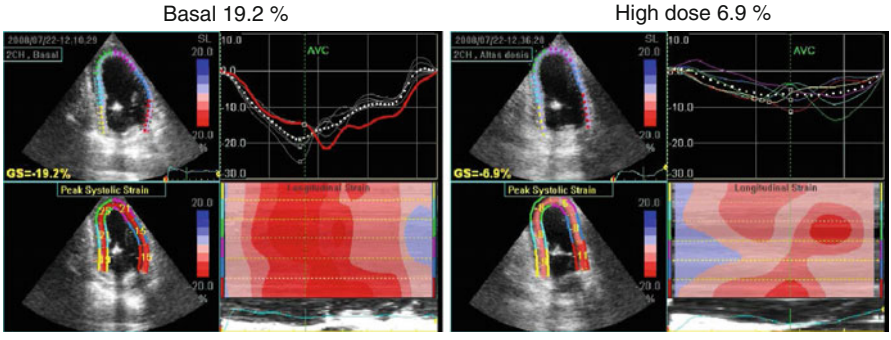


Fig. 23.4 A 2D speckle tracking image of a normal apex at rest (*left panel*) showing decreased contraction at peak dose (*right panel*). The quantitative assessment of velocity and direction of vectors by global strain helps to describe the motion information in an integrated and quantitative fashion (Courtesy of Dr. Jorge Lowenstein)

diastolic strain rates, which are evaluated by tissue Doppler techniques and may in theory be useful in detecting ischemia [64]. A major, limiting problem of 2D STE is the differences among vendors, driven by the fact that STE is performed on data stored in a proprietary scan line (polar) format, which cannot be analyzed by other vendors' software [11], with the lack of vendor interchangeability.

23.9 Three-Dimensional Echocardiography

Left ventricular volumes and LV ejection fraction can be assessed with great accuracy using real-time three-dimensional (3D) echocardiography, which has clear advantages over standard 2D echocardiography, both conceptually and practically. The technique is a major development in echocardiography over the last decade, having evolved from slow and labor-intense offline reconstruction to real-time volumetric imaging. The major advantage of this technique over more conventional 2D echocardiography is the improvement in the accuracy of the evaluation of cardiac chamber volumes, which is achieved by eliminating the need for geometric modeling and the errors caused by foreshortened views [65]. Another fundamental advantage of the 3D format is the advantage communicating with the patient, the other imaging specialists, and the cardiological community at large with the common language of all competing and complementary imaging techniques [65]. You do not need to be a radiologist to understand a 3D picture of the heart from MSCT or MRI, but you need to be a dedicated echocardiographer to try to understand a TD and TDSE. Eventually, the new technique will be faster to learn, easier to implement, and less operator dependent in the interpretation, also based on a robust quantitative package of excursion, synchronicity, shape, and volumes.

Two types of imaging modes, full-volume and multiplane mode, can be used to acquire and analyze stress echocardiography. Both modes have their particular benefits and limitations [66]. The multiplane mode is suitable for regional wall motion analysis, since regional function can be represented as a function of time, and a series of plots is obtained representing the change in volume for each segment throughout the cycle. In the presence of ischemia, minimum volume will be reached for each segment at different times, and ischemic segments will have higher end-systolic regional volumes (Fig. 23.5).

A complete 3D cardiac ultrasound image acquisition can be obtained in a shorter time than with 2D echocardiography, and this is a valuable advantage, especially when imaging children and adults during stress [66]. Parametric polar map displays (of the 2D data) of the timing and extent of regional contraction have been developed to simplify interpretation of results. The positive stress echocardiography response is characterized by higher dyssynchrony, greater heterogeneity, and larger end-systolic volumes than the negative stress echocardiography responses (Fig. 23.6) [67–72].

However, and in spite of this exciting potential, the overall accuracy of 3D stress echocardiography is at present no better, and the feasibility markedly lower, than 2D echocardiography [67–72]. The 3D version has a lower spatial resolution than 2D,

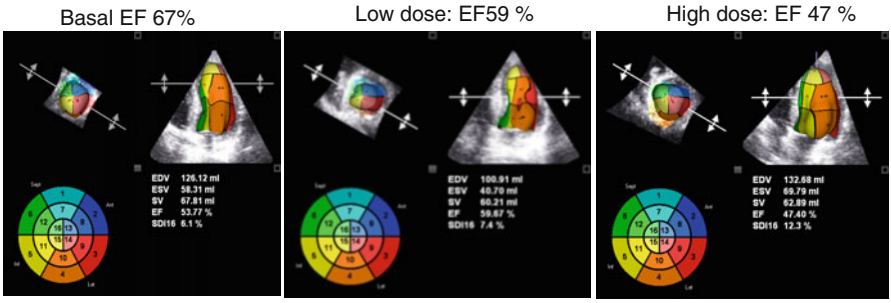


Fig. 23.5 A 3D positive stress echocardiography test. The positive test result is characterized by an area of reduced regional and global ejection fraction at peak stress (*right panel*) when compared to rest (*left panel*) and low dose (*middle panel*). A quantitative assessment of left ventricular volumes and stroke volume is possible at each stage. Courtesy of dr. Jorge Lowenstein

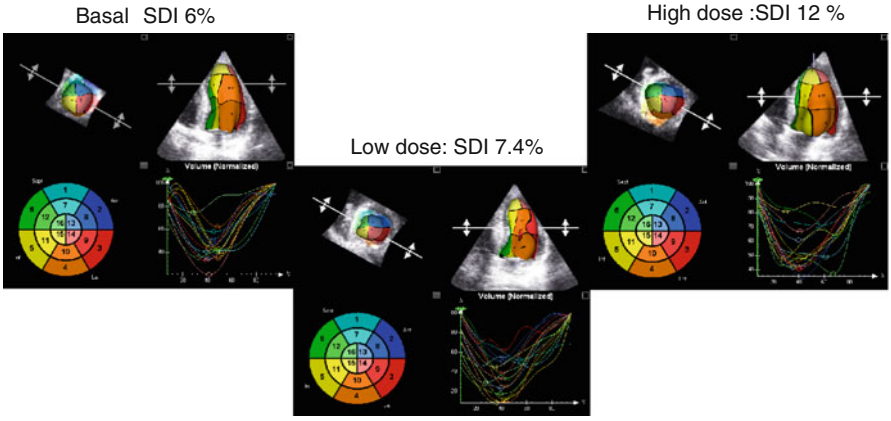


Fig. 23.6 A 3D positive stress echocardiography test with dyssynchrony assessment. The positive test result is characterized by an area of greater segmental dyssynchrony at peak stress (*right panel*) when compared to rest (*left panel*) and low dose (*middle panel*). During ischemia, the peak of contraction is reached by different segments at different time points. Courtesy of dr. Jorge Lowenstein

and the resolution becomes even worse when you need it more, at faster heart rates during stress (because of 3D echocardiography's frame rate of 40 fps, compared to 100 fps for 2D). However, the 3D evaluation of volumes (plus standard assessment of heart rate and blood pressure) is ideally suited for a quantitative and accurate calculation of a set of parameters allowing a complete characterization of cardiovascular hemodynamics (including cardiac output and systemic vascular resistance), left ventricular elastance (an immaculate index of left ventricular contractility, theoretically independent of afterload and preload changes heavily affecting the ejection fraction) [73], arterial elastance [74] (essential to characterize the distal impedance of the arterial system downstream of the aortic valve), ventricular–arterial coupling (a central determinant of net cardiovascular performance in normal and pathological

conditions), and diastolic function (through the diastolic mean filling rate). All these parameters were previously inaccessible or inaccurate or labor intensive and now become, at least in principle, available in the stress echocardiography laboratory since all of them need an accurate estimation of left ventricular volumes and stroke volume, both easily derived from 3D (Table 23.3).

It is expected that the technology will improve present critical areas of the technique, such as the need for transducers with higher frequencies, smaller footprints, full Doppler capabilities, and higher frame rates, especially important for stress echocardiography applications.

Table 23.3 Cardiovascular hemodynamics derived from real-time three-dimensional echocardiography (*RT3D*)

Parameter	Raw RT3D data	Formula	Normal values (rest)	Normal values (stress)	Meaning
Cardiac index	SV (EDV-ESV)	SV × HR	2.5 L min^{-1} m^{-2}	×2 (ex) ×2 (dob) ×1.5 (dip)	Cardiac pump function
Systemic vascular resistance	SV	80 × (MAP-5)/CO	900–1,300 (dyne × sec) cm^{-5}	–30 % (ex) –40 % (dip)	Vascular resistance
Systemic arterial compliance	SV	SVi/PP	0.50 (mL × m^{-2} mmHg)	–30 % (ex) +20 % (dip)	Arterial compliance
Ventricular elastance	ESV	ESP/ESV	7 mmHg mL^{-1} m^{-2}	×2 (ex) ×1.2 (dip) ×1.5 (pac)	LV contractility
Arterial elastance	SV	ESP/SV	4 mmHg mL^{-1} m^{-2}	×1.5 (ex)	Integration of arterial resistance, compliance, and heart rate
				×0.9 (dip) ×1.5 (pac)	
Ventriculoarterial coupling	SV and ESV	SV/ESV ventricular elastance/ arterial elastance	≥1.5	×1.5 (ex)	Ventricular elastance/ arterial elastance
				×1.3 (dip) ×1.0 (pac)	
Diastolic mean filling rate	SV	SV/diastolic time	100 ml m^{-2} s^{-1}	×3 (ex) ×1.5 (dip)	Diastolic function

ESP (end-systolic pressure) = SPA × 0.90. In the formula of systemic vascular resistances, 5 is an approximation of right atrial pressure. Diastolic time can be calculated from phonocardiogram or 2D echocardiography; with high heart rate, the diastolic time is progressively more reduced than systolic time
MAP mean arterial pressure, *PP* pulse pressure (systolic arterial pressure – diastolic blood pressure) *CO* cardiac output, *DIP* dipyridamole, *DOB* dobutamine, *EX* exercise, *HR* heart rate, *PAC* pacing, *SAP* sphygmomanometer systolic arterial pressure, *SV* stroke volume

23.10 Pitfalls

At times it seems that there is a mismatch between the space devoted to new technologies in major journals and meetings and the lesser coverage of everyday practice. To a certain extent, this is inevitable if new technology is to be trialed sufficiently to understand its benefits and limitations. Nonetheless, it also risks encouraging a cult of technology – all of us, as clinical cardiologists, researchers, and scientists, have a major bias in favor of technology. What we need to ensure is that technology in medicine is tested scientifically, that it is applied with data relating to cost and benefit, and that it is driven by patient needs rather than market forces [75]. Efficacy studies should be considered the "seed," and typically very selected patients are evaluated by a dedicated person, devoted (often full time) to the technology, in a research-oriented setting where resources are frequently granted by the manufacturer of the technology under scrutiny. This stage – while critical to the development of new technologies – should be followed by effectiveness studies, from which the clinician should be able to discern whether the technology provides clinically relevant information that is independent of, and incremental to, simpler and less expensive tests. In the current economic and cultural milieu, the "seed" of efficacy obtained under ideal conditions should not be mistaken for the "fruit" of effectiveness: the value of the technique when deployed in the field [76] (Table 23.4).

Any emerging biomarker should, like a new drug, withstand a chain of validation before arriving at clinical impact [77]. With new technologies, like new drugs, large-scale experience should be gathered before accepting the catchy definition promoted by the marketing offices as proven. The additional merits of the new technique should be weighted against the established and more easily accessible methods, and the new technologies should be assessed against other competitive imaging tools (Fig. 23.7).

Only at that point will an innovation in engineering be valid in physiological terms and will it give patients the promised diagnostic help, changing an attractive technological gadget into a medical advance [78]. Some of these techniques already have a clear clinical role outside stress echocardiography applications. Tissue characterization may allow a clinically relevant characterization of "soft" (more vulnerable, lipid rich) vs. "hard" (fibrocalcific) plaques, which can be imaged by ultrasound [79, 80]. Tissue velocity imaging is helpful for characterizing diastolic function

Table 23.4 New technologies between efficacy and effectiveness

	Efficacy	Effectiveness
Dictionary definition	Ideal conditions	Deployed in the field
Responsible physician	Research fellow in training	Wise, gray haired
Scientific interest	Present	Absent
Patient	Part of the method	The protagonist
Technology	Under validation	Validated
Results	Published, but true?	True, but unpublishable
Economic induction	Present	Absent

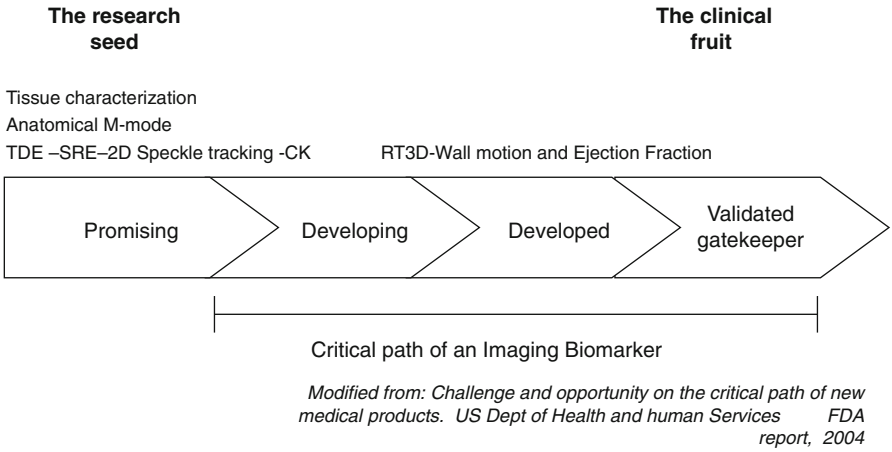


Fig. 23.7 The natural history of a new technology from initial seed of efficacy to established fruit of effectiveness (Modified from: Challenge and opportunity on the critical path of new medical products. US Dept of Health and human Services. FDA report, 2004)

through E/e′, used not in isolation but in a comprehensive assessment of left ventricular diastolic function [81, 82]. 2D-STE can demonstrate the presence of regional abnormalities and depressed strain in patients with normal ejection fraction and cardiac disease or diastolic heart failure [83]. RT3D is now the clinical gold standard for left ventricular mass and volume calculations and is extremely helpful in complex congenital and valvular disease [64]. However, when we come to the clinically driven practice of stress echocardiography, no technique can be considered clinically useful today, as concordantly stated by the US and European guidelines [11, 84, 85]. Maintenance of a critical attitude on the part of the clinical cardiologist and sonographer faced with the forest of new technologies proposed every year by the manufacturers is essential. What has been said about the Internet might be echoed by sonographers struggling with new technologies: "The adventure starts now but it is not the one that the marketing experts are talking about. It is the one that you will build with your own hands. How? First, learn to use the new machines. Second, beware of those who are saying they traced the way for you. Third, avoid the traps and pitfalls, and identify the routes. No one will do it for you" [86].

23.11 Clinical Guidelines

As expressed by the joint writing group of the American Society of Echocardiography and European Association of Echocardiography, new technologies "significantly contribute to the much needed process of the transformation of echocardiography from a subjective art of image interpretation to a set of objective diagnostic tools," but "this methodology is not yet ready for routine clinical use." In particular, two technologies are likely to enter soon the clinical armamentarium of SE: 2D-STE and

RT3D. Although there is an extensive research evidence that global longitudinal strain may detect subtle abnormalities of regional myocardial function not otherwise detectable with ejection fraction or regional wall motion analysis, three significant problems must be solved prior to clinical acceptance of 2D-STE : (1) across-vendor standardization of strain acquisition, analysis, and values to establish true reproducibility of parameters in real-world conditions and under stress (when image quality degrades); (2) assessment of clinical value over conventional ones in randomized, prospective, multicenter, outcome-based studies; and (3) impact of new parameters in decision-making and cost-effectiveness. Also RT3D has proven benefits in accuracy and reproducibility, but its methodology is still time-consuming and impedes optimal clinical workflow. Its impact on stress echo can be critically important, once automated quantification tools that could be used immediately as the images are acquired are developed [87].

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Contrast Stress Echocardiography

24

Jeane Mike Tsutsui and Eugenio Picano

24.1 Historical Background

Echocardiographic contrast agents are an important new advance in the practice of echocardiography [1, 2]. Initial attempts to better delineate endocardial borders used agitated saline, indocyanine green dye, or radiologic contrast agents. The history of myocardial contrast echocardiography (MCE) began in 1968, when an accidental injection of saline solution in the ascending aorta during an angiography examination caused the production of microbubbles that led to better echographic signals in the aorta lumen and cardiac chambers [3]. A major limitation was the large and variable size of the air bubbles, which could not transit the pulmonary circulation and opacify the left heart. The early 1990s saw the development of commercial agents with air- or gas-filled microbubbles, similar in size to red blood cells with a distribution similar to blood flow. Exciting reports described the potential of contrast echocardiography in diagnosis of coronary artery disease, the extent of risk area in acute myocardial infarction, infarct artery patency after thrombolytic therapy, microvascular integrity, myocardial viability, and coronary flow reserve. In the year 2000, three agents had been approved, and at least 13 other agents were undergoing evaluation [4]. At that time, more than $ US 1 billion had been spent worldwide to develop these agents and bring them to market.

While contrast echocardiography has many important applications, the greatest utility and benefit from this technique are expected from stress echocardiography. The information provided by contrast during stress echocardiography is potentially important and tremendously versatile: from improved border recognition (Fig. 24.1a) to myocardial perfusion (Fig. 24.1b) and from coronary flow velocity enhancement (Fig. 24.1c) to potentiation of regurgitant tricuspid jet velocity to analyze pulmonary artery systolic pressure (Fig. 24.1d). The addition of contrast may improve the image quality in all cases; however, it demonstrates unique advantages only in the assessment of myocardial perfusion, which has the highest potential value but unfortunately has been least convincingly validated in the clinical arena.

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As a consequence, and in striking mismatch with the enormous potential, echocardiographic contrast agent perfusion analysis is today performed in only a small minority of stress studies. The main clinically driven application of contrast is the left ventricular endocardial border delineation allowing the rescue of procedures that do not provide results of diagnostic quality, especially in patients with obesity and lung disease [5]. At present three agents are licensed for left ventricular opacification and endocardial definition: SonoVue (Bracco, Italy), Definity (called Luminity in Europe, Lantheus Medical Imaging, previously Bristol-Myers Squibb,

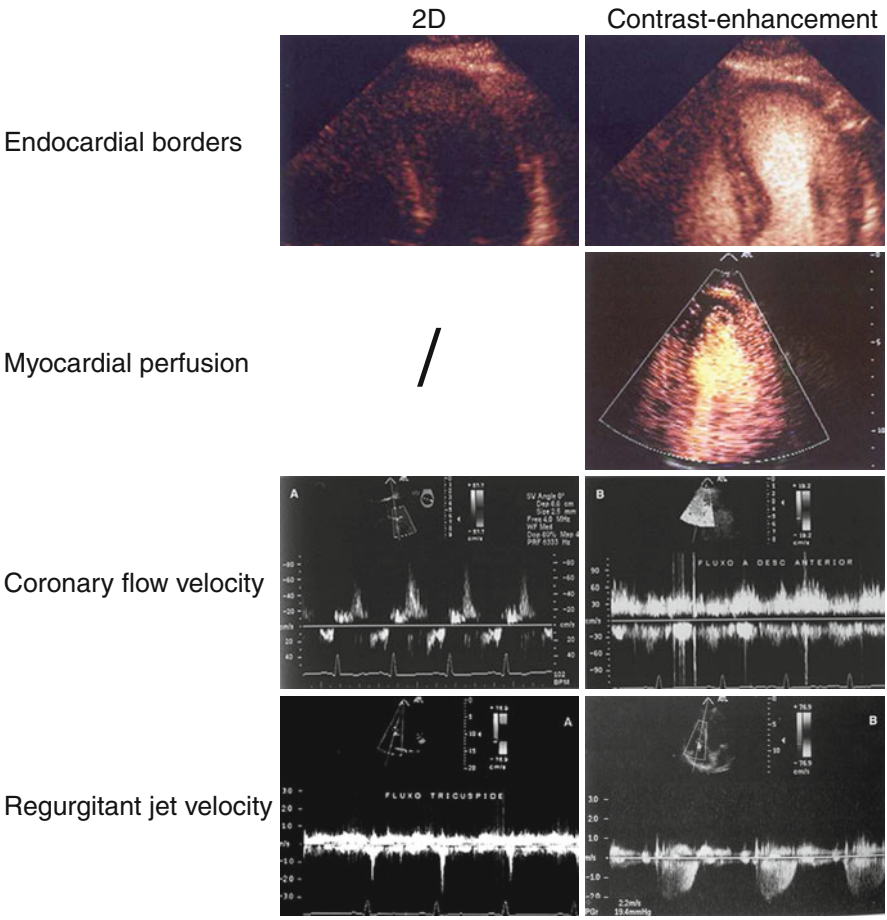


Fig. 24.1 The main potential clinical applications of contrast in the stress echocardiography laboratory: improved endocardial border definition (*first row*, ***panel a***), myocardial perfusion (*second row*, ***panel b***), pulsed-Doppler signal enhancement on left anterior descending coronary artery (*third row*, ***panel c***), and enhancement of tricuspid regurgitant jet velocity for analyzing pulmonary artery systolic pressure (*last row*, ***panel d***). **For each panel**, on the left, the noncontrast 2D image; on the right, the contrast-enhancement image. Myocardial perfusion imaging is only possible with contrast. (Courtesy of Dr. Ana Cristina Camorazano)

New York, NY, USA), and Optison (General Electric, Fairfield, CT, USA). Stress MCE has remained on the threshold of widespread clinical acceptance for at least 20 years, and it is still there, at the crossroads between success and failure. The safety of contrast was challenged by the issuance of a black box safety warning by the US Food and Drug Administration in October 2007, but a series of subsequent publications were reassuring on the safety record of contrast agents, and there is now consensus that contrast agents have a high benefit-to-risk ratio when used appropriately.

24.2 Pathophysiology of MCE

The pathophysiological rationale of MCE is simple and strong. The use of regional myocardial perfusion is a potentially useful diagnostic and prognostic marker of myocardial ischemia. Myocardial ischemia results in a typical cascade of events in which the various markers are hierarchically ranked on a well-defined time sequence [6]. Flow heterogeneity, especially between the subendocardial and subepicardial perfusion, is the forerunner of ischemia, followed by regional systolic dysfunction and only at a later stage by electrocardiographic changes and anginal pain (Fig. 24.2). The best way to unmask a perfusion defect is the use of a hyperemic stress. An epicardial coronary artery stenosis reduces the maximal flow achievable in the related territory, although the blood flow in resting conditions can be equal to that observed in regions supplied by normal coronary arteries. During hyperemia, perfusion heterogeneity will occur with lower blood flow increase in the regions supplied by the stenotic artery, even in the absence of regional ischemia (Fig. 24.3). The criterion of positivity is the presence of a reduced perfusion signal (flow tracer uptake) between different regions of the left ventricle or in the same region between rest and stress. The excellent spatial resolution of echocardiography makes it an

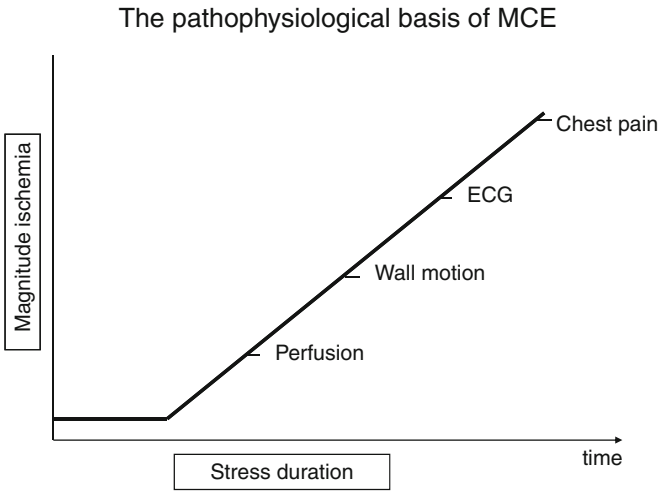


Fig. 24.2 The ischemic cascade. Perfusion abnormalities consistently precede wall motion abnormalities, theoretically supporting the use of MCE as a more sensitive diagnostic marker than systolic thickening in stress echocardiography

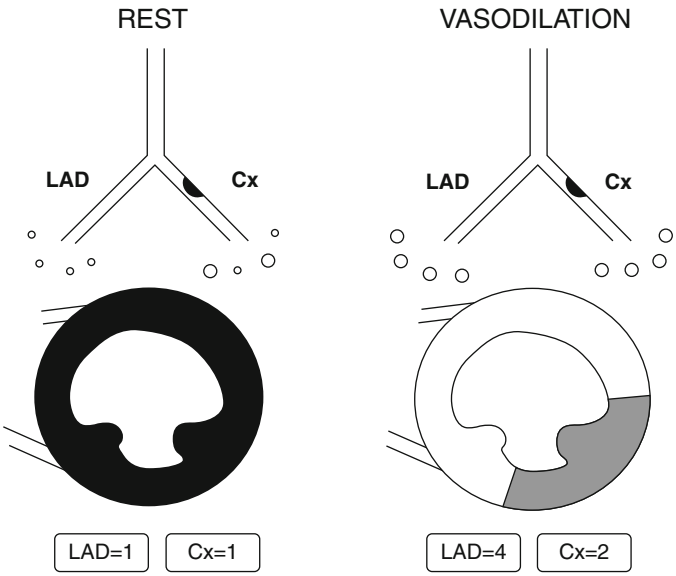


Fig. 24.3 Schematic illustration of the principle underlying myocardial perfusion imaging for the diagnosis of coronary artery disease. At rest, myocardial perfusion is homogeneous, with no differences between the territory of the normal coronary artery (*LAD* left anterior descending artery) and the diseased coronary artery territory (*Cx* left circumflex, with 80 % stenosis). The resting flow image (obtained, for instance, with thallium-201 scintigraphy or contrast echocardiography) does not show any inter-region variation. However, the perfusion in the territory of the stenotic coronary artery is maintained at the price of a partial exhaustion of coronary reserve, with partial dilatation of the arteriolar bed, represented by *larger circles* located downstream from the epicardial coronary arteries. The normal arteriolar tone is represented by *smaller circles* (normally vasoconstricted arterioles). During vasodilation obtained with a metabolic stimulus, such as exercise or with a pharmacological stimulus, such as dipyridamole, the arteriolar tone is lost, causing an increase in flow that will be greater in the normal coronary artery (which, at rest, has a preserved tone in the entire arteriolar district) than in the stenotic coronary artery (with lower coronary flow reserve). Perfusion imaging will see the stenosis mirrored in the myocardium as a region with relative underconcentration of flow tracer when compared with the normal contralateral region. The septal and anterior walls appear *brighter* (due to greater echocontrast concentration) when compared with the *darker* inferoposterior wall (lower echocontrast concentration)

ideal tool for this technique which can even detect small subendocardial perfusion defects. The use of MCE will therefore increase the sensitivity of the noninvasive diagnosis of coronary artery disease (CAD) simply based on wall motion [7–11]. In addition, it will also expand the power of prognostic stratification, since the long-standing experience with other imaging methods [including cardiovascular magnetic resonance (CMR) stress and stress echocardiography with CFR assessment with pulsed Doppler imaging of LAD] has proved that stress-induced wall motion changes identify those with a an adverse short-term prognosis. However, an isolated reduction in coronary flow reserve, occurring without wall motion abnormalities, may identify patients with a poorer long-term prognosis [12, 13]. In these patients, the underlying coronary anatomy may range anywhere from mild to moderate

epicardial coronary artery disease (relatively frequent when patients are studied on ischemia-masking anti-ischemic therapy) or normal coronary anatomy but with functionally important coronary microvascular disease. These patients have prognostically important forms of microvascular disease and are often found in syndrome X, hypertension, diabetes, and also cardiomyopathy and heart transplant rejection settings [14]. It has been demonstrated in some studies that myocardial contrast positivity adds prognostic information over and above wall motion abnormalities seen during stress echocardiography [15, 16]. Obviously, the strong pathophysiological roots will generate clinically useful fruits only if the method to assess perfusion is sensitive enough, reproducible, safe, and not vulnerable to artifacts. It is also essential to use perfusion not as a "stand-alone" but rather as a "running mate" criterion, to be added to regional wall motion assessment. In fact, perfusion (or the conceptually germane assessment of coronary flow reserve from Doppler assessment with the coronary flow velocity method) per se is unable to separate epicardial coronary artery disease from coronary microvascular disease and if used alone will be plagued by an exorbitant number of false-positive results [14].

24.3 Physics of Microbubbles and Modalities of Administration

Today, ultrasound contrast agents may be hospital produced or commercially produced. We now have the third generation of commercial agents available (Table 24.1). In hospital-generated agents, contrast is used for the right heart opacification and consists of an agitated saline solution containing air bubbles, which is intravenously injected. The right heart contrast is impressive, but the air quickly dissolves into the

Table 24.1 Characteristics of echocardiography contrast agents

Production	Composition	Use	Clinical use
Agitation, zero generation	Saline solution/Emagel mixed with room air	Enhance Doppler (tricuspid regurgitation) signal	Routine
Commercial, first generation	Polysaccharide + air	One pass only	Abandoned
Commercial, second generation	Lipid + octofluoropropane	Stable, long-lasting	Enhanced endocardial border delineation
	Plus albumin or polysaccharide shells and sulfur hexafluoride gas		Myocardial perfusion
Commercial, third generation	Ligands as microbubble shells	Cells and molecular imaging	Investigational
Commercial, fourth generation	Vehicle for genes and drugs	Local therapy delivery	Investigational
Commercial, fifth generation	Nanotechnologies	Passive and active targeting	Investigational

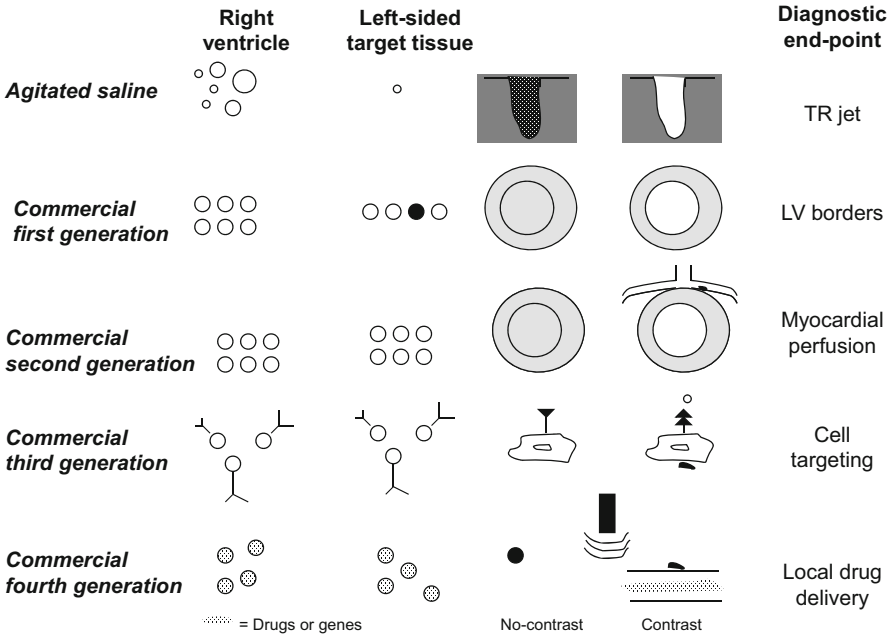


Fig. 24.4 The five different generations of contrast. The agitated preparation still has a role in right heart enhancement, for instance, with tricuspid regurgitation signal for pulmonary artery systolic pressure testing in primary pulmonary hypertension during exercise. With commercial first-generation contrast, bubbles had a more uniform size and passed the pulmonary circulation, facilitating left ventricular border recognition. Stability and homogeneity were further enhanced in second-generation contrast agents, designed for myocardial contrast perfusion imaging. With third-generation agents, "smart" bubbles are aimed with regard to specific antigens, in principle allowing cellular or receptor imaging. In the fourth-generation agents, therapeutic bubbles act as Trojan horses filled with drugs and genes that can be released through external ultrasound irradiation in the target organ

blood (Fig. 24.4, first row). The smaller bubbles that are capable of crossing the lung capillary bed do not survive long enough for imaging the left heart because the air quickly dissipates into the blood. In commercial contrast agents, persistence is achieved using an impermeable shell or a higher-density encapsulated gas that is relatively insoluble in blood (Table 24.2). In fact, gas composition is one of the most important factors in maintaining microbubble size in the circulation. First-generation commercial agents (such as Levovist) contained room air, which is 78 % nitrogen; since nitrogen rapidly diffuses in blood, these microbubbles survive only a few seconds. To overcome this problem, slowly diffusing, insoluble gases (such as octofluoropropane) were incorporated into second-generation microbubbles, providing greater stability and contrast effect duration.

Another emerging application is the chemical remodeling of the passive external shell, which can become active, with smart ligands that can bind selectively to specific antigens or cells. This can be used with positive molecular or cellular

Table 24.2 The currently available second-generation microbubble contrast agents

	SonoVue	Optison	Luminity (Definity in the USA)
Gas	Sulfur hexafluoride	Perfluoropropane	Perfluoropropane
Shell composition	Predominantly phospholipid	Human albumin	Predominantly phospholipid
Mean bubble size (μm)	2–8	3.0–4.5	1.1–2.5
Patients with side effect (%)	11	17	8
Most frequent side effects	Headache, chest pain	Headache, nausea	Headache, back pain
Manufacturer	Bracco	General Electric Healthcare	Lantheus Medical Imaging

Adapted from [17]

imaging, for instance, to image atherosclerotic or apoptotic cells. An exciting further development in microbubble engineering has been obtained by modifying the shell, so that it can be loaded with drugs or genes [18]. This "Trojan horse" is unloaded by destroying the microbubble in the target organ through external ultrasound.

Contrast agents can be administered either via a bolus injection or continuous infusion. Bolus injections have the advantages of using lower contrast volumes and are simple to administer. However, they often result in attenuation in the image plane for a transient period, and there is often only a short period, during the decay phase, when the contrast agent concentration is appropriate for analysis of myocardial blood volume. Infusions of contrast agents are more complex to administer and usually require a larger volume of agent. However, they need less operator involvement during the stress study, and it is easier to adjust the infusion rate to optimize myocardial opacification without excessive attenuation. A constant contrast concentration is better suited to quantification of myocardial blood flow [19] and for 3D echocardiography image acquisition, which needs to be performed over several consecutive cardiac cycles.

Microbubbles enhance echocardiographic images because they oscillate under acoustic pressure in a very peculiar way. Under low-energy pressure, they oscillate linearly, reflecting ultrasound at the insonation frequency (fundamental). Ultrasound with an intermediate energy level induces nonlinear oscillations of microbubbles, resulting in generation of frequencies other than the fundamental frequency (multiples of the fundamental frequency, harmonics). Under high-intensity ultrasound (within the energy levels used for diagnostic imaging) microbubbles are destroyed. Although cardiac tissue produces harmonic frequencies, the intensity is much lower than microbubbles. Therefore, imaging techniques that cause selective reception of harmonic frequencies will detect signals emanating from microbubbles rather than cardiac tissues.

24.4 MCE Methodology

MCE imaging technology attempts to detect contrast microbubbles in the very small quantities with which they occur in the myocardium, while suppressing the myocardial tissue signal [20]. The three main technical approaches are summarized in Table 24.3. In summary, we can use destructive high ultrasound power (high mechanical index, MI) techniques, which are very sensitive to contrast but provide no simultaneous wall motion information. Alternatively, we can use low-power real-time imaging, which is slightly less sensitive for myocardial contrast, but does provide wall motion information and excellent left ventricular opacification. Real-time perfusion imaging has many potential advantages. The technique is relatively easy to use, many artifacts can be avoided, and wall motion information is obtainable alongside perfusion, making this technique particularly valuable during stress echocardiography. In the past decade, real-time very low (<0.1) MI techniques have been available on nearly all ultrasound systems. The very low MI imaging (pulse inversion Doppler, power modulation, contrast pulse sequencing) are inherently tissue cancellation techniques that eliminate or reduce myocardial and valvular signals in the absence of contrast. They have been used in multiple clinical studies to examine perfusion and improve detection of myocardial ischemia.

Myocardial perfusion can be evaluated both semiquantitatively and quantitatively. A semiquantitative contrast score is generally used: 0 = no enhancement, 1 = patchy enhancement, and 2 = homogeneous enhancement (Fig. 24.5). A contrast score index may be calculated by dividing the sum of the contrast scores for each segment by the number of segments analyzed. When using real-time imaging technique, the reduced myocardial perfusion could represent either reduced intensity at all times and/or delayed appearance of contrast either compared to other segments or requiring >2 s during stress. Quantitative software programs can be used to obtain off-line analysis of the refilling curves [21]. Once injection of a myocardial contrast agent has occurred, within a few seconds, the agent will be present within the myocardial capillaries, and once a steady state is achieved, the signal intensity represents the myocardial blood volume (A). High MI impulses (flash) can be used to destroy the microbubbles in the myocardium followed by replenishment of microbubbles (Fig. 24.6). The rate of increase in intensity following bubble

Table 24.3 Contrast imaging methods

Methods	Synonymous	Output power (MI)	Bubble destruction	Left ventricular borders	Wall motion
Harmonic power Doppler	Angiopower	High (>0.5)	+	–	–
Grayscale harmonics	Power pulse inversion; ultra-harmonics	Low (0.2–0.5)	+	+	–
Real-time contrast imaging	Power modulation; power pulse inversion; contrast pulse sequencing	Very low (<0.1)	–	+	+

MI mechanical index

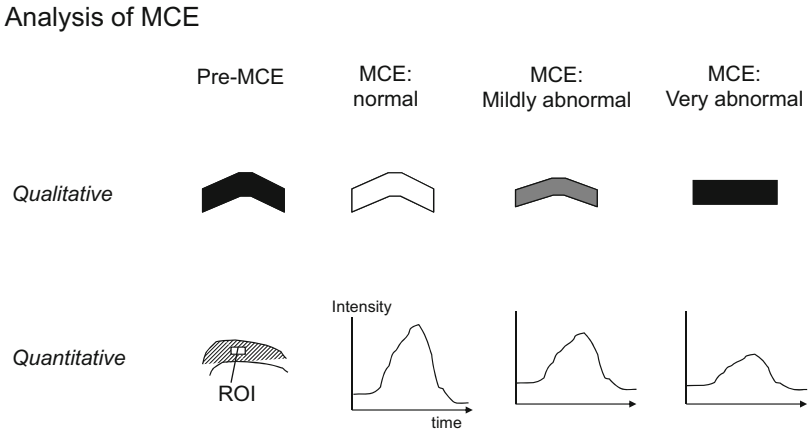


Fig. 24.5 The two possible types of analysis of MCE signal: qualitative (*upper row*) or quantitative (*lower row*). The qualitative analysis focuses on the presence and homogeneity of opacification. The quantitative analysis creates a time–intensity curve based on a region of interest in the myocardium and estimates flow from the steepness of the filling phase and amplitude of the signal (higher flows identified by steeper rise and brighter intensity)

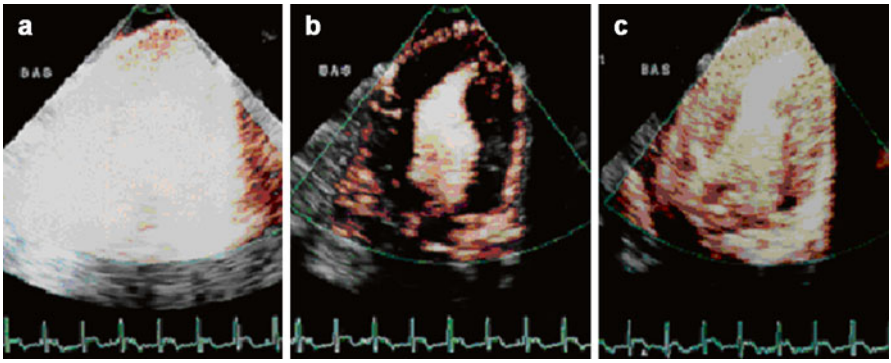


Fig. 24.6 Real-time myocardial perfusion imaging technique. (**a**) High mechanical index impulse (flash) causes complete microbubble destruction. (**b**) Absence of myocardial perfusion immediately after flash. (**c**) Replenishment of myocardial with microbubbles with normal perfusion in all segments

destruction with several high-energy pulses represents red blood cell velocity (β), and the product of A×β is proportional to myocardial blood flow (Fig. 24.7). Dedicated software can automatically construct background-subtracted plots of peak myocardial contrast intensity, A, and the slope of the replenishment curve depicting mean microbubble velocity, β reserve, and myocardial blood flow can be derived. Coronary flow reserve (i.e., stress myocardial blood flow/rest myocardial blood flow) can then be calculated from regions of interest in segments perfused by each of the three coronary arteries.

Stress testing with MCE requires consideration of the choice of the stress. Ideally, the technique needs a maximal vasodilatory stimulus to expand the dynamic range

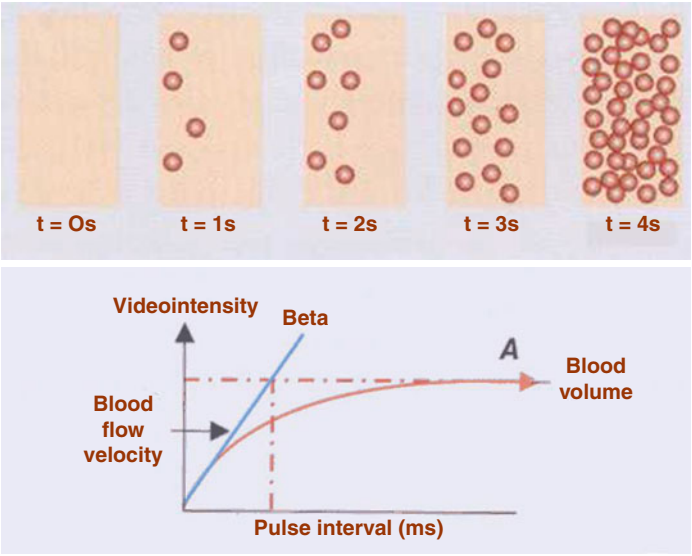


Fig. 24.7 (**a**) Time to filling of myocardium by bubbles, in resting conditions and without significant obstruction. (**b**) Relationship between blood volume and flow velocity with quantitative estimation of myocardial blood flow through a combination of beta (flow velocity) and A (blood volume)

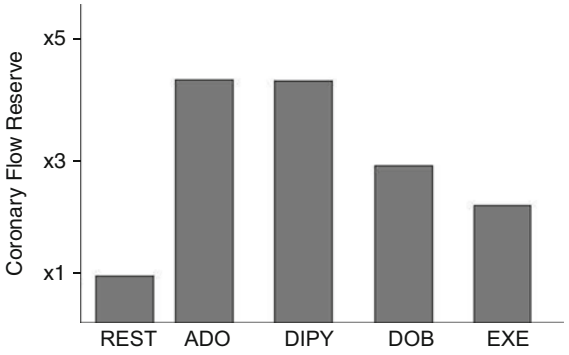


Fig. 24.8 The vasodilatory effect (ordinates, times resting flow = 1) for four different stressors (*x-axis*). Vasodilators (adenosine or dipyridamole, which accumulates endogenous adenosine) are stronger hyperemic stressors than exercise or dobutamine. Modified from Iskandrian [22]

of differentiation between normally perfused and hypoperfused regions. This clearly favors vasodilators when compared to dobutamine or exercise, since the former creates a three- to fourfold increase in coronary flow reserve, as opposed to only a two- to threefold with dobutamine or even maximal exercise [22]: Fig. 24.8. The adopted stressor should also optimize the ischemic potential of the simultaneous wall motion assessment, and therefore high doses are required [23, 24]. Vasodilatory stresses also have the clear advantage of minimally degrading the image quality, which is significantly reduced by dobutamine [25] and, to a greater extent, by exercise [26]. This is always important in stress echocardiography, since image quality is the major determinant of test accuracy and reproducibility [27, 28]. It is even

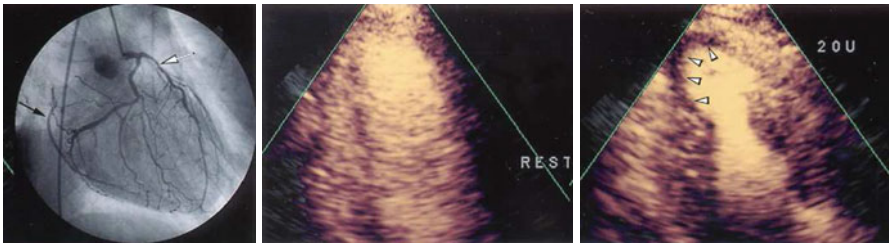
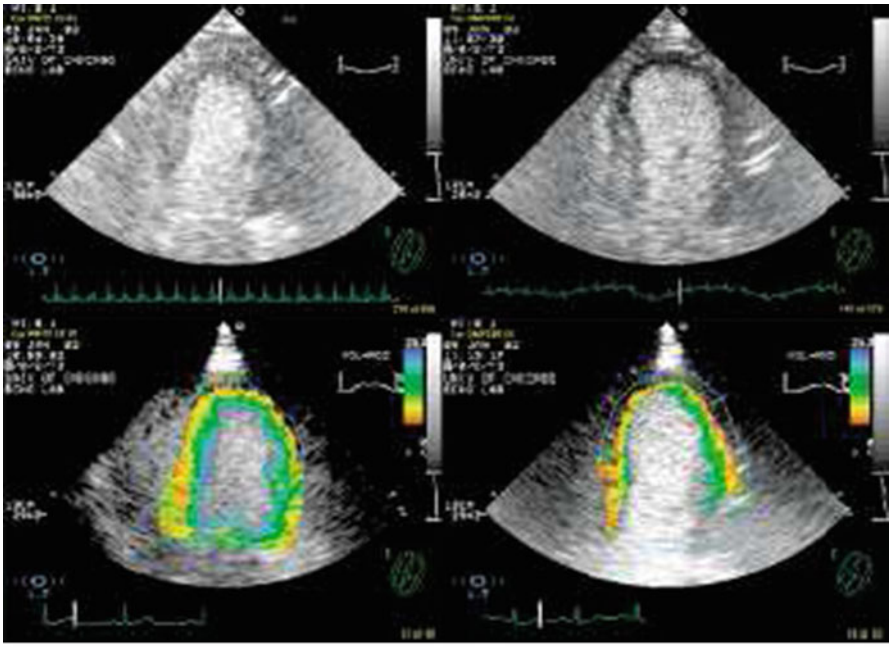


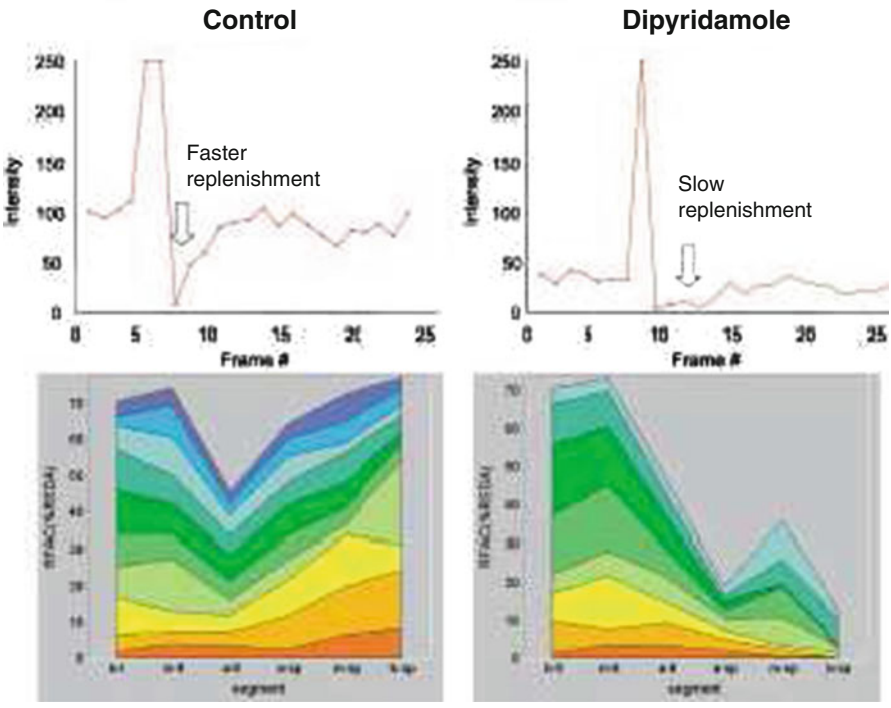
Fig. 24.9 An example of an inducible inferior and apical myocardial perfusion defect (*arrowheads*) during dobutamine stress echocardiography following a 0.3-ml bolus intravenous injection of Optison. These images were obtained in real time at frame rates of more than 25 Hz and pulse inversion Doppler. The subsequent coronary angiogram (left main injection) demonstrates that the right coronary artery fills from the left main injection because of a 100 % right coronary stenosis. In addition, there is a long left anterior descending stenosis (*arrows*) (Courtesy of Dr. Thomas Porter)

more important with stress contrast, since the technique is exquisitely sensitive to artifacts, due to attenuation, variable ultrasound scan planes, and heart rate increase. During stress, a regional wall motion abnormality accompanied by a transient perfusion defect unequivocally localizes myocardial ischemia (Fig. 24.9). The superior image quality of contrast pharmacological stress echocardiography is also ideally suited for the combination of wall motion, perfusion, and quantitation with new technologies such as color kinesis (Fig. 24.10), 3D, or speckle tracking, all techniques in which the signal-to-noise ratio must be excellent for robust endocardial border recognition during stress [29, 30].

24.5 Pitfalls

In spite of the extensive literature supporting its use, the diffusion of MCE in clinical practice remains disappointingly low, with only 10 % of stress echo units utilizing the technique [31]. There are technical, economic, and regulatory problems for this underutilization [32]. There is the need for an intravenous line, and establishment of adequate access is important for optimized contrast stress test. Gain settings for the optimization of myocardial contrast may differ from those used for wall motion, and the ability to detect perfusion abnormalities may be reduced if assessment of wall motion is – as it should be – the primary diagnostic end point. To overcome this problem, very low MI techniques are recommended, but still not familiar for most laboratories. It is recognized that MCE is highly sensitive in detecting resting myocardial perfusion defect. However, specificity can be detrimentally altered by attenuation artifacts mainly in basal segments and the left ventricular lateral wall. If that occurs, the addition of wall motion analysis may improve specificity, since resting myocardial perfusion defect should always be associated with myocardial segmental abnormality. Another possible artifact during MCE is the presence of swirling or reduced contrast in the apex of the left ventricle. The way




Control
Dipyridamole
Faster replenishment
Slow replenishment
Intensity
Frame #
segment

to overcome these artifacts is to increase the contrast infusion rate or lower the MI. We may also move the focus temporarily to the near field for better evaluation of the left ventricular apex.

No contrast agent is currently approved by the FDA or EMA for myocardial perfusion assessment, and use for this purpose remains "off-label." Perfusion imaging is ideally suited to be paired with vasodilator stress, still underutilized when compared to exercise or dobutamine, during which perfusion imaging is more difficult for tachycardia and dyspnea. Ultrasound contrast, like all contrast agents, is not completely safe [33, 34]. The risks were clearly overstated in the FDA original 2007 warning [17]; however, life-threatening reactions are rare but may occur in <1 in 10,000 [35]. The current FDA labeling warns that most serious reactions occur within 30 min of administration and suggests to always have resuscitation equipment and trained personnel readily available – but this is the general rule in stress echo laboratory (see Chap. 10) with or without contrast use. Finally, the cost of contrast varies, but in Europe is around €50 and in the USA around $ 100 per exam. It is reimbursed in some states in the USA, but not in others. It is not separately reimbursed in most countries, and this makes the stress echocardiography (receiving a flat reimbursement of €150–400) less economical if contrast is added.

24.6 Clinical Indications

Ultrasound contrast agents are indicated for patients with suboptimal echocardiographic images at rest, for improvement of left ventricular opacification and endocardial border detection [35]. Both ACCF/AHA 2011 and ESC 2013 guidelines recommend the use of contrast agents when 2 or more contiguous segments (17 segment LV model) are not well visualized at rest. The use of contrast during stress

Fig. 24.10 Simultaneous quantitative assessment of myocardial perfusion and function during an adenosine stress test. *Top left*: the presence of uniform intramyocardial contrast enhancement and color kinesis (CK) bands of uniform thickness qualitatively indicate normal myocardial perfusion and function at rest, respectively. *Right*: diminished intramyocardial contrast in the apex together with thinning of the CK color bands in the same segments qualitatively indicates a dipyridamole-induced apical perfusion defect and wall motion abnormality. *Bottom*: videointensity curves and CK histograms obtained from the above images. *Left*: quantitative assessment of normal myocardial perfusion and function at rest. The videointensity curve demonstrates rapid intramyocardial contrast replenishment after a high-energy ultrasound impulse, while the CK histogram demonstrates normal RFAC in all myocardial segments. *Right*: dipyridamole-induced an apical myocardial perfusion defect with corresponding apical and septal hypokinesis. The segmental videointensity curve demonstrates a slow rate of intramyocardial contrast replenishment following high-energy ultrasound destruction, reflecting a perfusion abnormality. The CK histogram below quantifies the percentage reduction in RFAC in the apex and septum (Courtesy of Dr. Roberto Lang). *RFAC* regional fractional area change, *REDA* regional end-diastolic area

echocardiography not only enhances image quality, but improves reader confidence and enhances accuracy for detection of CAD [36, 37]. MCE allows assessment of myocardial perfusion beyond wall motion thickening assessment during pharmacological stress but is not recommended for clinical use by neither specialty recommendations nor general cardiology guidelines (Table 24.4). Several reports have demonstrated that MCE adds value over the analysis of wall motion during stress test for the diagnosis of angiographically significant CAD using different stressors (exercise, dobutamine, vasodilators), although protocols are still heterogeneous [8–10, 38, 39]. When compared with isolated analysis of wall motion abnormalities, a potential advantage of MCE is the capability to detect greater ischemic burden with therapeutical implications, particularly in patients with MVD [9, 38]. In a meta-analysis involving 11 studies and 674 patients, MCE has been demonstrated with slightly higher sensitivity than myocardial scintigraphy for detecting CAD, with similar specificity [38]. In another large multicenter study, MCE was shown to be more sensitive than SPECT for the detection of CAD [40]. Therefore, in comparison with other imaging modalities, MCE is an easy-to-perform and safe bedside technique for the assessment of myocardial perfusion. More importantly, the prognostic value of perfusion defects during stress MCE has already been demonstrated for predicting death and nonfatal myocardial infarction [15, 16, 41]. Finally, in a prospective study, the role of MCE in the clinical arena was recently shown [42]. MCE was performed during physiologic and pharmacological clinical stress echocardiographic studies, and the value of myocardial perfusion was categorized as of benefit (subclassified as incremental benefit over wall motion or greater confidence with wall motion) or of no added benefit. Integration of MCE into clinical testing was feasible despite multiple operators, use of physiologic or pharmacologic stressors, and the time constraints of clinical care. MCE was demonstrated to be either of incremental benefit over wall motion analysis or added confidence with wall motion analysis in the majority of cases. The conclusion was that although wall motion analysis remains the cornerstone of ischemia detection during stress echocardiography, MCE can be incorporated into clinical services to enhance further the diagnostic accuracy of stress echocardiography.

Stress MCE may also be used for evaluating patients in the emergency department with suspected acute coronary syndromes but no evidence of ongoing ischemia (Fig. 24.11) [43–45]. In the setting of acute myocardial infarction, MCE at rest may provide information on the size of risk area, the presence and amount of collateral flow, the status of myocardial revascularization after epicardial recanalization, and the amount of no reflow. MCE can provide useful information on myocardial viability either early after myocardial infarction or in patients with

Table 24.4 Appropriate and inappropriate use of contrast in stress echocardiography

	A	M	R
≥2 Contiguous segments unreadable	√		
Pulsed Doppler CFR velocity, perfusion imaging			√
<2 Contiguous segments unreadable			√

chronic ischemic left ventricular dysfunction [46–48]. The good spatial resolution of MCE allows for the assessment of transmurality of infarction, which correlates well with delayed gadolinium enhancement on CMR imaging for predicting contractile reserve during dobutamine stress [49].

Finally, CFR and microvascular blood flow reserves have also been established as important predictors of prognosis in patients with other cardiovascular disease besides CAD. Quantitative MCE holds the potential to provide a more accurate estimation of the myocardial blood flow because a contrast agent is a microvascular flow tracer and, thus, seems to better reflect the microcirculatory physiopathology. This technique has advantages over other methods because it can provide information regarding two components of tissue perfusion and myocardial blood flow velocity and volume, in all left ventricular coronary artery territories. Vasodilator stress MCE has been shown valuable for assessing improvements on myocardial blood flow reserve after medical therapy for better control of metabolic abnormalities, such as diabetes mellitus and dyslipidemia [50, 51]. In patients with heart failure and left ventricular dysfunction, exercise training in a supervised hospital-based setting resulted in a significant increase of microvascular reserve, demonstrated by dipyridamole stress quantitative MCE [52]. In addition, microvascular reserve has been proven an independent predictor of death and need for transplantation in patients with dilated cardiomyopathy (Fig. 24.12) [53, 54].

Although interesting, it is important to emphasize that these findings reflect results of single-center studies. The sonic, medical, and economic advantage of

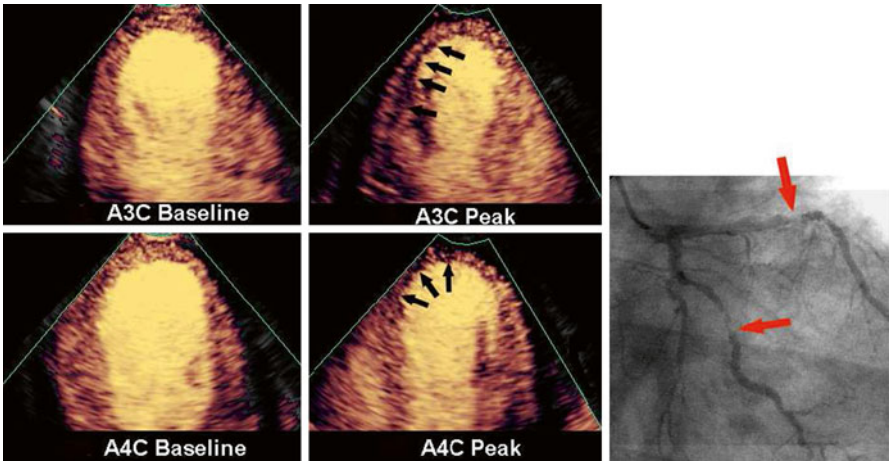


Fig. 24.11 Example of real-time perfusion myocardial contrast echocardiography from a patient admitted in the emergency room with suspected acute coronary syndrome. *Left panels* show normal homogeneous myocardial perfusion at rest in apical three-chamber (A3C) and four-chamber views (A4C). At peak dobutamine stress there was perfusion defect in the posterior (A3C Peak) and apical region of septum (A4C Peak). Coronary angiography demonstrated significant lesion in the left anterior descending artery and left circumflex (*arrows*, *right panel*) (Reproduced with permission Senior et al. [40])

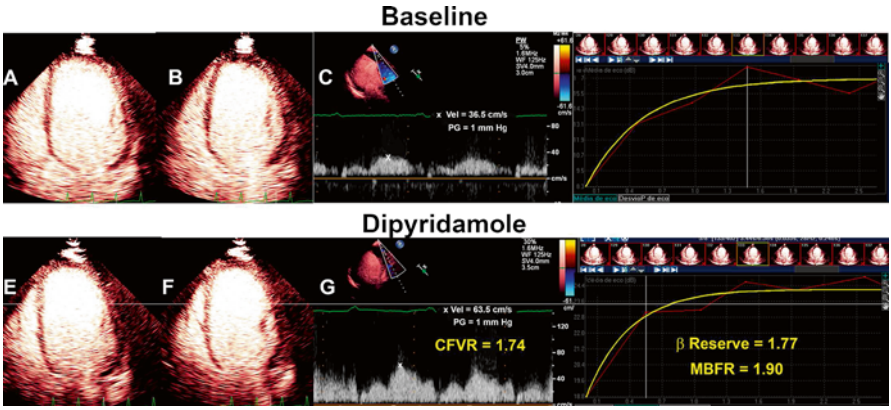


Fig. 24.12 Echocardiographic images at baseline (superior panel) and during dipyridamole stress (inferior panel) from a 49-year-old man with Chagas disease. Real-time myocardial contrast echocardiography at apical 4-chamber view demonstrated dilated left ventricle during diastole (**a**) and systole (**b**) with ejection fraction of 15 % and increased left atrium. During dipyridamole stress, no changes were observed in wall motion analysis (**e** and **f**). There was no significant increase in diastolic velocities in distal left anterior coronary artery with dipyridamole stress (**c** and **g**) resulting in coronary flow velocity reserve (CFVR) of 1.74. Appearance curves of contrast quantification at baseline (**d**) and during dipyridamole (**h**) demonstrated depressed β reserve (1.77) and myocardial blood flow reserve (MBFR = 1.90). This patient died 6 months after dipyridamole stress (Reproduced with permission Lima et al. [53])

ultrasound perfusion imaging would be immense. However, multicenter studies and more robust demonstration of MCE benefits for its incorporation in the clinical practice are still necessary. Other exciting applications of contrast for cell or molecular imaging or for drug or gene delivery remain investigational at present.

Table of Contents Video Companion

See stress echo primer, case 6 (intracoronary contrast stress echo).

See also, in the section illustrative cases, case number 26, 27, and 28 (by Nicola Gaibazzi, MD, Parma, Italy).

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Diastolic Stress Echocardiography

25

Maurizio Galderisi and Eugenio Picano

25.1 The Background of Diastolic Stress Echo

The increase of left ventricular (LV) filling pressure (LVFP) is the most important determinant of dyspnea (shortness of breath) and even of prognosis in patients with chronic heart failure, independent on the values of LV ejection fraction (EF) [1, 2]. The estimation of LVFP is traditionally obtained invasively by right cardiac catheterization which allows to measure pulmonary capillary wedge pressure (PCWP) as an indirect, though accurate, estimate of left atrial (LA) pressure [3, 4]. Nowadays, LVFP may be estimated in a completely noninvasive fashion by Doppler echocardiography. Current recommendations encourage the use of pulsed tissue Doppler for calculating the ratio between the preload-depending transmitral E velocity and the average of septal and lateral velocities of the earliest diastolic motion (e′) of the mitral annulus. This average velocity largely reflects the rate of myocardial relaxation, not depending on pressure flow gradients [5]. In addition to be very feasible and widely available, E/e′ ratio predicts outcome after acute myocardial infarction [6], in patients with heart failure [7] and arterial hypertension [8] and in those mechanically ventilated in intensive care unit [9]. E/e′ ratio can be also applied in clinical practice to drive medical therapy and titrate cardiac drugs in patients with chronic heart failure [10].

A healthy subject has a considerable reserve that can support increased demand from exercise and stress, but when one has significant LV diastolic dysfunction, the normal reserve is significantly reduced, producing shortness of breath. This reduced "diastolic" reserve capacity can be better identified by a stress test designed specifically to assess this reserve [11].

Patients with LV diastolic dysfunction may have a similar hemodynamic profile (in terms of cardiac output [CO] and LVFP) at rest as healthy subjects with normal LV diastolic function. With exercise, however, healthy subjects are able to increase CO without increasing LVFP significantly, because of increased myocardial relaxation, which results in more efficient early diastolic suction with much lower minimal LV diastolic pressure. Reduced myocardial relaxation is one of the earliest

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manifestations of LV mechanical dysfunction [12]. Relaxation properties are substantially reduced in all forms of myocardial disease, including myocardial ischemia, hypertensive heart disease, hypertrophic cardiomyopathy, and heart failure with preserved ejection fraction (HFpEF). It is well known that patients with LV diastolic dysfunction display a deficiency in enhancing myocardial relaxation during exercise compared with healthy subjects who present a normal enhancement of exercise-induced myocardial relaxation [13]. Accordingly, patients with LV diastolic dysfunction may achieve the required CO only at the price of increasing LVFP, because the sufficient early suction mechanism for normal LV filling during early diastole is not available. In this view, the diastolic stress echo can be particularly useful in patients reporting unexplained dyspnea but presenting normal LV systolic function (= normal EF) and LVFP at rest.

25.2 The Rationale of Using E/e′ Ratio for Diastolic Stress Echo

During each cardiac cycle, myocardial relaxation precedes LV early diastolic filling, whereas LV ejection occurs during systole. When myocardial relaxation is normal, most of LV filling occurs during early diastole and the remaining part with atrial systole. When relaxation is reduced, mechanism of LV filling depends on myocardial relaxation and LVFP. If relaxation is reduced and LVFP is still normal, the majority of LV diastolic filling occurs during atrial systole [14]. If relaxation is reduced and LVFP increases, the increased pressure exerts its primary influence and atrial systole may not contribute much for LV filling. Early diastolic velocity (e′) of the mitral annulus has a good inverse correlation with the invasively obtained relaxation parameter *tau* [5].

Because early diastolic mitral flow velocity (E) is sensitive to preload (and therefore increases with increasing LVFP) and because e′ velocity (which is reduced in all the different kinds of LV diastolic dysfunction) is relatively not sensitive to preload, it is expectable that the E/e ratio has been shown to have accurate correlation with invasive LVFP not only at rest [5] but also with exercise [15–17].

25.3 Cutoff Point Values for Normalcy of E/e′ Ratio After Exercise

Changes in mitral and PW tissue Doppler septal velocities after maximal (mean heart rate = 153 bpm) treadmill exercise in healthy subjects of middle age (mean age = 59 years) (Table 25.1) [18] correspond to an increase of both E and e′ velocities, without significant variation of E/e′ ratio.

Of note, although both transmitral E velocity and mitral annular e′ velocity are more vigorous and increase in young subjects, E/e′ ratio is almost identical in older

Table 25.1 Changes in mitral and tissue Doppler septal velocities with exercise in healthy subjects

Variable	Baseline	Postexercise
E peak velocity (cm/s)	73 ± 19	90 ± 25
A peak velocity (cm/s)	69 ± 17	87 ± 22
DT (ms)	192 ± 40	176 ± 42
e′ (cm/s)	12 ± 4	15 ± 5
E/e′ ratio	6.7 ± 2.2	6.6 ± 2.5

Modified from Nagueh et al. (2009) [5]

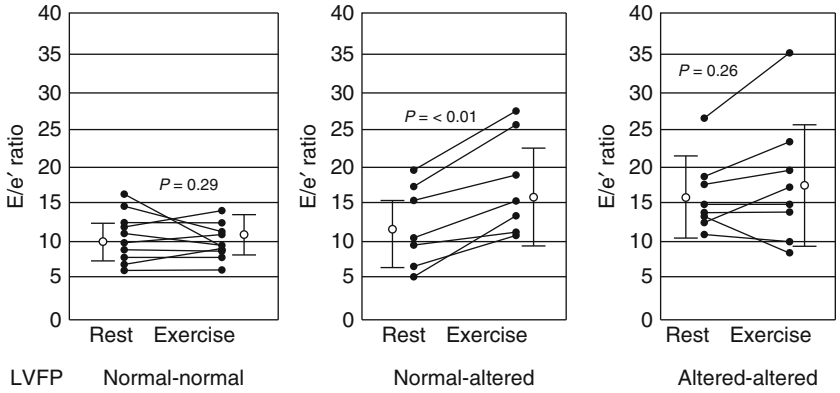

Fig. 25.1 The three possible changes of the E/e′ ratio early after bicycle exercise (Modified from Ha et al. [11]). *LVFP* left ventricular filling pressure

and younger healthy subjects [19]. Hence, the same normal value of E/e′ (<10 for normal LV filling pressure using medial e′) can be used as a noninvasive estimate of LVFP for all subjects regardless of their age. On the other hand, in patients with LV delayed relaxation, the exercise-induced e′ velocity increase is much less than that of transmitral E velocity such that the E/e′ ratio increases.

Summarizing, subjects can present three possible responses to the exercise (Fig. 25.1):

1. *Normal* (*at rest*) – *normal* (*postexercise*): no significant change of E/e′ ratio (Fig. 25.2)
2. *Altered* (*at rest*) – *altered* (*postexercise*): E/e′ ratio is abnormally high at rest and remains high after exercise.
3. *Normal* (*at rest*) – *altered* (*postexercise*): E/e′ ratio is normal at rest but increases abnormally after exercise (Fig. 25.3).

The third response to stress is an important option to unmask mechanisms of LV diastolic dysfunction and heart failure – especially in patients with unexplained dyspnea.

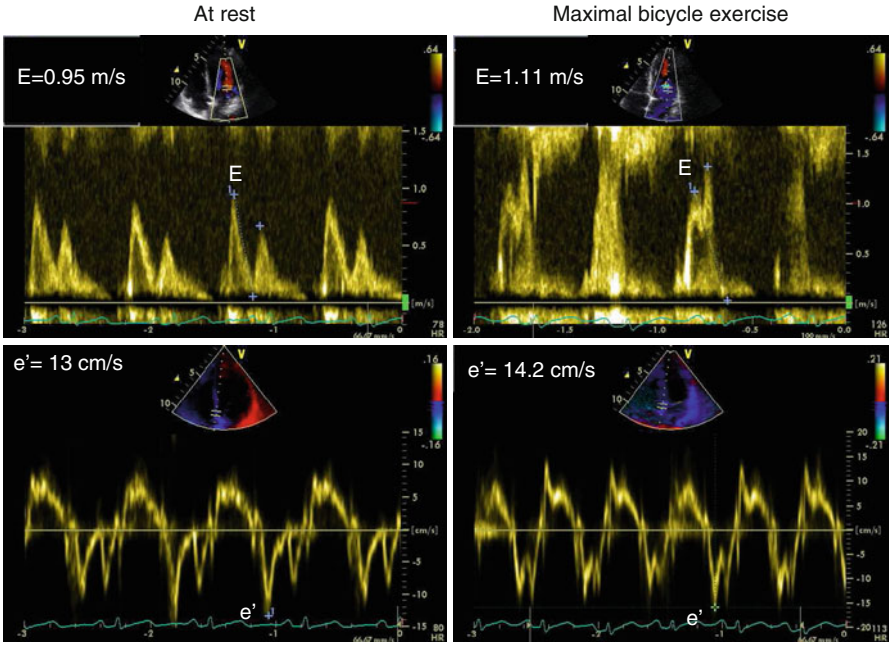

Fig. 25.2 A typical normal (at rest) – normal (postexercise) response

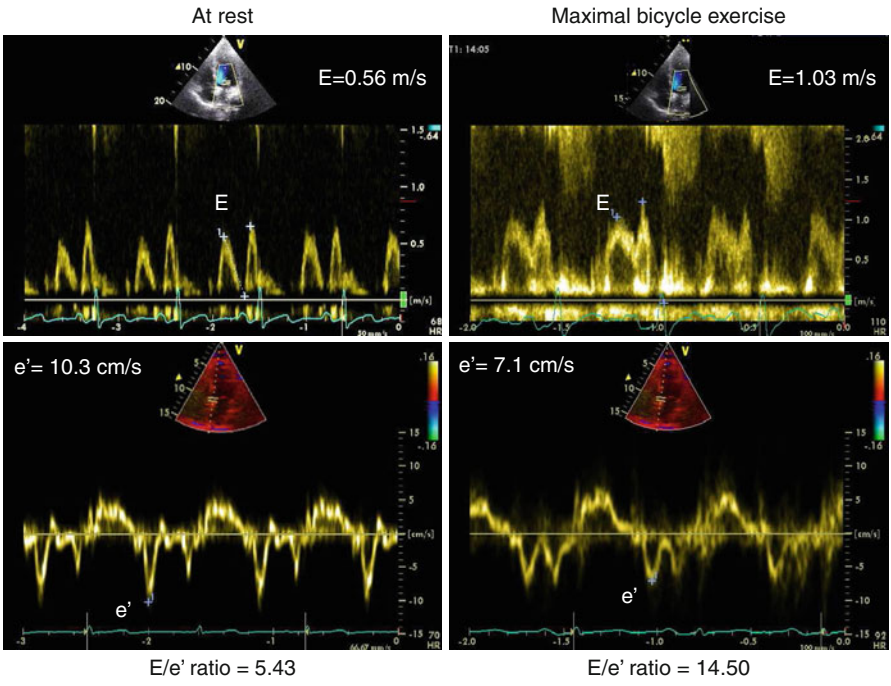

Fig. 25.3 A typical normal (at rest) – altered (postexercise) response in a patient with unexplained effort dyspnea

25.4 Additional Parameters to Be Evaluated by Diastolic Stress Echo

CW Doppler signal of tricuspid regurgitation can be additionally evaluated in order to provide quantitative information on pulmonary arterial systolic pressure (PAPs) increase induced by exercise [20, 21]. Upper normal PAPs have been fixed to be 30 mmHg at rest and 40 mmHg with exercise. Exercise-induced pulmonary arterial hypertension (defined as PAPs ≥50 mmHg) is prognostic for adverse outcomes on long-term follow-up, especially when combined with an increase in estimated LV filling pressure [20].

25.5 Why Exercise Is the Best Modality for Diastolic Stress Echo

Any stress on the heart, including simple sinus tachycardia, is also a powerful diastolic stress, since the positive lusitropic (enhanced LV relaxation) effects of adrenergic stress (or exercise) induce better LV filling in a shorter time. Accordingly, the *exercise* is the best modality for diastolic stress echo. In fact, the normal diastolic response to exercise includes an initial stage corresponding to LV end-diastolic volume increase and LV end-systolic volume reduction (= increased contractility), a plateau at intermediate to high stress level, up to a point when LV diastolic reserve is exhausted and LV filling declines. This drop occurs at lower heart rates in the presence of LV diastolic dysfunction: the lower the diastolic LV filling, the lower the stroke volume and, for any given level of LV systolic dysfunction, the worse the prognosis.

Exercise stress echocardiography can be performed by either supine bicycle or treadmill, with the first to be preferred because of the possibility of obtaining much better imaging. The quantitative assessment of E/e′ ratio and PAPs should be performed at rest and soon after the end of exercise. The rationale of performing this assessment after the exercise completion is based on the observation that in cardiac patients E velocity increase remains stable for a few minutes after the exercise cessation and that the delayed recording of transmitral pattern avoids the problems in measuring appropriately E peak velocity deriving from the fusion of E and A velocities at faster heart rates, i.e., at the maximal exercise.

Diastolic stress echo has been also performed with *dobutamine* infusion, but the results obtained using this stressor appear to be controversial in the heart failure setting [22–24], while its diagnostic role is recognized in patients with coronary artery disease developing dyspnea during the test [25]. Another study showed that a persistent restrictive LV filling pattern with dobutamine was associated with poor long-term outcomes in patients with ischemic cardiomyopathy [26]. In general, dobutamine does not appear to be very sensitive in assessing LV diastolic dysfunction, because diastolic pressure may drop with dobutamine infusion.

Very recently, preload stress echo [27] has been proposed to estimate LV end-diastolic pressure-volume relationship during a preload augmentation maneuver by

measuring the changes in transmitral flow pattern (TFP) velocity during *leg-positive pressure* (LPP). LPP is obtained by a leg massage machine which can maintain a constant loading pressure around the legs for 5 min. By using this method, a setting of 90 mmHg has been applied because this pressure does not significantly increase either heart rate or systolic blood pressure. LV diastolic dysfunction can be divided into three categories according to TFP:

1. Restrictive or pseudonormal (PN = E/A ratio 1.0 to 1.5 + E velocity deceleration time <200 ms) already at rest
2. Impaired relaxation (IR = E/A ratio < 1 + E velocity deceleration time >240 ms) at rest and during LPP (stable IR)
3. IR at rest and PN during LPP (unstable IR)

Of note, event-free survival appears to be significantly lower in unstable IR than in stable IR and unstable IR is an independent predictor of all cause mortality [27]. However, this method has been preliminarily evaluated and is limited by the lack of a validation cohort. Large multicenter studies are warranted to introduce LPP in the clinical practice.

25.6 When Diastolic Stress Echo Should Be Performed

The most important indication for diastolic stress echo is represented by unexplained dyspnea, especially with exertion, a very common symptom particularly in the old age. Although effort dyspnea may be an angina equivalent, the incidence of stress-inducible ischemia is very low in patients referring for effort dyspnea [28]. Conversely, the long-term prognosis of patients complaining dyspnea is worse than those of those with chest pain [29].

Another important role of diastolic stress echo is to provide an accurate diagnosis of diastolic heart failure or HFpEF [30, 31]. LV filling pressure estimated by E/e′ was found to be elevated at rest and/or with exercise in less than half of 148 patients with clinically suspected HFpEF using the ESC criteria [30].

Diastolic stress testing can be used also for detecting subclinical diastolic dysfunction [32] and predicting long-term prognosis. Holland et al. showed that increased LV filling pressure (E/e′ > 13) with exercise had an incremental prognostic power to clinical parameters [33].

25.7 Limitations of Diastolic Stress Echo

Potential limitations of diastolic stress echo include mainly patients with LV regional dysfunction, mitral valve disease (mitral regurgitation and mitral stenosis with annular calcification), mechanical valve prosthesis, and atrial fibrillation.

In patients with LV regional dysfunction, the average of 4 sites of the mitral annulus (anterior and inferior in addition to septal and lateral) could be considered

to improve the test accuracy. The value of E/e′ ratio is debated already at rest in patients with mitral valve disease and in those with mechanical prosthesis. E/e′ ratio can be used as an accurate estimate of LVFP at rest, but its value has not been demonstrated during stress echo, in relation with the combination of tachycardia and RR variability, in presence of atrial fibrillation.

25.8 Implications

The diastolic assessment should be included into all exercise stress echocardiographic tests by measuring mitral inflow velocity, tissue Doppler-derived mitral annular velocities, and retrograde tricuspid gradient of tricuspid regurgitation. This kind of assessment cannot be considered time expensive since the suggested measurements do not take more than a few extra minutes. These measurements can be performed after obtaining wall motion, soon after the end of the exercise, when the heart rate falls down and mitral inflow E and A velocities appear to be well separated. When diastolic filling pressure is elevated with exercise, it remains elevated for several minutes, which provides sufficient time for diastolic function assessment during the recovery from exercise.

The reliability of diastolic stress testing depends on accurate measurement of LV diastolic functional parameters. One of main technical issues is to obtain correct mitral annular velocity by positioning appropriately the sample volume and adjusting properly the tissue Doppler gain setting.

Table of Contents Video Companion

See, in the section illustrative cases: case number 29 (By Maria Joao Andrade, Carnaxide-Lisbon, Portugal).

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Endothelial Function in the Stress Echocardiography Laboratory

26

Rosa Maria Bruno and Eugenio Picano

26.1 Introduction

Endothelial dysfunction is an early stage of atherosclerotic disease [1], characterized mainly by reduced NO availability. In this early stage, no structural lesions are present, but the functional alteration may progress at the cardiac level to impairment in coronary flow reserve in the intermediate stage and then to stress-induced dysfunction in the advanced stages (Fig. 26.1). A direct evaluation of endothelial function is hardly possible, due to NO extremely short half-life. Mirroring endothelial physiology, in vascular reactivity tests, non-pharmacological or pharmacological stimuli for NO release, and thus for endothelium-dependent vasodilatation, are administered. Different techniques have been developed to assess endothelial function in humans, both invasive and noninvasive, exploring endothelial function in different districts. Some of them, such as flow-mediated dilation (FMD), employ the same basic echocardiography hardware of stress echocardiography testing [1]. The additional technological and cultural burden required to implement the technique is high for a hypertension specialist or a cardiologist without cardiovascular ultrasound training and only modest for a cardiologist already skilled in cardiovascular ultrasound. The study of endothelial function is attractive for a cardiologist because of the potential it has to supply important pathophysiological, diagnostic, and prognostic information currently missed by our noninvasive testing modalities. Endothelial dysfunction is a key factor in the onset and development of atherosclerosis, hypertension, and heart failure, as it is also a serious candidate to bridge the gap between hemodynamic atherosclerotic burden and occurrence of clinical events [2]. It is placed exactly in the physiological blind spot of stress echocardiography, which somewhat measures the functional or hemodynamic impact of a coronary stenosis but is unable to assess the status of endothelial function, allegedly responsible for many catastrophic cardiovascular events.

Endothelial dysfunction is also and mainly a biomarker of atherosclerosis. In 2001, a working group of the National Institutes of Health standardized the definition of a biomarker as a “characteristic that is objectively measured and established as an indicator of normal biological pathologic processes, pathogenic processes, or

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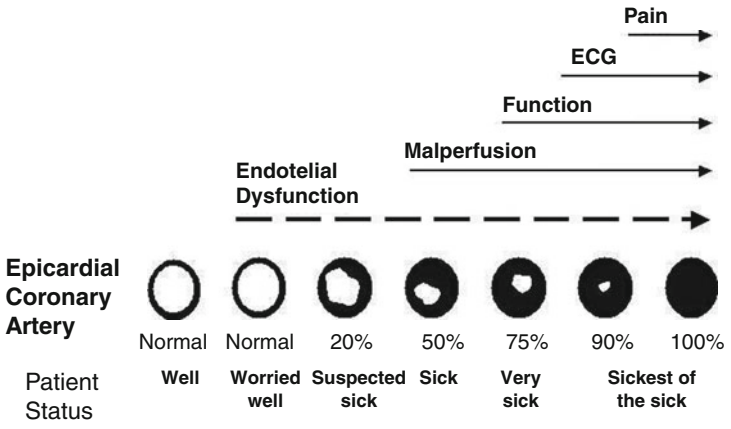

Fig. 26.1 The timeline of atherosclerosis. Endothelial dysfunction occurs early in the natural history of atherosclerosis

pharmacologic responses to a therapeutic intervention" [3]. A biomarker may be measured on a biosample (such as a blood test, for instance, the D-dimer as a biomarker of vulnerable blood) or it may be an imaging test (for instance, echocardiogram for vulnerable myocardium). A simplistic way to think of biomarkers (including endothelial dysfunction) is as indicators of a disease trait (risk factor or risk marker), a disease state (preclinical or clinical), or a disease rate (progression). Biomarkers may also serve as surrogate end points. Although there is limited consensus on this issue, a surrogate end point is one that can be used as an outcome in clinical trials to evaluate the safety and effectiveness of therapies in lieu of measurements of true outcome of interest. Surrogate end points (for instance, endothelial dysfunction in hypertensives in lieu of major cardiovascular events) have the advantage that they may be gathered in a shorter time frame and with less expense than end points such as morbidity and mortality, which require large clinical trials for evaluation. A biomarker will be of clinical value only if it is accurate, it is reproducibly obtained in a standardized fashion, it is acceptable to the patient, it is easy to interpret by the clinician, it has high sensitivity and specificity for the outcome it is expected to identify, and it explains a reasonable proportion of the outcome independent of established predictors (in case of atherosclerosis, Framingham Heart Study risk score) [3]. As a biomarker of atherosclerosis, endothelial dysfunction assessed by brachial ultrasound meets only some of these criteria (Table 26.1), and the deceptively simple methodology and pathophysiologically sweet appearance of the technique may harbor, at the present stage of technology and knowledge, substantial inaccuracies.

26.2 Historical Background

Endothelial surface totals about 27,000 m^2, an extension similar to a football field, and represents the largest epithelial surface of the body. It was long considered "little more than a sheet of nucleated cellophane," according to the definition of

Table 26.1 Ultrasound biomarkers for identifying the vulnerable patient

	Methodology standardized	Methodology available/ convenient	Linked to disease progression	Addictive to FHS risk score	Tracks with disease treatments
Arterial vulnerability					
Structural markers (carotid IMT)	++	+	++	+	+
Functional markers (endothelial dysfunction)	+	+	+	?	++
Myocardial vulnerability					
Structural markers (LVH, LV dysfunction)	++	++	++	?	++
Functional markers (stress echo)	++	++	++	++	++

Adapted and modified from Vasan [3]
LVH left ventricular hypertrophy, *LV* left ventricle, *FHS* Framingham heart study
++ good evidence, + some evidence, ? unknown or ambiguous data

Florey, the Nobel Prize winner for medicine for his work on penicillin. Actually, the endothelium not only serves as a nonthrombogenic diffusion barrier to the migration of substances in and out of the bloodstream but also as the largest and most active paracrine organ of the body, producing potent vasoactive, anticoagulant, procoagulant, and fibrinolytic substances [3]. First discovery of biological effects of NO was made in 1977 by Dr. Murad (University of Virginia), who demonstrated that the vasodilating effect of nitrate compounds was due to NO release. An independent group guided by Dr. Furchgott (University of New York) discovered in 1980 that, in isolated rabbit aorta, acetylcholine-induced vasodilation occurred only in the presence of an intact endothelium, releasing an endothelium-derived relaxing factor that was identified as NO in 1986 by Dr. Ignarro (UCLA). In 1998 Furchgott, Ignarro, and Murad won the Nobel Prize in Medicine for their discoveries about biological role of NO [4]. In 1992, the journal *Science* dedicated the cover page to nitric oxide (NO), referring to it as the molecule of the year. In that very same year, Celermajer proposed a novel method to assess endothelial function in a totally noninvasive way through ultrasound assessment of postischemic hyperemia in the forearm [5]. This postischemic flow-mediated dilation (FMD) is largely mediated by NO. Clinical assessment of endothelial function shifted from the venous occlusion plethysmographic method, exclusively used by a few research-oriented centers mostly interested in hypertension and clinical pharmacology, to the widespread availability of the echocardiography laboratory, crowded by cardiologists, who expect clinically relevant information from the technique [6]. The plethysmographic technique is complex, time-consuming, technically demanding, and invasive, requiring highly

skilled expertise and intra-arterial scalar administration of acetylcholine (to assess endothelial function) and nitroprusside (to assess endothelium-independent vasodilation) [6]. The ultrasonic technique immediately showed potential for much broader applications, repeated assessment, and large-scale diagnostic and prognostic validations. Both plethysmographic and ultrasonic techniques assess endothelial function in the brachial artery. With invasive cardiac catheterization, endothelial function can be assessed directly in the coronary artery segments by measuring the vasoconstrictor response to intracoronary acetylcholine administration [4] (Table 26.2). Indeed by this technique, the first demonstration of endothelial dysfunction in humans was obtained [7]. Since endothelial dysfunction is a systemic process, it can be assessed in both the coronary and peripheral circulation. Intracoronary and intrabrachial infusions of vasoactive agents offer direct quantification of vascular response to NO and are considered the gold standard for endothelial function testing. However, these methods are invasive and not suitable for bedside evaluation.

26.3 Physiology of Normal Endothelium

The endothelium lies between the lumen and the vascular smooth muscle (Fig. 26.2). Although it is only one cell layer thick, it senses changes in hemodynamic forces, or bloodborne signals by membrane receptor mechanisms, and is able to respond to

Table 26.2 Methods to assess endothelial function in humans

	Intracoronary angiography	Brachial artery ultrasound	Venous occlusion plethysmography
Target endothelium	Coronary	Systemic	Systemic
Arterial catheterization	Yes (coronary)	No	Yes (brachial)
Radiation exposure	Yes	No	No
Intra-arterial acetylcholine	Yes (intracoronary)	No	Yes (intrabrachial)
Endothelium-dependent stimulus	Pharmacological (acetylcholine)	Physical (postischemic hyperemia)	Pharmacological (acetylcholine)
Intra-arterial nitrates	Yes (intracoronary)	No	Yes (intrabrachial)
Endothelium-independent stimulus	Coronary nitrates	Sublingual nitrates	Intra-arterial nitroprusside
Risk	Yes	No	Yes
Dedicated hardware	No	Yes	Yes
Cost	Very high	Low	High
Time required	Hours	Minutes	Hours
Key parameter	Coronary diameter	Brachial diameter	Forearm blood flow
Setting	Catheterization lab	Echocardiography lab	Clinical pharmacology
Interest	Pathophysiology	Clinical and pathophysiology	Pathophysiology

physical and chemical stimuli by synthesis or release of a variety of vasoactive and thromboregulatory molecules or growth factors [8]. These are secreted into the lumen or abluminally toward the smooth muscle, affecting vessel tone and growth (Fig. 26.2). In addition to its universal functions, the endothelium may have organ-specific roles (such as control of myocardial contractility by coronary artery and endocardial endothelium) that are differentiated for various parts of the body [8]. As a result of their unique location, endothelial cells experience three primary mechanical forces: pressure, created by the hydrostatic forces of blood within the blood vessel; circumferential stretch or tension, created as a result of defined intercellular connections between the endothelial cells that exert longitudinal forces on the cell during vasomotion; and shear stress, the dragging friction force created by blood flow [8]. Among these forces, shear stress appears to be a particularly important hemodynamic force because it stimulates the release of vasoactive substances (including NO) and changes gene expression, cell metabolism, and cell morphology (Fig. 26.3). Many blood vessels respond to an increase in flow, or more precisely shear stress, by dilating (Fig. 26.3). This phenomenon is designated flow-mediated dilation, and its principal mediator is endothelium-derived NO produced by endothelial nitric oxide synthase (eNOS). NO is also produced under the stimulus of agonists (acetylcholine, bradykinin, and others), acting on specific endothelial receptors, and this property is exploited by other vascular reactivity tests, as already mentioned. Other mediators such as endothelium-derived prostanoids or the putative endothelium-derived hyperpolarizing factor can cause vasodilation if NO is deficient. In physiological conditions, endothelial function is dependent on both

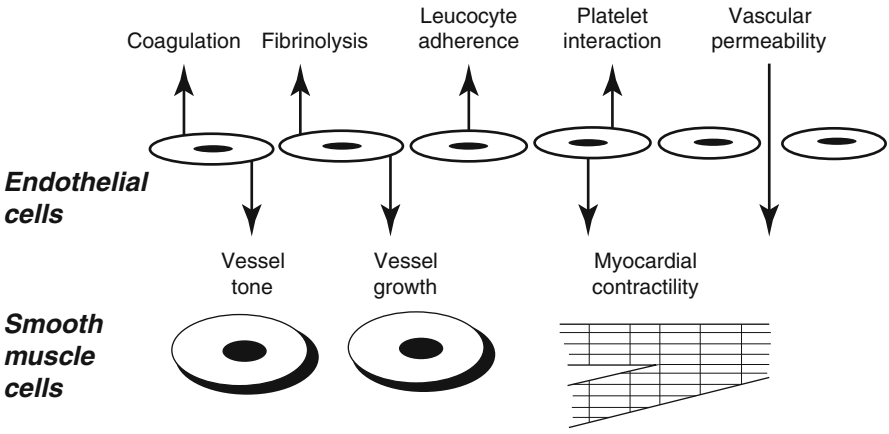

Fig. 26.2 The functional versatility of the endothelial cell. Factors secreted into the lumen (*upward arrows*) include prostacyclin and t-PA, which influence coagulation. Cell-surface adhesion molecules (such as intercellular adhesion molecules-1, ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1) regulate leukocyte adhesion. Factors secreted abluminally (toward the smooth muscle, *downward arrows*) may influence vessel tone and growth. Coronary artery and endocardial endothelium may also influence myocardial contractility (From Celermajer [8], with permission)

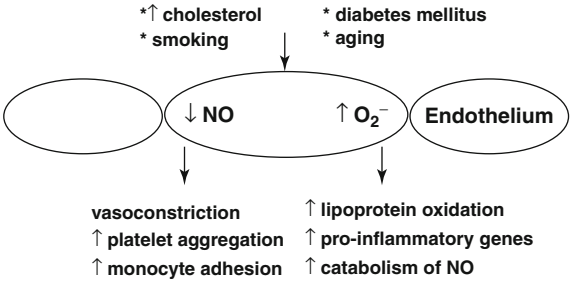

Fig. 26.3 A radical view of endothelial dysfunction. In the presence of certain risk factors, endothelial cells may produce less nitric oxide (NO) or more oxygen-derived free radicals (such as O_2^-) or both. This may lead to a variety of proischemic or proatherogenic effects (From Celermajer [8], with permission)

physical and functional integrity of endothelium, which is able to regulate and preserve vascular homeostasis by inhibiting platelet activation, vasoconstriction, and mitogenesis. Homeostasis is maintained by the balance between protective factors, mainly NO but also other factors such as prostacyclin and endothelium-derived hyperpolarizing factors, and dangerous factors such as angiotensin-II, endothelin-1, tromboxane, and other prostaglandins. The biological link between endothelial damage and atherosclerosis may be related to the decreased arterial bioavailability of NO. The half-life of NO and therefore its biological activity are critically influenced by the presence of reactive oxygen species (ROS) such as superoxide: this free radical rapidly reacts with NO to form the highly reactive intermediate peroxynitrite ($ONOO^-$). The formation of nitroso compounds has multiple negative effects: reducing NO availability, having direct vasoconstrictor and cytotoxic effects, and impairing the activity of the prostacyclin synthase and eNOS. Other ROS, such as the dismutation product of superoxide hydrogen peroxide and hypochlorous acid, cannot be considered as free radicals, but have a powerful oxidizing capacity, which further contribute to oxidative stress within vascular tissues. In aging and in the presence of cardiovascular risk factors, ROS-determined NO-degradation is the most important cause of reduced NO availability, and thus endothelial dysfunction, while reduced NO production has a marginal role. The main sources of increased oxidative stress in cardiovascular diseases are the nicotinamide dinucleotide phosphate (NADPH) oxidase, the xanthine oxidase, mitochondria, and, under certain conditions, even eNOS itself [9]. These changes may in turn result in certain proischemic or proatherogenic effects (Fig. 26.4).

26.4 Methodology

The ultrasound technique for assessing endothelial function is attractive because it is noninvasive and allows repeated measurements. However, it also has technical and interpretative limitations [10, 11]. Until recently, the clinical instability of the technique had been magnified by absolute methodological deregulation on how to collect and interpret data. When evaluating endothelial function, these important

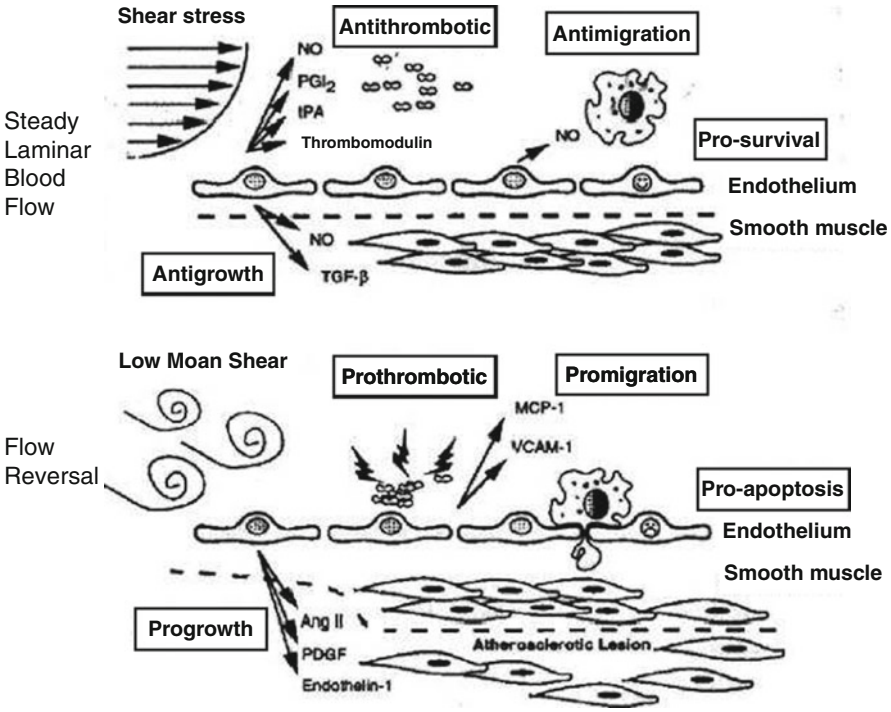

Fig. 26.4 Endothelial cell biology and shear stress. Steady laminar shear stress promotes release of factors from endothelial cells that inhibit coagulation, migration of leukocytes, and smooth muscle proliferation, while simultaneously promoting endothelial cell survival. Conversely, low shear stress and flow reversal favor the opposite effects, thereby contributing to the development of atherosclerosis (From Celermajer [8], with permission)

factors should be taken into consideration, such as subject preparation, protocol, technique, and analysis modality.

In 2002, this methodological tower of Babel was replaced by the guidelines issued by the International Brachial Artery Reactivity Task Force [10], which aimed to minimize the sources of variability associated with patient, acquisition, analysis, and interpretation (Fig. 26.5). Later on, these indications were updated to include recent technological developments and physiological discoveries [6, 12, 13]. Because the magnitude of brachial artery diameter change is a fraction of a millimeter, the technique requires extreme accuracy in the methodology. According to these guidelines, the patient should avoid, whenever possible, exercise, caffeine, alcohol, drugs, stimulants, and medications for a consistent period of time (at least 6 h). A careful drug history should be taken. For premenopausal women, menstrual cycle phase should be considered. Repeated measures should take place at the same time of the day. Lab setting is also critical for attaining a good reproducibility. The room should be quiet and temperature controlled; a stereotactic probe holder and a dedicate software for beat-to-beat image analysis are fundamental equipment. A linear

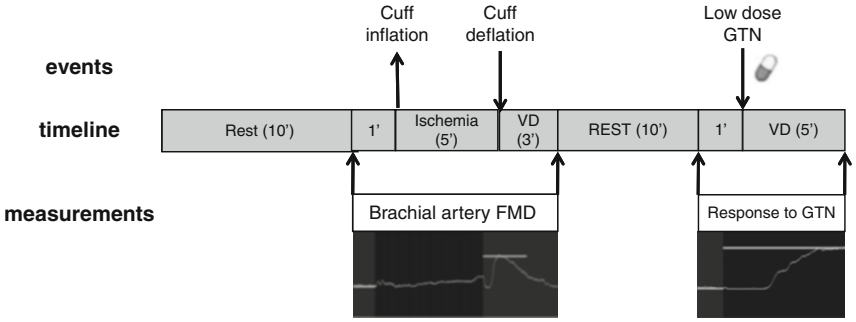

Fig. 26.5 Schematic drawing of the ultrasound imaging of the brachial artery. *Upper panel*: timeline of events. *Middle panel*: ultrasound imaging of the brachial artery. *Lower panel*: cuff and transducer position (Modified from Roman et al. [11], with permission)

array transducer with a minimum frequency of 7 MHz is used to acquire images with sufficient resolution for subsequent analysis, together with continuous and simultaneous measurement of Doppler signal, in order to calculate shear rate together with brachial artery diameter changes. The brachial artery is imaged above the antecubital fossa in the longitudinal plane. A segment with clear anterior and posterior intimal interfaces between the lumen and vessel wall is selected. After baseline rest image acquisition, arterial occlusion is created by cuff inflation to suprasystolic pressure, typically 50 mmHg above systolic pressure or about 250 mmHg, for 5 min. Lower-arm occlusion is preferred, either for physiological reasons (NO-dependency appears to be greater for lower cuff in comparison to upper cuff occlusion) or for technical reasons (greater image stability over time and reproducibility). Interestingly, both techniques retain a similar predictive role for CV events [14]. An exogenous NO donor, such as low dose (25–50 mcg) or high dose (0.4 mg) of sublingual nitroglycerin, is then administered to test smooth muscle function [15]. Peak vasodilation occurs 3–4 min after nitroglycerin administration. Nitroglycerin should not be given to individuals with clinically significant bradycardia or hypotension or in chronic treatment with nitrates. The available technology now makes it possible to acquire arterial diameter continuously and automatically using computer edge-detection algorithms, thus examining the entire time course of brachial diameter and flow velocity in response to reactive hyperemia (Fig. 26.6). This approach is now mandatory, since it considerably improves the reproducibility of the technique [16, 17].

26.5 Diagnostic Value of Endothelial Dysfunction for Detection of Coronary Artery Disease

The integration of endothelial function in the stress testing laboratory has already provided some clinically relevant information. The electrocardiographic ischemic response during stress testing is in fact highly predictive of an altered systemic endothelial dysfunction. This endothelial dysfunction can occur with stenotic (Fig. 26.7) or normal (Fig. 26.8) coronary arteries.

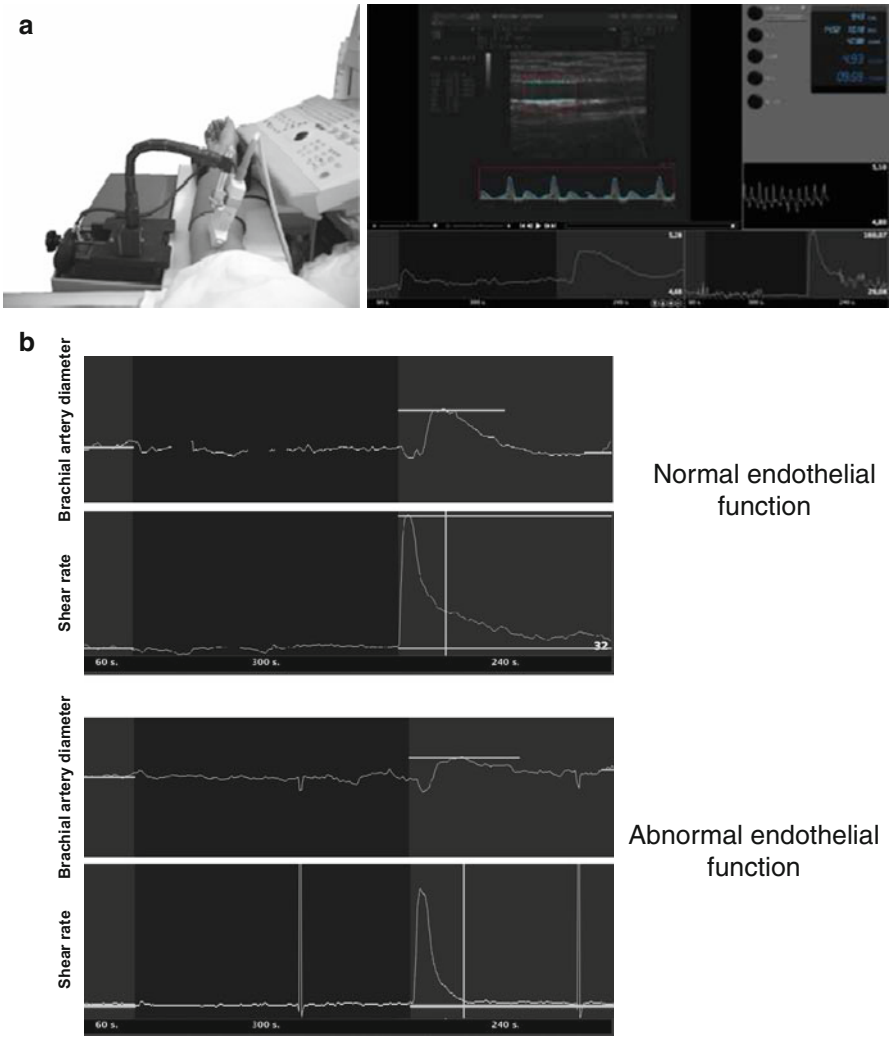

Fig. 26.6 Showing the automated edge-detection system (**a**), with online visual feedback on the quality of the detected signal. Brachial artery flow-mediated vasodilation is obtained with a brachial artery diameter measured using an operator-independent, automated software (Quipu srl; Pisa, Italy). In (**b**), two examples are shown, of a normal (*upper panel*) and an abnormal (*lower panel*) endothelial function

The electrocardiographic information is therefore considered a misleading false-positive response compared to an angiographic standard, but a true-positive result when a physiologically relevant gold standard such as endothelial dysfunction is considered [19–21]. Coronary endothelial dysfunction was more marked in patients with exercise-induced myocardial ischemia (detected by 201-Tl SPECT) but without hemodynamically significant epicardial artery stenoses [18]. In resistant hypertensive patients, a reduced FMD was an independent predictor of a positive dipyridamole myocardial perfusion imaging [19]. Furthermore, FMD was

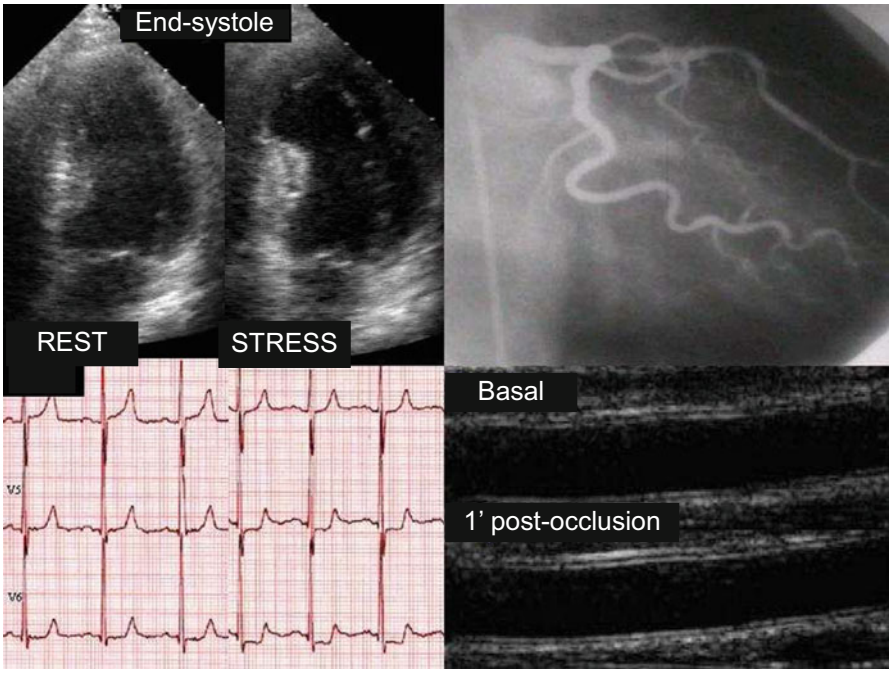

Fig. 26.7 Illustrative example of a typical pattern of test results in a patient with significant proximal stenosis of the left anterior descending artery (*right upper panel*). Exercise stress echocardiography testing (with representative end-systolic frames) reveals a dyskinetic septoapical segment (*left upper panel*) and significant ST-segment depression at peak stress (*lower left panel*); depressed brachial artery flow-mediated vasodilation (FMD) is also displayed on the *lower right panel* (From Palinkas et al. [21], with permission)

cross-sectionally and longitudinally correlated with anatomical measurements of coronary artery disease in a cohort of postmenopausal women [20]. However, the diagnostic accuracy of endothelial dysfunction does not seem sufficient for noninvasively predicting coronary artery disease in the clinical practice (Fig. 26.9) [21].

This cannot be surprising since flow-mediated vasodilation is impaired, independently of underlying coronary artery disease, in patients with coronary risk factors such as hypercholesterolemia [22], hypertension [23], smoking [24], diabetes mellitus [23], hyperhomocysteinemia [25], and aging [26]. In addition, lipid-lowering therapy [27], antioxidants [28], estrogen replacement therapy [29], and treatment with angiotensin-enzyme inhibitors [30] have each been shown to improve the flow-mediated vasodilation response but cannot affect anatomically significant coronary artery disease.

26.6 Prognostic Value of Endothelial Dysfunction

The prognostic value of endothelial dysfunction is founded on a strong pathophysiological basis and it is supported, at present, by growing clinical evidence, in patients at low risk and in those with known or suspected coronary artery disease.

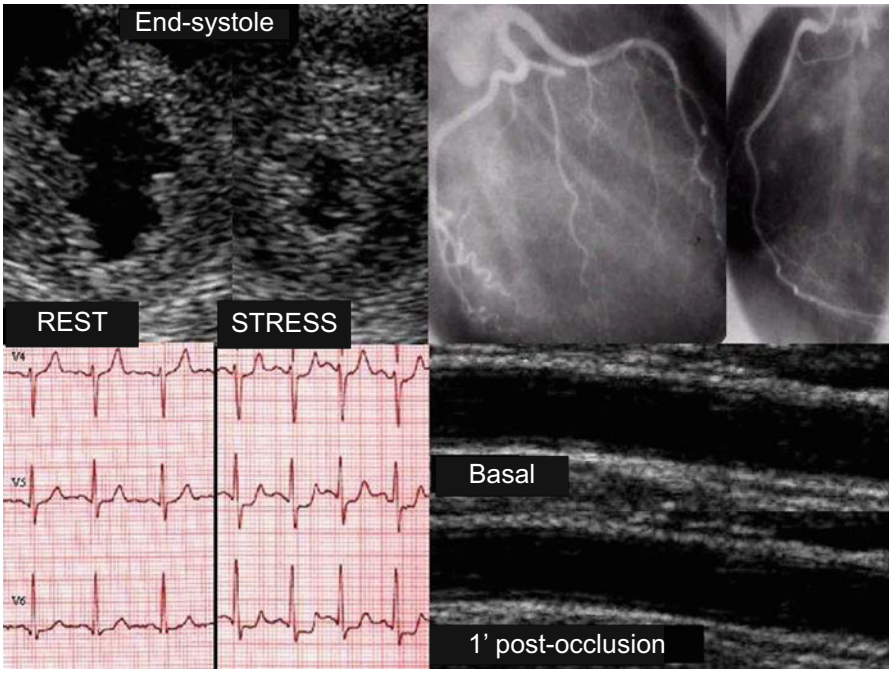

Fig. 26.8 Illustrative example of a typical pattern of test results in a patient with an anginal syndrome and normal coronary angiogram (*right upper panel*). Dipyridamole stress echocardiography testing (with representative end-systolic frames) reveals hyperkinetic wall motion response at peak stress (*left upper panel*) but significant ST-segment depression at peak stress (*left lower panel*); brachial artery FMD confirmed systemic endothelial dysfunction (*right lower panel*) (From Palinkas et al. [21], with permission)

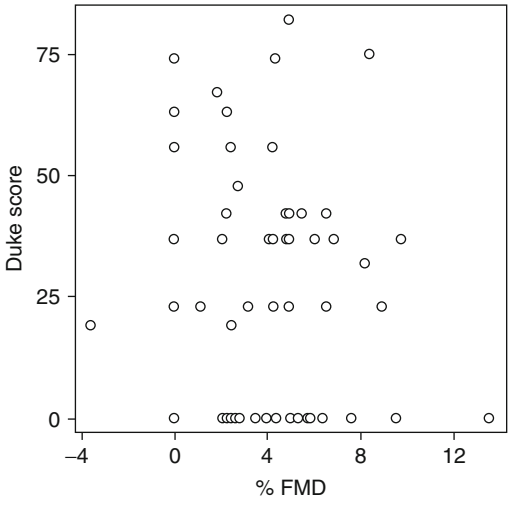

Fig. 26.9 Scatter plot diagram for angiographically assessed Duke score (*y-axis*) and percent flow-mediated vasodilation (% FMD, *x-axis*) fails to show any significant relationship (From Palinkas et al. [21], with permission)

From the pathophysiological viewpoint, the mechanism by which endothelial dysfunction may lead to cardiac events is multifactorial. One possible mechanism is myocardial ischemia secondary to endothelial dysfunction, even in the absence of obstructive coronary artery disease. Patients with abnormal coronary endothelial function often show a positive stress perfusion scintigraphy [18, 31]. Another possible mechanism by which coronary endothelial dysfunction may contribute to cardiac events is through acceleration of coronary atherosclerosis, as evidenced by the development of obstructive coronary artery disease. This is also supported by the observation that in cardiac transplant patients, coronary endothelial dysfunction precedes the development of coronary atherosclerosis [32]. A number of studies have examined the prognostic value of flow-mediated dilation (FMD) of the brachial artery in predicting subsequent cardiovascular event risks, and 32 of them [33–63] have been pooled in a 2014 meta-analysis on over 15,000 individuals [64], clearly showing that brachial FMD is an independent predictor of cardiovascular events and all-cause mortality in patients both without [33–44] and with [45–63] established cardiovascular disease (Fig. 26.10). In particular, 1 % higher FMD at baseline is associated with −13 % cardiovascular events incidence in a adjusted multivariable analysis, both in low-risk and high-risk populations [65]. A systematic review comparing different imaging biomarkers of atherosclerosis for cardiovascular event prediction as compared to standard assessment in terms of calibration, discrimination, and net reclassification found only limited evidence for the use of FMD [66]. However, in the two studies considered in this review, FMD reproducibility was unacceptably low in comparison to current standards [44],

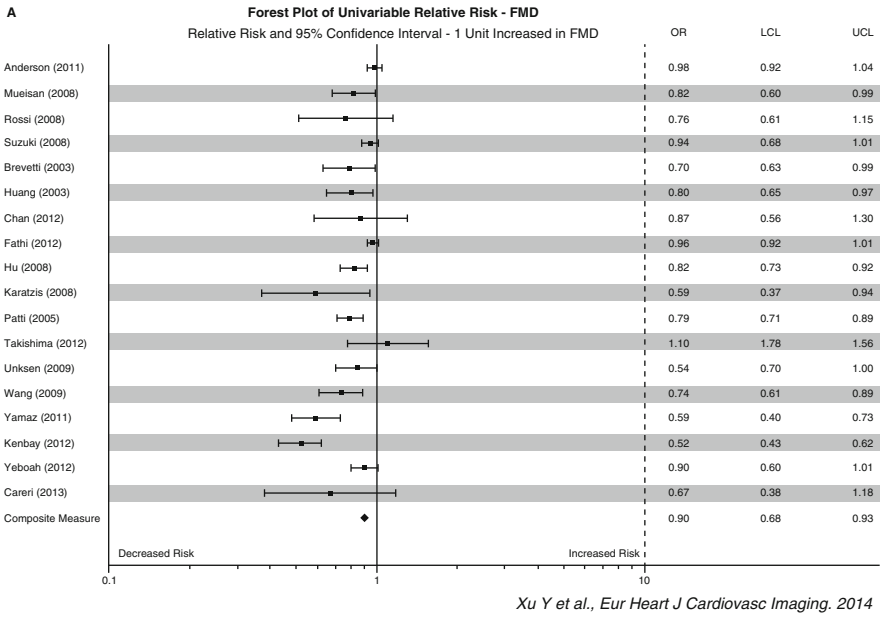

Fig. 26.10 A 2014 meta-analysis showing the capability of endothelial dysfunction to predict future cardiovascular events. In *parenthesis*, number of patients in each study (From Xu et al. [64])

making it impossible to draw firm conclusions based on current literature. Thus, whether FMD has a significant predictive value for cardiovascular events remains a matter of debate.

Notably, both hyperemia-induced shear stress and velocity changes showed even stronger correlations with the presence of cardiovascular risk factors than FMD. In the FATE study, which included 1574 middle-aged apparently healthy men at low cardiovascular risk, hyperemic velocity in the brachial artery was associated with future clinical events, independently from Framingham risk score [34]. As already mentioned, flow velocity measures can be acquired simultaneously with the classical FMD approach, providing additive information. Low-flow-mediated constriction is also a novel measure, complementary to FMD since it explores the response to resting shear stress levels and is mediated by endothelium-derived factors others than NO, potentially used for cardiovascular risk stratification [67].

26.7 Other Clinical Uses of Flow-Mediated Dilation

Most of pharmacological and non-pharmacological interventions able to reduce cardiovascular risk and events are also able to improve endothelial function. The main advantage of endothelial function assessment in interventional trials as surrogate endpoint is that, at variance with more established markers of atherosclerosis such as intima-media thickness, it responds rapidly to therapies, allowing prompt selection of new drugs or other bioactive substances [68].

Another promising field of clinical application of endothelial function assessment needs to be considered. Lack of restoration of endothelial function despite conventional treatment might identify a subset of "nonresponder" patients, who might be suitable for more intensive or new therapeutic approaches. In a study conducted in 251 Japanese men with newly diagnosed stable coronary artery disease and concurrent endothelial dysfunction, FMD was repeated after 6 month of optimized individualized therapy. Those patients with persistently impaired FMD had significant higher event rates in the follow-up period (26 % over 31 months) compared to those with normal FMD (10 %) [69]. In a similar study, endothelial function was assessed in 400 postmenopausal hypertensive women without evidence of coronary artery disease at baseline and 6 month after effectively treating blood pressure. In those women whose FMD has not improved, there was a nearly sevenfold increase in CV events over the average 67-month follow-up [70].

26.8 Pitfalls

The technique requires a highly skilled sonographer, highly standardized measurement conditions (including time of the day, temperature, drug administration), and suitable ultrasound machine with high-resolution ultrasound and specialized computer software for automated image analysis. Technical challenges with the measurement led to considerable variability of measurements even among experienced laboratories [71]: however after three decades of research, noninvasive techniques

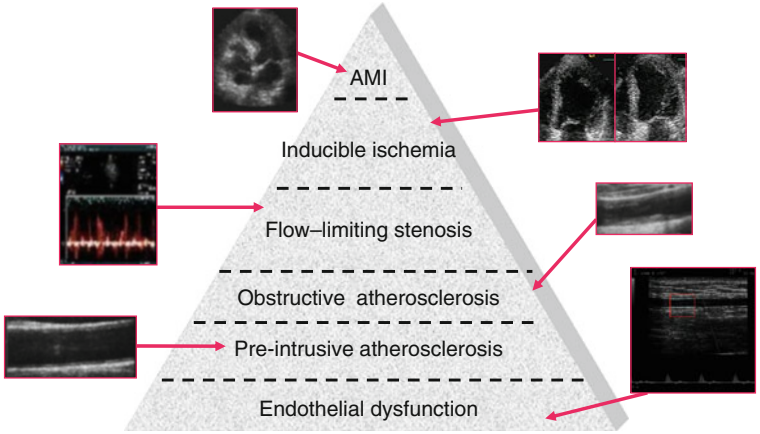

Fig. 26.11 The pyramid of atherosclerosis and the ultrasound imaging tools devoted to each of the segments of the disease: from the asymptomatic, clinically silent large base of the pyramid (endothelial dysfunction by brachial artery ultrasound) to the clinically obvious tip of the pyramid, represented by the baseline regional left ventricular dysfunction. *AMI* acute myocardial infarction

for endothelial function assessment are finally reaching solid standardization and good reproducibility. The most intriguing future development is based on the possibility that flow-mediated dilation might identify a subset of patients in which conventional treatments are not sufficient. However to date, there are no published trials evaluating the impact of specific therapy on clinical outcome in patients identified as having abnormal peripheral endothelial function.

26.9 Clinical Guidelines

Owing to the importance of asymptomatic organ damage as an intermediate stage in the continuum of vascular disease (Fig. 26.11), and as a determinant of overall cardiovascular risk, signs of organ involvement should be sought carefully by appropriate techniques if indicated, for instance, in hypertensive patients.

In this setting, measurement of carotid intima-media thickness or aortic stiffness is reasonable for detecting hypertensive patients at high cardiovascular risk [72]. Other methods such as endothelial dysfunction "cannot be supported for clinical use," since outcome data are relatively scant and the techniques available for investigating endothelial responsiveness to various stimuli are laborious and time-consuming (Table 26.3). In the near future, an effort should be made in order to study endothelial function in clinically critical districts, such as coronary, cerebral, and pulmonary circulation. Although our methods are suboptimal, endothelial dysfunction is certainly more susceptible to a reversal than a flow-limiting, ischemia-producing plaque determining stress echocardiographic positivity. Despite endothelial function measurements are not yet recommended by guidelines for cardiovascular prevention in asymptomatic individuals [71], the abovementioned

Table 26.3 Cardiovascular risk assessment in asymptomatic adults

	A	M	R	COR	LOE
Peripheral arterial flow-mediated dilatation (FMD) studies are not recommended for cardiovascular risk assessment in asymptomatic adults			√	III	B

From Mancia et al. [72]
A appropriate, *M* may be appropriate, *R* rarely appropriate, *COR* class of recommendation, *LOE* level of evidence

recent studies using noninvasive approaches and an improved standardization in noninvasive methodologies might make endothelial function assessment entering routine evaluations in cardiovascular prevention and disease.

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Part IV

In Front of the Patient. Clinical Applications in Different Patient Subsets

27 Special Subsets of Angiographically Defined Patients: Normal Coronary Arteries, Single-Vessel Disease, Left Main Coronary Artery Disease, Patients Undergoing Coronary Revascularization

Antonella Moreo, Maria Joao Andrade, and Eugenio Picano

27.1 Normal Coronary Arteries

In patients undergoing coronary angiography for investigation of chest pain, the incidence of normal or near-normal coronary arteriographic findings varies between 10 and 20 % [1]. In general, patients without significant epicardial coronary artery disease have an excellent prognosis, but not all nonsignificant stenoses are created prognostically equal, since coronary events are rare in patients with smooth, normal arteriograms, sixfold more frequent in patients with mild (0–20 % stenosis), and 15-fold more frequent in patients with moderate (20–40 %, and still nonsignificant) lesions [2]. Even with most conservative reading criteria, stress echocardiography positivity occurs in 10–20 % of patients with angiographically nonsignificant coronary artery disease [3]. The presence of minor, nonsignificant coronary angiographic abnormalities is four times more frequent in patients with an abnormal stress echocardiogram than in patients with a normal one [3]. At long-term (9 years) follow-up, hard events are more frequent in patients with positive stress echocardiographic results than in those with negative stress echocardiographic results [4] (Fig 27.1, left panel). Within the lower-risk subset of patients with negative stress echo by wall motion criteria, the risk is higher in patients with reduced coronary flow reserve assessed with flowmetry of the left anterior descending coronary artery [5] (Fig. 27.1, right panel)

The "anatomical lies" of stress echocardiography, i.e., false-positive responses occurring in patients with nonsignificant epicardial coronary artery disease, can be turned into "prognostic truths" when long-term outcome is considered. Milder forms of reduction in regional coronary flow reserve and/or abnormal coronary microcirculatory function may occur in patients with angiographically normal coronary arteries and may give rise to a positive perfusion scan, as described in the alternative

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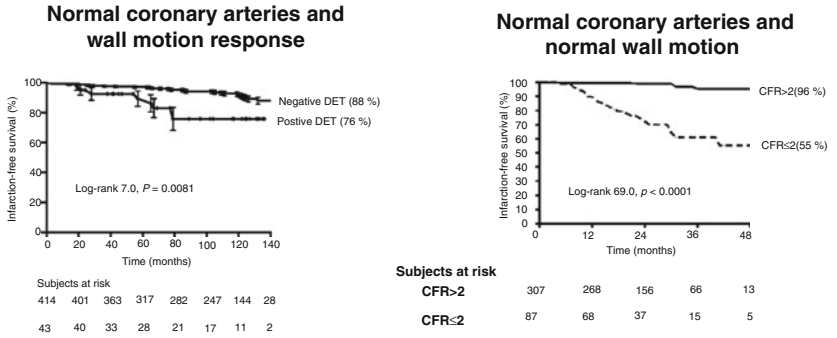

Fig. 27.1 Cumulative rates of survival free of hard cardiac events (death and nonfatal infarction) in patients with normal coronary arteries. The prognosis is worse in the 10 % of patients with inducible wall motion abnormalities (*left panel*). In the low-risk subset of patients with negative wall motion response, the prognosis is worse in the 30 % of patients with reduced coronary flow reserve (*right panel*) (Modified from Sicari et al. [4, 5])

ischemic cascade (see Fig. 3.5 in Chap. 3). More advanced degrees of reduction in coronary flow reserve may lead to subendocardial underperfusion above the threshold necessary to trigger a critical ischemic mass evoking the transient dyssynergy. The prerequisite of stress echocardiography positivity is true myocardial ischemia.

27.2 Myocardial Bridging

Myocardial bridging is defined angiographically as systolic compression (>50 % lumen diameter decrease) of an intramyocardial segment of a normal epicardial coronary artery ("milking sign"). Patients with myocardial bridging are often asymptomatic, but this anomaly may be associated with exertional angina, acute coronary syndrome, cardiac arrhythmias, syncope, or even sudden death [6].

Although historically myocardial bridges have been diagnosed with invasive coronary angiography, this technique has a low sensitivity. Cardiac computed tomography is the preferred noninvasive imaging modality because it can visualize not only the coronary lumen but also the vessel walls and the neighboring myocardium [6]. Intravascular coronary ultrasound detects both the systolic compression (≥10 % during the cardiac cycle) and a characteristic echolucent "half-moon" appearance in the tunneled vessel under the bridge [7]. Intracoronary or transthoracic Doppler show a peculiar flow pattern in the bridge segment with "fingertip" phenomenon, a steep rise in the flow velocity at early diastole followed by a sharp deceleration and subsequent plateau. These flow patterns such as the diastolic fingertip pattern with no or decreased systolic antegrade flow can be explained by the systolic compression of the bridge segment and release of the vascular lumen during early diastole. The early diastolic spike is most probably due to the antegrade coronary flow meeting the still compressed (delayed relaxation) narrow bridge segment.

The subsequent sharp deceleration in coronary flow velocity results from compression release and an increase in the vascular lumen. After the release of the compression, the lumen of the bridge segment remains unchanged in the second half of diastole and therefore corresponds to the plateau of the flow pattern at this phase [7]. Because of systolic squeezing of the bridge segment, reversed antegrade flow may occur during this phase.

Anginal symptoms may be reproduced with exercise, pacing, and dobutamine or dipyridamole stress [8–11]. Stress echo can be useful to assess the functional impact of these abnormalities – not always clinically meaningful. Symptomatic patients with myocardial bridging and evidence of ST-segment depression and effort angina during exercise-electrocardiography show frequent and reversible perfusion defect during dipyridamole stress echocardiography. Perfusion changes are accompanied in one-third of cases by true wall motion abnormalities in the LAD territory of bridging during stress [9] and may show, in a subset, true inducible ischemia as a distinctive septal wall motion abnormality with apical sparing [10–12].

This is well consistent with the concept that myocardial bridging can have a spectrum of functional responses, from fully normal wall motion and perfusion (in the majority of cases) to isolated perfusion defects (in 30 % of cases), to more functional severe wall motion abnormalities. The documentation of inducible ischemia is also interesting from a pathological viewpoint, since it usually believed that myocardial bridging should not cause ischemia as it primarily affects only systolic and not diastolic flow, when most of subendocardial perfusion occurs. However, at high heart rates, diastole shortens and the systolic contribution to coronary blood flow increases significantly. The presence of a focal functional abnormality in the septum suggests that the hemodynamic disturbance and, thereby, ischemia, is local in the myocardial bridge, involves at least one septal branch within the myocardial bridge segment, and recognizes the Venturi effect as the most likely hemodynamic mechanisms [10]. With marked constriction, and especially during high flow states (associated with exercise or dobutamine or dipyridamole), coronary blood flow velocity increases and the perfusion pressure decreases within the narrowed myocardial bridge region, leading to focal ischemia and septal buckling. Stress echo also usually observes a characteristic apical sparing, which also can be reconciled with a Venturi effect since, distal to the bridge, the vessel area increases, resulting in a decrease in velocity and pressure recovery accounting for the normal function in the myocardial territory perfused by the post-bridge left anterior descending coronary artery. Obviously, although this is the most typical stress echo pattern, variations may occur, since the constriction may not be uniform within all bridges and can change with time and be modulated by drugs (typically attenuated by beta-blockers and calcium channel blockers or enhanced by nitrates) and can change with time.

The treatment of patients can be theoretically guided by results of stress echo. In fact, in asymptomatic or paucisymptomatic patients with no perfusion defect or wall motion abnormalities, no therapy is warranted. In symptomatic patients, the effects of medical therapy (with beta-blockers and/or calcium channel blockers) might be predicted by changes in stress echo positivity response. It is important to remember that pure vasodilatory agents such as nitroglycerin should be used cautiously in

these patients, since they can worsen symptoms by intensifying systolic compression of the bridged segment and vasodilating segments proximal to the bridge, thereby exacerbating retrograde flow in the proximal segment and reducing the myocardial ischemic threshold [6]. In patients refractory to medical therapy with still perfusion defects and, especially, wall motion changes in spite of maximal and appropriate medical therapy, surgical treatment can be indicated – in view of the generally disappointing results of PCI – with supra-arterial myotomy or coronary artery bypass grafting. However, no randomized data are available, and in view of the heterogeneous response of stress echo (ranging from normal response to isolated perfusion abnormalities, up to wall motion changes), larger registries and, if possible, randomized trials based on stress echo-driven treatment choices are warranted to shed light on prognostic outcome and optimal therapeutic strategy in patients with myocardial bridging refractory to medical therapy.

27.3 Single-Vessel Disease

The natural history of patients with single-vessel disease is generally benign but heterogeneous [13]. The 4-year infarction-free survival rate is higher for a negative stress echocardiography than for a positive stress echocardiography result in medically, but not invasively, treated patients (Fig. 27.2). Moreover, a significant higher 4-year infarction-free survival rate is found in invasively vs. medically treated

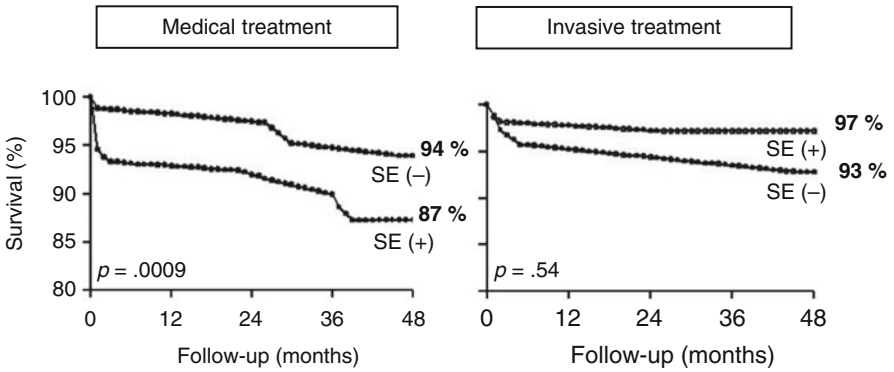

Fig. 27.2 Cumulative rates of survival free of hard cardiac events (death and nonfatal infarction) in patients with single-vessel disease treated medically or invasively. Patients had pharmacological stress echocardiography with dipyridamole ($n = 576$) or dobutamine ($n = 178$). Among medically treated patients, event-free survival was worse in those with positive results on pharmacological stress echocardiography than in those with negative results; this indicates the usefulness of pharmacological stress echocardiography in risk stratification of patients in an angiographically benign subgroup. No difference in survival was seen between invasively treated patients with positive results and invasively treated patients with negative results, which suggests that ischemia-guided revascularization can exert a maximal prognostic beneficial effect in these patients (Modified from Cortigiani et al. [14])

patients with a positive, but not in those with a negative stress echocardiography test result [14]. The prognostic value of stress echocardiography test results outperforms the impact of the degree of stenosis (50, 75, 90 or 100 %) and location of disease (left anterior descending, left circumflex, or right coronary artery), which are recognized as powerful prognostic predictors. These data conflict with the practice of performing coronary revascularization on the basis of coronary anatomical findings only, without preprocedural evaluation of the patient by noninvasive stress testing. This practice is a very frequent and particularly disturbing therapeutic option, overloading the health care system [15] and conflicting with the recommendation of the European Society of Cardiology/European Association for Cardiothoracic surgery Guidelines. According to these guidelines, a preprocedural demonstration of myocardial ischemia is necessary, since to date there is no evidence that coronary revascularization is effective in reducing either mortality or subsequent myocardial infarction in patients with single-vessel disease [16].

27.4 Left Main Coronary Artery Disease

Significant left main artery stenosis is the single most prognostically important lesion involving the coronary arteries. In patients with left main coronary artery stenosis, regardless of the presence of symptoms, surgery can significantly improve survival as compared to medical therapy. Left main coronary artery disease is a formal contraindication to any further form of stress testing (see Table 19.5). Nevertheless, since testing is often done before coronary angiography, several series have reported on stress echocardiography results in this subset of patients. The overall picture is that pharmacological stress testing is reasonably safe with dipyridamole [17], dobutamine, or exercise [18], and although no pathognomonic response for left main coronary artery disease can be recognized, the stress echocardiography pattern in the time and space domain is characterized by a shorter stress time, greater extent and severity of the induced dyssynergy, more frequent antidote resistance, and longer recovery time. All these conditions should raise the suspicion of left main equivalent coronary artery disease and warrant urgent coronary angiography.

27.5 Patients Undergoing Coronary Revascularization

Coronary artery revascularization with either coronary artery bypass surgery or percutaneous coronary intervention is an effective therapeutic procedure in the management of properly selected patients with coronary artery disease. For patient selection and assessment of procedure efficacy, a functional evaluation of stenosis is mandatory. As stated by Gruntzig at the dawn of the angioplasty era, “imaging postcatheterization permits evaluation of the physiologic significance of an observed lesion and to determine the potential effect of dilatation on perfusion distal to the lesion” [19]. In addition, a preangioplasty imaging evaluation “provides a baseline

for noninvasive postangioplasty monitoring of the procedure's success. As with the patient who has undergone bypass surgery, subjective symptoms are usually a good guide, but are not sufficient for the longitudinal evaluation of the procedure" [19]. The practical impact of stress echocardiography in assessing revascularization procedures has been shown both in coronary artery bypass surgery [20–24] and in coronary angioplasty [25–37]. The main tasks of physiological testing in revascularized patients can be summarized as follows:

1. Anatomical identification of disease and geographical localization, with physiological assessment of stenosis of intermediate anatomical severity and identification of target lesion in multivessel disease
2. Risk stratification to identify asymptomatic patients more likely to benefit, in terms of survival, from a revascularization procedure (Table 27.1)
3. Identification of myocardial viability in region with dyssynergy at rest
4. Following revascularization, identification of restenosis or graft occlusion or disease progression, with abnormal results also predictive of subsequent events

According to the conceptual framework outlined in Fig. 18.1, it is also easy to assess the results of the revascularization procedure, which may be completely successful (with disappearance of inducible ischemia; Fig. 27.3) or partially successful (with persisting inducible ischemia; Fig. 27.4).

The timing of postangioplasty stress echocardiography varies widely, ranging from 24 h to 1 week in the various studies. All of these studies demonstrated a comparable reduction in stress echocardiography positivity rates, ranging from 70 to 100 % before and from 10 to 30 % after angioplasty [38]. Stress echocardiography testing performed early after percutaneous transluminal coronary angioplasty does not seem to suffer from the reduced specificity that limits the usefulness of perfusion stress testing in this setting [39] and can be linked to the transient reduction in coronary flow reserve for reversible microvascular damage [5].

The possible physiological benefit on the regional coronary reserve determined by revascularization appears to be the most likely explanation for the improvement in stress test results. A consistently positive stress echocardiography test after angioplasty has an unfavorable prognostic implication, placing the patient in a subset at high risk for recurrence of symptoms [31, 35, 40–46], as also shown by meta-analysis of seven stress echo studies in over 5,000 patients [47].

Table 27.1 Stress-imaging driven revascularization to improve prognosis in stable CAD under optimal medical therapy

Proven large areas of	Class	Level	Ref
Ischemia (>10 % of LV)	I	B	ESC 2013
Dyspnea/heart failure with >10 % of LV with ischemia/viability area supplied by stenosis >50 %	II	B	ESC 2013

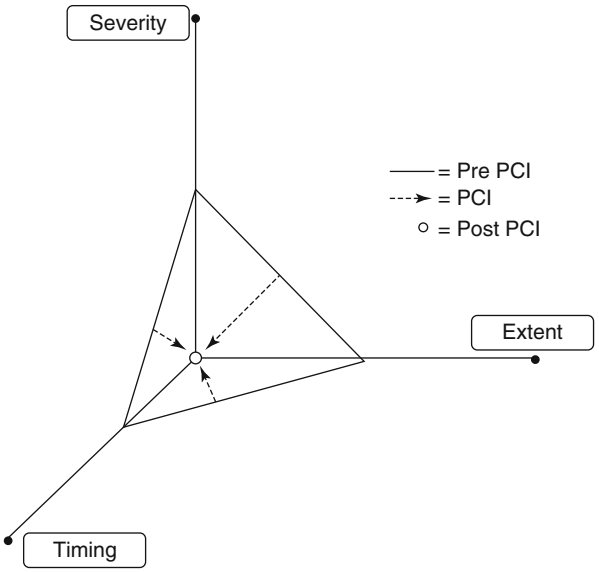

Fig. 27.3 A completely successful percutaneous coronary intervention (*PCI*). Following the intervention, the stress echocardiography test result becomes completely negative, ideally placed at the origin of the system of coordinates localizing the stress-induced ischemia

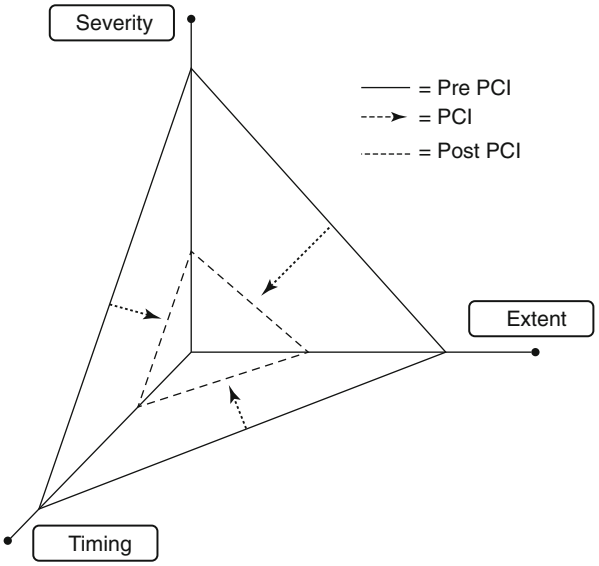

Fig. 27.4 A partially successful percutaneous coronary intervention (*PCI*). The severity of the ischemic response is proportional to the *area of the triangle*, whose vertices are placed on the coordinates of ischemia. The area obviously shrinks following intervention, but the test remains positive, suggesting a primary failure, an incomplete revascularization, or an early restenosis

Table 27.2 Indications to stress echocardiography after coronary revascularization (PCI or CABG)

	Appropriate	May be appropriate	Rarely appropriate
Symptomatic:			
Evaluation of ischemic equivalent	√		
Asymptomatic:			
≥5 years after CABG		√	
≥2 years after PCI		√	
<2 years after PCI			√
<5 years after CABG			√

PCI percutaneous coronary intervention, *CABG* coronary artery bypass graft

The limited, or even total, lack of improvement in the test response after angiographically successful angioplasty may have several explanations [38]. The residual stenosis may be anatomically insignificant and yet hemodynamically important because there is a poor correlation between the percentage of lumen reduction and regional flow reserve, particularly very early after angioplasty. Restenosis may be difficult to recognize on postangioplasty angiograms because of the apparent improvement in luminal dimensions secondary to extravasation of contrast into the media to the plaque, with fissuring and dissection.

The current indications to stress echocardiography after coronary revascularization are summarized in Table 27.2 [48].

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28 Special Subsets of Electrocardiographically Defined Patients: Left Bundle Branch Block, Right Bundle Branch Block, and Atrial Fibrillation

Lauro Cortigiani and Eugenio Picano

28.1 Left Bundle Branch Block

Left bundle branch block is a frequent, etiologically heterogeneous, clinically challenging, and diagnostically hostile entity. Approximately 2 % of patients referred for cardiac stress testing show stable or intermittent left bundle branch block [1]. Although left bundle branch block is a recognized predictor of unfavorable cardiac outcome [2–4], the prognosis is primarily determined by the underlying cardiac pathology, including coronary artery disease, hypertension, idiopathic dilated cardiomyopathy, and aortic valve stenosis [5, 6]. The presence of left bundle branch block makes an ECG uninterpretable for ischemia, and thus, a stress imaging technique is necessary. The presence of an abnormal sequence of left ventricular activation determines increased diastolic extravascular resistance in left bundle branch block [7] (Fig. 28.1), with lower and slower diastolic coronary flow, accounting clinically for the observed reduction in coronary flow reserve in patients with left bundle branch block [8], a reasonable pathophysiological substrate of the stress-induced defect often observed by perfusion imaging in patients with normal coronary arteries [9].

The altered electrical activation also affects septal wall motion, which may range anywhere between a normal and a paradoxical movement (see Fig. 4.8). Normal thickening is observed in the presence of a less abnormal activation sequence (QRS duration <150 ms) and preserved contraction capability (Fig. 28.2).

The paradoxical wall motion is more frequent, with a markedly abnormal activation sequence (QRS >150 ms) and/or septal fibrosis.

In spite of the difficulty posed by the abnormal wall motion, stress echocardiography is the best option for the diagnosis of coronary artery disease [10–14]; it is more specific than perfusion imaging [10, 12], and its sensitivity is good, albeit reduced in the left anterior descending territory only in presence of a

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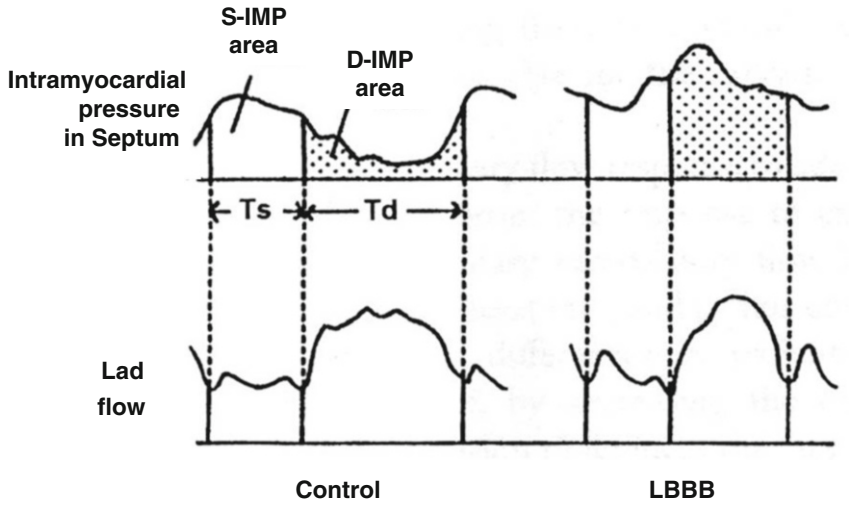

Fig. 28.1 Experimental data obtained with intramyocardial pressure (*IMP*) monitoring and left anterior descending (*LAD*) flowmetry in the dog. With normal conduction (*left panel*), the coronary flow is mostly diastolic, during the phase of cardiac cycle when extravascular resistances (expressed by intramyocardial pressure) are lowest. The induction of left bundle branch block (*LBBB*) increases diastolic resistances and reduces coronary flow. S, systolic; D, diastolic (Modified from [7])

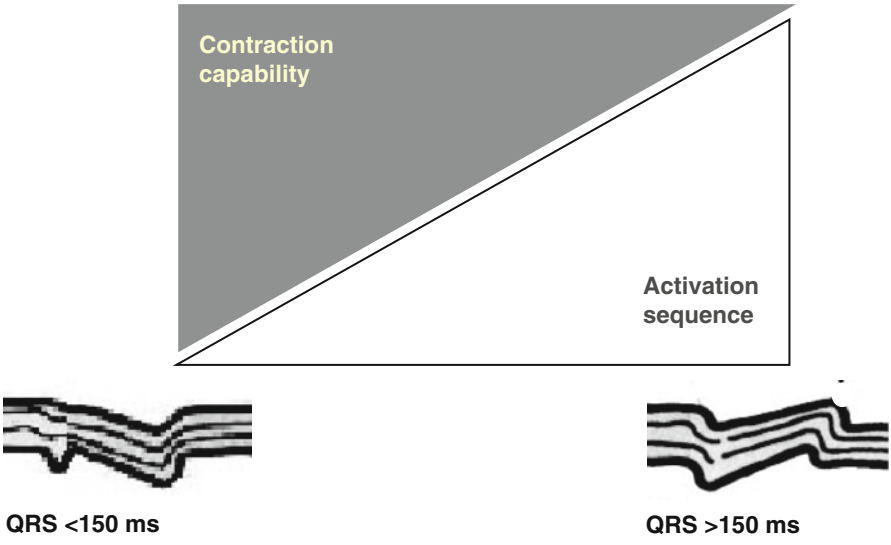

Fig. 28.2 The two major determinants of interventricular septal motion in LBBB: contraction capability and activation sequence. Paradoxical wall motion is more frequent with wide QRS and/or septal fibrosis. The early systolic septal beaking is present in both contraction patterns

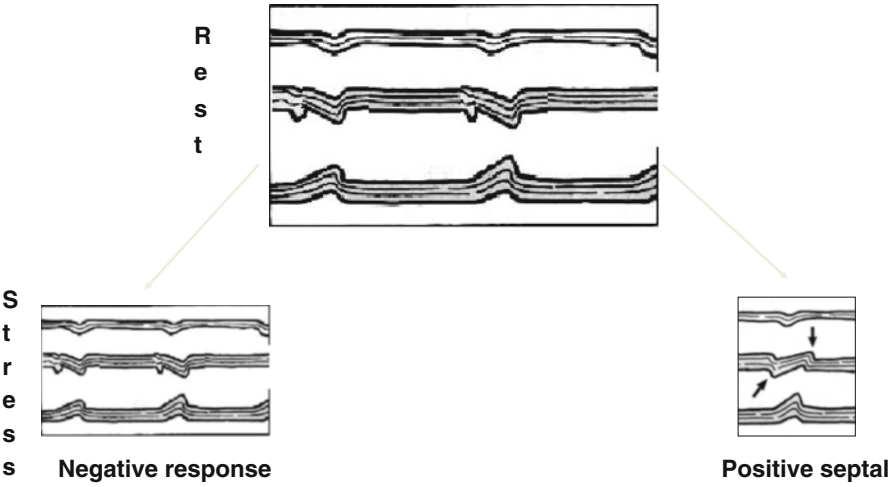

Fig. 28.3 Different types of wall motion response during stress (*lower panels*) in a patient with left bundle branch block, showing early systolic downward septal motion or beaking with normal wall motion at rest (*upper panel*). During stress, the response can be negative (*lower left panel*), with normal to increased septal motion and thickening. The stress can induce an ischemic response on the septum (*right panel*): in this case, both motion and thickening are reduced

dyskinetic septum in the baseline echocardiogram [11] (Fig. 28.3). The prognostic value of stress echocardiography is excellent, additive when compared to clinical and resting echocardiography variables, and especially pronounced in patients without previous myocardial infarction [13, 14]. The diagnostic and prognostic value of stress echo can be critically improved by adding the simultaneous evaluation of coronary flow reserve (CFR) on left anterior descending artery [15] or myocardial perfusion with contrast echocardiography [16] or contrast-enhanced cardiac magnetic resonance [16]. In practical terms, out of ten patients with left bundle branch block referred to stress echo, about two have inducible wall motion abnormalities, and an additional three have isolated (without wall motion abnormalities) reduction in CFR (Fig. 28.4).

This isolated sign of CFR <2 allowed an effective risk stratification in patients missed by negative wall motion criteria, particularly in the case they had been tested under medical therapy, predicting a nearly eightfold higher annual mortality rate and a tenfold higher annual event rate when compared with CFR <2 (Fig. 28.5).

The current guideline recommendations are summarized in Table 28.1. [17].

28.2 Right Bundle Branch Block

Right bundle branch block is present in 2 % of patients with chronic coronary artery disease and in 3 % of subjects referred for noninvasive assessment of coronary artery disease [1]. Although patients with right bundle branch block and no clinical

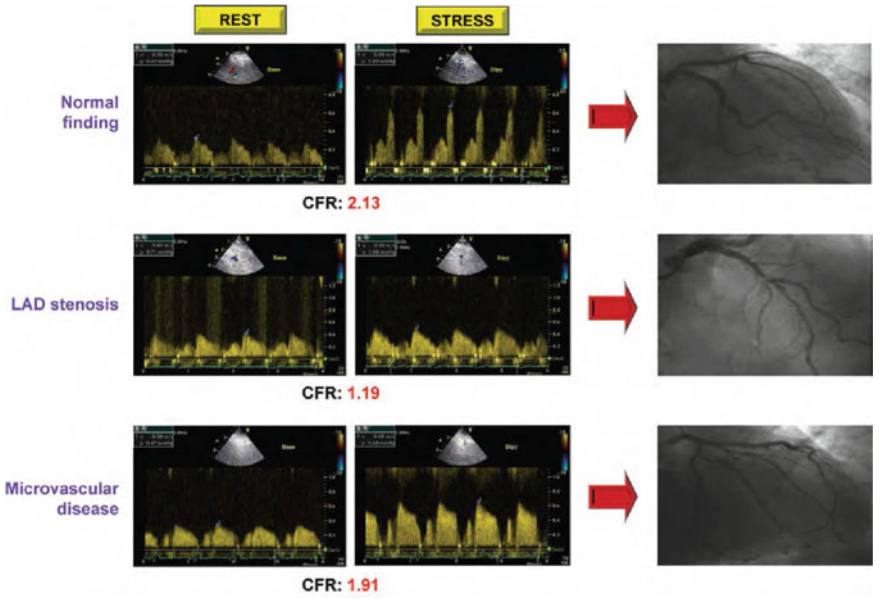

Fig. 28.4 Examples of coronary flow reserve assessed by transthoracic Doppler of the mid-distal portion of left anterior descending artery. Coronary flow reserve is calculated as the ratio between peak diastolic coronary flow velocity at hyperemia and its value in resting condition. The normal finding is characterized by CFR >2 associated with angiographically normal coronary arteries (*upper row*). In the presence of significant stenosis of the left anterior descending artery, CFR is ≤2 (*second row*). Coronary flow reserve can be ≤2 also in the presence of normal coronary anatomy, indicating underlying microvascular disease (*third row*) (From Ref. [15])

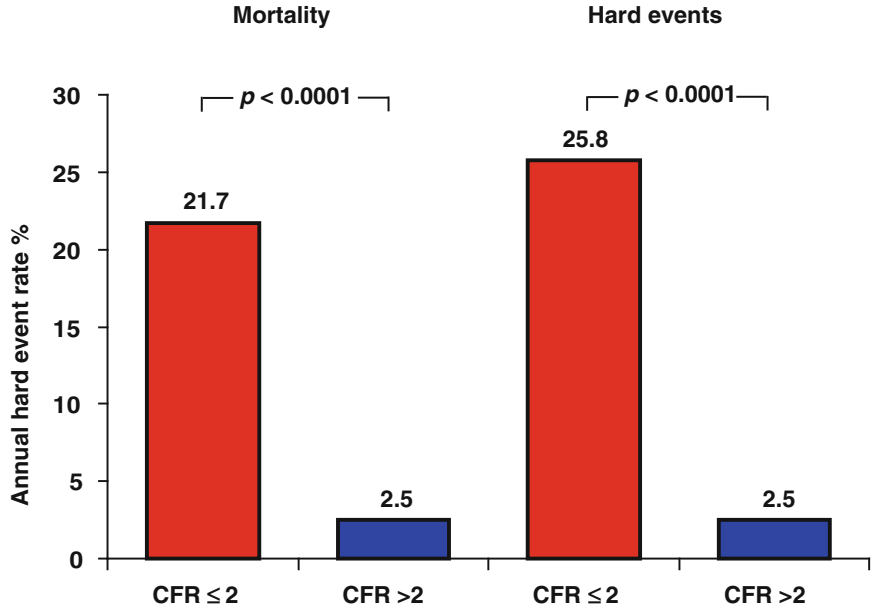

Fig. 28.5 The annual mortality and death or MI rate in patients on the basis of the coronary flow reserve on the left anterior descending artery ≤2 or >2. (From Ref. [15])

Table 28.1 Recommendations for cardiac stress imaging in left bundle branch block

	COR	LOE	Ref
Pharmacological stress echocardiography or SPECT should be performed in patients with LBBB	II a	B	ESC 2013 [17]

COR class of recommendation, *LOE* level of evidence

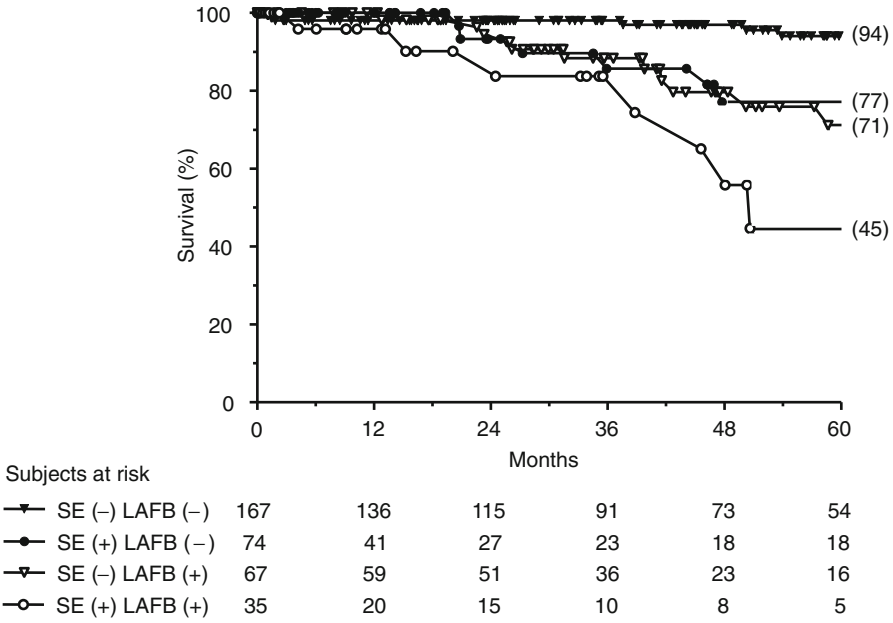

Fig. 28.6 Kaplan-Meier survival curves according to the absence (–) or presence (+) of ischemia at stress echocardiography (*SE*) and the absence (–) or presence (+) of left anterior fascicular block (*LAFB*) on the resting electrocardiogram. All patients had right bundle branch block (Modified from Cortigiani L et al. [18])

evidence of cardiovascular disease generally have a favorable outcome [3, 6, 9], right bundle branch block in subjects with chronic coronary artery disease is predictive of a more severe left ventricular dysfunction, an extensive coronary artery disease, and a mortality rate that is approximately twice as high [4]. Stress echocardiography is an excellent diagnostic choice since right bundle branch block does not affect regional wall motion. In addition, it provides an efficient prognostic stratification, additive to simple resting electrocardiogram parameters such as left anterior fascicular block [18]. In populations referred to pharmacological stress echocardiography testing, three levels of risk are identified on the basis of stress echocardiography results and presence or absence of left anterior fascicular block: a low risk, in the case of no ischemia and no left anterior fascicular block (almost 50 % of the entire population), an intermediate risk in the case of ischemia or left anterior fascicular block only, and a high risk in the case of both ischemia and left anterior fascicular block (Fig. 28.6) [18].

28.3 Atrial Fibrillation

The prevalence of atrial fibrillation increases with the age of the population, being less than 1 % in subjects under the age of 60 years and greater than 5 % in those over the age of 70 years [19, 20]. Approximately 70 % of individuals with atrial fibrillation are between 65 and 85 years old [21]. Coronary artery disease is one of the most common cardiovascular conditions associated with atrial fibrillation, present in 18 % of chronic cases [22]. Although exercise electrocardiography is the cornerstone of noninvasive diagnostic techniques, in the presence of atrial fibrillation, it shows several limitations. In particular, advanced age and other clinical conditions that limit the patient's functional capacity (including heart failure and bronchopulmonary disease) can reduce the feasibility of the test in patients with atrial fibrillation. In addition, atrial fibrillation is often associated with factors lowering the specificity of exercise-induced ECG changes, such as hypertension, left ventricular hypertrophy, and digitalis therapy.

Very short diastolic intervals can contribute to false-positive responses during exercise testing in atrial fibrillation, since diastolic perfusion of the subendocardium is impaired. Stress echocardiography is an effective modality for investigating atrial fibrillation patients. In spite of the pronounced chronotropic response (and thus the lower doses administered), dobutamine stress echocardiography provides useful diagnostic and prognostic information in these patients [22]. Moreover, the prognostic value of the test is comparable in patients with atrial fibrillation and sinus rhythm [23]. As for the safety of dobutamine stress in atrial fibrillation, conflicting results have been reported. While no dobutamine-induced adverse effects were observed in a series of 92 patients [24], a significantly greater occurrence of cardiac arrhythmias was described in 69 patients with atrial fibrillation compared to controls with sinus rhythm [23]. No data are available at this time on stress echocardiography using vasodilator agents in atrial fibrillation.

Atrial fibrillation can be also a complication of stress, relatively more frequent with dobutamine, during which it occurs in 1 % of patients [24]. The risk of developing atrial fibrillation is higher (up to 10 %) in patients with a history of atrial fibrillation, increased left atrial diameter, right bundle branch block, decreased heart rate, or arterial hypertension [25]. Most patients return to sinus rhythm spontaneously within 1 h. Patients with persistent atrial fibrillation can be safely dismissed from the echocardiography laboratory to have outpatient follow-up within 24 h unless they have suboptimal heart rate control, hypotension, significant symptoms, or markedly abnormal findings on stress echo.

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Special Subsets of Clinically Defined Patients: Elderly, Women, Outpatients, Chest Pain Unit, Noncardiac Surgery, Cancer

29

Rosa Sicari, Albert Varga, and Eugenio Picano

29.1 Elderly Patients

Individuals over 65 years of age account for 12 % of the total population in the USA, twice the proportion 20 years ago. This group is expected to increase by 20 % in the next decade and is predicted to constitute more than 20 % of the population by the year 2030. Moreover, the proportion of individuals aged 80 and over in EU Member States currently represents 4.7 % of the total population and is projected to increase to 12.1 % in 2060 [1]. As the prevalence and severity of coronary artery disease (CAD) show a striking growth with age [2, 3], the assessment of risk in elderly and very old (>80 years) is and will be increasingly important in the next future. Unfortunately, in these patients, the predictive value of a test may be negatively affected by reduced life expectancy. On the other hand, due to the high prevalence of CAD in this subset, a negative test result may likely be a false-negative one [3]. Exercise electrocardiography shows limited feasibility in very old patients, mainly due to neuromuscular weakness; physical deconditioning; or neurologic, orthopedic, peripheral vascular, or respiratory limitations. In addition, test specificity declines as age increases [3] because of repolarization abnormalities on resting electrocardiogram due to hypertension [4], left ventricular hypertrophy [4, 5], or digoxin intake [6]. Stress echocardiography has been found to confer effective prognostic contribution in elderly individuals [7–16]. Pharmacologic stress echocardiography provides useful prognostic information in patients >65 years of age. However, its prognostic value decreases with increasing age [12] (Fig. 29.1). In particular, ischemia failed to add prognostic information in subjects >80 years of age, and in this subset it does not predict mortality [16] (Fig. 29.2). The stratification strategy should be tailored and designed on patients' profile. In patients older than 80 years, stress echocardiography does not provide additive information on outcome. Elderly patients with positive stress echocardiography test results tended to receive less coronary angiography and fewer revascularization procedures when compared to the overall population [7]. Advanced age often directs physician's decision on therapeutic strategy, but this policy in time may adversely affect outcome, since a dramatic change in the natural history can be achieved by properly targeted interventions oriented by

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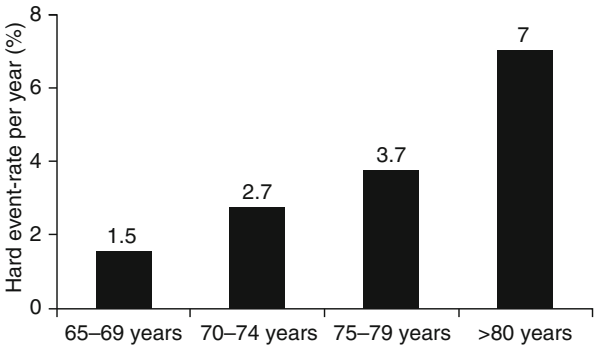

Fig. 29.1 Annual hard event rate per year of a normal test result in different age groups (From Cortigiani et al. [12])

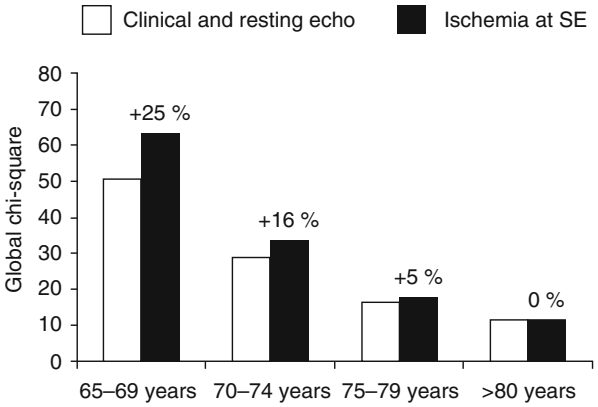

Fig. 29.2 Incremental prognostic value of ischemia at stress echocardiography (*black bars*) over clinical and echocardiographic findings at rest (*white bars*) in different age groups (Adapted from Cortigiani et al. [16])

physiologic testing results. With current advances in surgical techniques and intraoperative myocardial protection, elderly patients with multivessel disease and even significant baseline dysfunction can undergo coronary artery bypass surgery with a low in-hospital mortality rate and an excellent short-term survival rate. Stress echocardiography is a suitable and effective tool for risk stratification in this setting.

29.2 Women

The diagnostic specificity of exercise electrocardiography and myocardial perfusion scintigraphy is definitely lower in women than in men. Reduction of coronary flow reserve in syndrome X (mostly affecting female patients), hormonal influences for exercise testing, and breast attenuation for nuclear technique are potential explanations. In contrast, echocardiography combined with exercise or pharmacologic agents

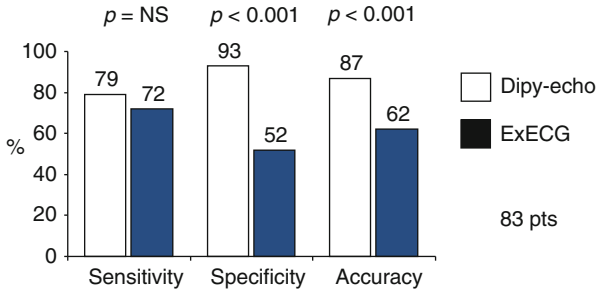

Fig. 29.3 Graphic display of the analyzed variables for the exercise electrocardiography test (*black bars*) and the dipyridamole echocardiography test (*white bars*) in a group of 68 women without previous myocardial infarction (From Masini et al. [17])

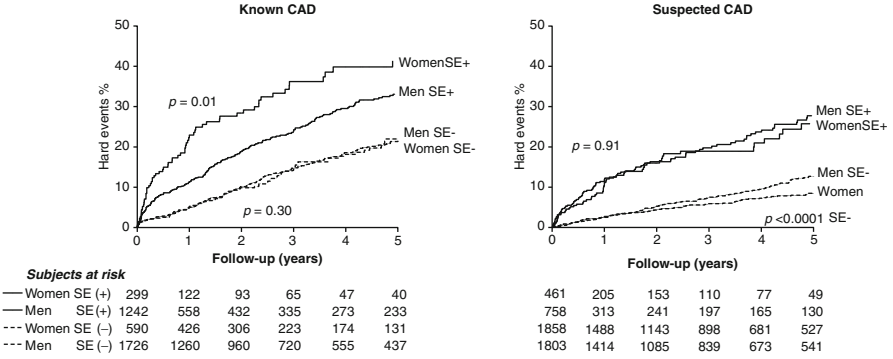

Fig. 29.4 Hard event rate for women and men with known and suspected coronary artery disease separated on the basis of presence (+) and absence (–) of ischemia at stress echocardiography (SE). Number of patients per year is shown (Adapted from Cortigiani et al. [20])

provides similar sensitivity but a better specificity as compared to exercise electrocardiography [17, 18] and perfusion scintigraphy [19]. In women, the prognostic value of stress echocardiography is high, similar to that in men [20]. In patients with chest pain of unknown origin, a normal test is associated with <1 % event rate at 3 years of follow-up, while an ischemic test is a strong and independent predictor of future events [21]. Moreover, stress-induced ischemia adds prognostic information on top of clinical and exercise electrocardiography data [22]. In contrast to ECG stress test and perfusion imaging, stress echocardiography is an "equal opportunity" test, with no difference in diagnostic and prognostic accuracy between males and females. When exercise electrocardiography gives positive or ambiguous results, stress echocardiography is warranted [23]. The choice of an imaging test in this setting should take into account the radiologic burden. The radiation burden for a perfusion scintigraphy ranges between 500 and 1500 x-rays with an estimated cancer risk of 1 in 400 to 1 in 1000. This risk is 37 % higher in women than in men, mainly because of the high radiosensitivity of the breast [24]. Recommendations from the European Society of Cardiology suggest to use non-ionizing imaging techniques especially in highly vulnerable subjects such as younger women [25] (Figs. 29.3 and 29.4).

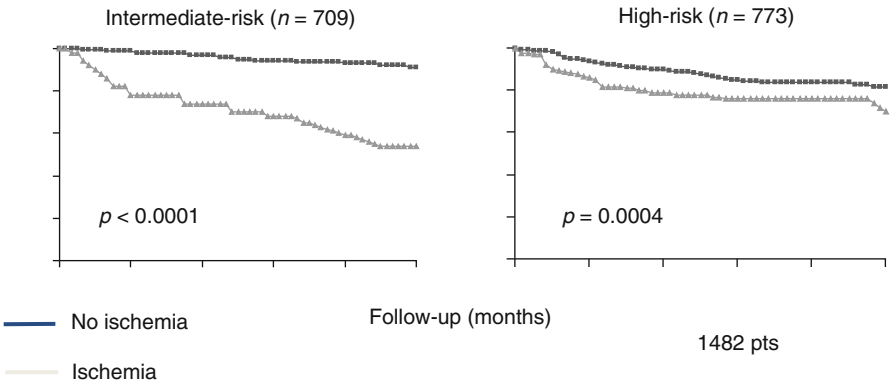

Fig. 29.5 Kaplan–Meier survival curves (considering hard events as an end point) in patients stratified according to presence (*ischemia*) or absence (*no ischemia*) of wall motion abnormalities during pharmacological stress echocardiography (with either dipyridamole or dobutamine). The separation is more obvious in patients with intermediate risk on the basis of clinical presentation (*left panel*), when compared to patients with high risk (*right panel*) (Modified from Cortigiani et al. [30])

29.3 Outpatients

In industrial countries, outpatient investigations account for more than 85 % of the increasing costs of the total workload. Also in these patients, exercise electrocardiography testing remains the most effective and safest diagnostic exam. The prognosis for patients with a normal exercise ECG and a low clinical risk for severe CAD is excellent [26]. Stress echocardiography does not replace stress ECG as a screening method for both clinical and economic reasons [27]. However, in patients with nondiagnostic or ambiguous test results, stress echocardiography testing in properly selected patients can be effectively performed in outpatients, with excellent safety and risk stratification capability [28–30] (Fig. 29.5). According to ESC guidelines on stable angina, stress imaging test for risk stratification is recommended in patients with a nonconclusive ECG (Class I, Level of evidence B) (3).

29.4 Chest Pain Unit Patients

In the USA, more than 6 million people go to emergency departments because of acute chest pain [31]. Some of these patients have coronary artery disease; roughly 2–10 % have myocardial infarction. However, most of them have conditions totally unrelated to a cardiac disease. All these patients will undergo diagnostic testing and will be observed over time and eventually admitted in a cardiology department. Therefore, inappropriate admission of noncardiac chest pain is an enormous, avoidable cost for society and loss of time for the patient. Unnecessary admission to coronary care units costs over 2000 per day and imposes both undue stress and potential morbidity on patients [31]. Several strategies have been proposed to assess

effectively these patients, but this approach may lead to overtreatment. Moreover, it is not clear whether such interventions modify outcome when compared to a more conservative strategy. To help the cardiologist (and the patient) find the narrow pathway between risks of inappropriate discharges and the cost of aggressive admission policy, stress testing has been identified as a useful tool. Patients who are more likely to benefit from testing are those with low-to-intermediate probability of angina on clinical grounds, since those with typical chest pain should be admitted anyway and referred to coronary angiography. In those patients with low-to-intermediate probability, stress testing is an effective choice. Stress testing can be performed with exercise electrocardiography, which is an excellent option with a very good negative predictive value for events in patients who can exercise maximally and who have an interpretable ECG [32]. In a large study [33], stress echocardiography predicted hard events, including all-cause mortality, independently and incrementally beyond that predicted by conventional clinical risk factors (including the TIMI risk score) and resting left ventricular function. An ischemia-guided revascularization with angioplasty is the most frequent therapeutic choice. The majority of patients had a negative stress echocardiography test result (i.e., with no inducible ischemia and no wall motion abnormalities) and were discharged home, usually without experiencing cardiac events in the subsequent 1 year of follow-up (Table 29.1). In other words, out of ten patients – who were otherwise ready for discharge – at least one has true myocardial ischemia detected by stress echocardiography. This patient can be identified and referred to coronary angiography to be revascularized. The remaining nine patients have a negative test result and can be discharged, with a probability lower than 1 % of having a heart attack in the following 12 months [34–42].

Table 29.1 Stress echo in chest pain unit

Author, year	Stress of choice	Patients (*n*)	Mean follow-up (months)	NPV (%)	Rate of positivity
Trippi et al. (1997) [34]	Dobutamine	139	3	98.5	8/139 (5 %)
Colon et al. (1999) [35]	Exercise	108	12.8	99	8/108 (7 %)
Gelejinse et al. (2000) [36]	Dobutamine	80	6	95	36/80 (45 %)
Orlandini et al. (2000) [37]	Dipyridamole	177	6	99	5/177 (3 %)
Buchsbaum et al. (2001) [38]	Exercise	145	6	99.3	5/145 (3 %)
Bholasingh et al. (2003) [39]	Dobutamine	377	6	96	26/377 (7 %)
Bedetti et al. (2005) [40]	Dipyridamole	552	13	98.8	50/552 (10 %)
Conti et al. (2005) [41]	Exercise	503	6	97	99/503 (20 %)

NPV negative predictive value

Recently, coronary CT has been added to the imaging armamentarium as a fast and effective tool to effectively rule out significant CAD. Two recent large reports [43, 44] confirm that CCTA reduces time of observation in the emergency department when compared to conventional strategies with stress testing. In these studies, the event rate was very low (less than 1 % had a myocardial infarction and no patient died), reducing the impact of CCTA on outcome. These results do not show any benefit on outcome but patients received more tests, a high radiation burden with all the downstream risks [25]. The question again is not which test is best but if any test should be performed in low-to-intermediate-risk patients who can be clinically followed-up at no cost [45].

The efficiency of our diagnostic strategies should be weighted against the long-term risks, which is part of the very same definition of appropriateness [46]. The Choosing Wisely campaign reminds us to order tests only when benefit outweighs risks [47]. Once a test is indicated, the choice cannot be neutral and should take into consideration the radiation burden of each test and its potential impact on the individual patient (male vs. female, younger vs. older subjects) [25]. If this is done, there is little doubt that stress echocardiography has decisive advantages for playing a central role in the noninvasive strategy in the ED. Also for stress echocardiography, however, the ER is a frequent source of inappropriate indications [48–50] (Table 29.2). The most appropriate indication remains the patient with low-to-intermediate pretest probability [43, 44]: MSCT might be chosen as a second-line noninvasive test for intermediate-risk patients in whom stress echocardiography is unfeasible or gives ambiguous results. In high-risk patients, direct referral to coronary angiography is warranted. Cardiac magnetic resonance is promising in patients with acute coronary syndrome in the emergency department [51, 52], but its application is currently limited by restricted access. In perspective, it would become an ideal choice in patients with nondiagnostic or ambiguous stress echocardiography results.

Table 29.2 Stress echocardiography in acute coronary syndrome

	Appropriate	Uncertain	Inappropriate
Intermediate pretest probability (no dynamic ST changes *and* serial cardiac enzymes negative)	√		
Risk assessment without recurrent symptoms or signs of heart failure	√		
Pt with prior positive perfusion scintigraphy or positive MSCT		√	
Low pretest probability, ECG interpretable, and able to exercise			√
Routine evaluation prior to hospital discharge (in asymptomatic post-PCI patient)			√
High pretest probability of CAD			√
ECG ST elevation			√

MSCT multislice computed tomography, *ECG* electrocardiogram, *PCI* percutaneous coronary intervention, *CAD* coronary artery disease

29.5 Noncardiac Surgery

Perioperative ischemia is a frequent event in patients undergoing major noncardiac vascular or general surgery, and coronary disease is known to be the leading cause of perioperative mortality and morbidity following vascular and general surgery [53, 54]. The diagnostic/therapeutic corollary of these considerations is that coronary artery disease – and therefore the perioperative risk – in these patients has to be identified in an effective way preoperatively. This is not feasible in an accurate way with either clinical scores (such as Detsky's or Goldman's score) or rest echocardiography, only. The updated ESC guidelines recommend an imaging stress testing before high-risk surgery in patients with more than two clinical risk factors and poor functional capacity (Class I, Evidence C) [54]. The criteria of high-risk surgery are reported in Table 29.3.

Stress echocardiography has been proven to be an effective tool for risk stratification when compared to perfusion scintigraphy [55–67]. Its advantages are due to lower costs and the lack of ionizing radiations, and in this particular setting, it is more feasible than exercise stress echo. The experience with either dipyridamole or dobutamine indicates that these tests have a very high and comparable negative predictive value (between 90 and 100 %), allowing a safe surgical procedure [68]. A negative test result is associated with a very low incidence of cardiac events and allows a safe surgical procedure [68–70]. The positive predictive value is relatively low (between 25 and 45 %): this means that the postsurgical probability of events is low. Stress echocardiography shows a comparable diagnostic and prognostic accuracy when compared to perfusion imaging. The risk stratification capability is high for perioperative events and also remains excellent for long-term follow-up [71, 72]. Other techniques such as CMR and CCTA are available, but the evidence is too

Table 29.3 Surgical risk estimate according to type of surgery of intervention

Low-risk: <1 %	Intermediate-risk: 1–5 %	High-risk: >5 %
Superficial surgery	Intraperitoneal: splenectomy; hiatal hernia repair, cholecystectomy	Aortic and major vascular surgery
Breast	Carotid Symptomatic	Open lower limb revascularization or amputation or thromboembolectomy
Dental	Peripheral arterial angioplasty	Duodeno-pancreatic surgery
Endocrine thyroid	Endovascular aneurysm repair	Oesophagectomy
Eye	Head and neck surgery	Repair of perforated bowel
Reconstructive	Neurological or orthopaedic: major (hip and spine surgery)	Adrenal resection
Carotid asymptomatic (CEA or CAS)	Renal transplant	Total cystectomy
Gynaecology minor	Intra-thoracic: non-major	Pneumectomy
Orthopaedic minor		Pulmonary or liver transplant
Urological minor (TURP)		

Table 29.4 Stress echocardiography in noncardiac surgery

	Appropriate	Uncertain	Inappropriate
High-risk surgery + intermediate-risk patient (poor exercise tolerance ≤4 METS and/or >3 risk factors)	√		
Intermediate-risk surgery + intermediate-risk patient (poor exercise tolerance ≤4 METS and/or ≥3 risk factors)		√	
Intermediate-risk surgery + low-risk patient (good exercise tolerance)			√
Low-risk surgery + intermediate-risk patient			√
High-risk surgery + asymptomatic up to 1 year after normal catheterization, noninvasive test, or previous revascularization			√

METS metabolic equivalents, defined as the amount of oxygen consumed while sitting at rest

scant to be recommended. Moreover, costs and risks should be weighed in the model of stratification and high-tech imaging techniques do not seem to be adequate for a large-scale assessment. Stress testing should be used in the diagnostic algorithm only when its result might influence perioperative management and outcome. To date, it appears reasonable to perform coronary revascularization before peripheral vascular surgery in the presence of a markedly positive result of stress echocardiography in which standard medical therapy appears insufficient to prevent a perioperative cardiac event. A more conservative approach – with watchful cardiological surveillance coupled with pharmacological cardioprotection with beta-blockers – can be adopted in patients with less severe ischemic responses during stress [54]. Concerns have been raised on the initiation of beta-blockers before surgery without titration (to avoid hypotension and heart rate) and in low-risk patients [73]. Interestingly, clearly inappropriate indications for preoperative risk stratification before noncardiac surgery (intermediate-risk surgery in patients with good exercise capacity and low-risk surgery) account for 25 % of all inappropriate testing in large-volume stress echocardiography laboratories [48–50, 74] (Table 29.4), and therefore, this field provides a key opportunity for quality improvement and targeted educational programs to achieve measurable improvements in results.

29.6 Cancer Survivors After Chemo- and Radiotherapy

Cardiac toxicity is one of the most concerning side effects of anticancer therapy with either radiotherapy or chemotherapy (such as anthracyclines, taxanes, doxorubicin, and trastuzumab) [75]. The gain in life expectancy obtained with anticancer therapy can be compromised by increased morbidity and mortality associated with its cardiac complications [76, 77]. There are no prospective studies on the use of stress echocardiography in this setting. Recently, the European Association of Cardiovascular Imaging has emanated two consensus statements on the use of imaging in patients

undergoing chemotherapy or radiotherapy [78, 79]. Stress echo is recommended for initial detection and follow-up of patients with known or suspected coronary artery disease [80], and it is also indicated in patients with LV systolic dysfunction for assessment of dobutamine-induced contractile reserve, which is associated to a better prognosis for any given level of resting LV dysfunction [81, 82]. Prospective studies are needed in order to establish the role of physiologic testing in this setting and its potential additive value over rest echocardiography.

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Stress Echo in Microvascular Disease

30

Leda Galiuto and Eugenio Picano

30.1 Coronary Microvascular Disease

Coronary microcirculation is a fundamental portion of the coronary artery tree, as it contains most of the coronary blood volume and represents the main regulator of the coronary blood flow. Arterioles, capillaries, and venules originating from the major coronary artery branches and extending inside myocardium, with a diameter less than 300 μm, constitute the whole coronary microcirculation. While in the past only epicardial segments of coronary arteries were recognized to be potentially diseased by atherosclerotic process, in the last years growing evidences have suggested that some impairment may also affect the microcirculation. Interestingly, coronary microvascular impairment greatly contributes to pathophysiology of many cardiac diseases and to patient prognosis. As worth of note, different degrees of coronary microvascular impairment can be found both with and without epicardial obstructive atherosclerosis: indeed, recently, coronary microvascular abnormalities have been described in patients with normal coronary angiograms. Several conditions can be clustered together in the syndrome of microvascular disease (Table 30.1) [1]. In some of these conditions, the abnormalities of the microvasculature represent important markers of risk and may even determine myocardial ischemia, thus becoming important therapeutic targets [1].

Actually, while obstructive atherosclerosis of the epicardial coronary arteries is well established to cause myocardial ischemia, the link between microvascular disease with normal coronary arteries and myocardial ischemia has been questioned for a long time. Nevertheless, there is evidence that any reduction in coronary flow reserve in patients with normal epicardial coronary arteries can be attributed to microvascular disease in the absence of epicardial vasospasm [1].

The term "chest pain with normal coronary angiogram" has been used to encompass a broad range of conditions (Table 30.2). Some patients often have coronary artery disease ranging from minimal disease to coronary stenosis up to 50 % of luminal diameter and different comorbidities including diabetes and

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Table 30.1 Clinical cardiac conditions characterized by coronary microvascular impairment

Coronary microvascular impairment in the presence of obstructive epicardial coronary artery disease	It may occur in the context of either stable coronary artery disease or acute coronary syndromes with or without ST segment elevation and can be sustained by numerous factors
Coronary microvascular impairment in the presence of myocardial diseases	It is found with primary (genetic) cardiomyopathies (e.g., dilated and hypertrophic) and secondary cardiomyopathies (e.g., hypertensive and valvular) and is sustained in most instances by adverse remodeling of intramural coronary arterioles
Coronary microvascular impairment in the absence of obstructive coronary artery disease and myocardial diseases	This type represents the functional counterpart of traditional coronary risk factors (smoking, hypertension, hyperlipidemia, and diabetes and insulin-resistant states)
Iatrogenic coronary microvascular impairment	This type occurs after coronary recanalization and seems to be caused primarily by vasoconstriction or distal embolization

Adapted from Camici and Crea [1]

Table 30.2 Chest pain with "normal" coronary arteries: more than syndrome X

Appropriate nosography	Findings
Minor, initial coronary artery disease (up to 30 % stenosis)	Abnormalities of non-smooth coronary arteries
Early possible cardiomyopathy	Resting regional or global LV dysfunction, left bundle branch block
Variant angina	Coronary vasospasm
Secondary microvascular disease	LV hypertrophy, mitral valve prolapse, diabetes, hypertension
Dynamic LV outflow tract obstruction	LV outflow tract obstruction
Normal coronary microcirculation	Normal CFR
Microvascular disease (cardiac syndrome X)	Reduced CFR (<2.0)
True ischemia with microvascular disease	Metabolic or mechanical ischemia

LV left ventricle, *CFR* coronary flow reserve

arterial hypertension [2]. Other patients may display minimal irregularities on the arteriogram: these patients with minor forms of coronary artery disease (even a 20 % stenosis) have a prognosis which is worse than those with completely normal coronary angiogram [3]. Patients with regional or global wall motion abnormalities on resting echocardiogram or left bundle branch block either on the resting or exercise electrocardiogram, despite normal coronary arteries, develop dilated cardiomyopathy over time [4]. Finally, some patients with chest pain and normal coronary artery may be affected by microvascular disease due to

diabetes, arterial hypertension, and hyperlipidemia or may have symptoms related to valve disease (including mitral valve prolapse) and epicardial artery spasm. Two cardiac conditions characterized by coronary microvascular disease still remain to be fully understood: cardiac syndrome X and tako-tsubo cardiomyopathy. Their pathophysiology is intriguing and their diagnosis may be challenging.

Distinctive feature of the cardiac syndrome X is effort chest pain associated with significant ischemic ST segment changes during exercise test in patients with normal coronary arteries. Such diagnosis requires exclusion of other cardiac conditions potentially determining the coronary microvascular disease (Table 30.2). Clinical history, electrocardiogram, and resting transthoracic echocardiogram are therefore essential for identifying patients with true cardiac syndrome X that probably represent no more than 10 % of all patients with chest pain and supposedly normal coronary arteries. The term "syndrome X" (originally the Group X in the 1973 paper by Arbogast and Bourassa) was coined to stress the uncertainty over the pathophysiology of chest pain [5]: still now, it remains unclear whether the chest pain in these patients is ischemic or nonischemic in nature.

Tako-tsubo cardiomyopathy is an emerging clinical syndrome presenting with acute chest pain or dyspnea, associated with ST-T segment abnormalities, regional myocardial dysfunction, typically localized at the left ventricular apex and usually extended over a single-vessel territory, slight serum cardiac enzyme release, and absence of significant coronary lesions at coronary angiography. Initially, it is clinically indistinguishable from an acute coronary syndrome, but myocardial involvement completely and rapidly recovers in a few days or weeks, making tako-tsubo cardiomyopathy a unique model of transient and completely reversible myocardial dysfunction, in the absence of significant coronary artery disease. Several etiopathogenetic mechanisms have been proposed, such as multivessel epicardial spasm, catecholamine-induced myocardial stunning, spontaneous coronary thrombus lysis, and acute microvascular spasm [6]. Coronary microvascular dysfunction plays a major role in such syndrome: extensive literature has demonstrated that an acute and spontaneously reversible impairment of coronary microcirculation is associated with the transient myocardial contractile dysfunction considered as a distinctive sign of the cardiomyopathy. A reduced microvascular blood flow during the acute phase of tako-tsubo cardiomyopathy, associated to severe reduction of both myocardial fatty acid and glucose metabolisms, has been shown by nuclear imaging tools. Moreover, a transmural perfusion defect within dysfunctional segments has been found at myocardial contrast echocardiography during the acute phase of tako-tsubo cardiomyopathy (Fig. 30.1) [6]. As confirmation, coronary flow reserve evaluated invasively at coronary angiography and noninvasively at transthoracic dipyridamole stress echo is reduced.

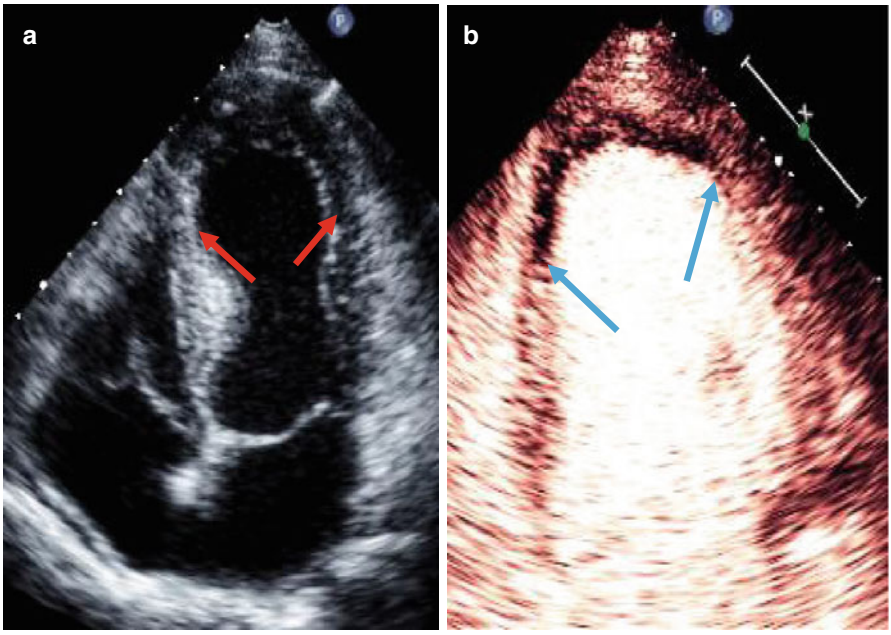

Fig. 30.1 Standard echocardiography (**a**) and myocardial contrast echocardiography (**b**) images in 4-chamber view during the acute phase of tako-tsubo cardiomyopathy. Systolic frame clearly displays contractile dysfunction involving the entire left ventricular apex (between *arrows*). In the same region, the reduction of myocardial blood flow due to coronary microvascular impairment is visualized as completely absent opacification of myocardial wall

30.2 Pathophysiology of Microvascular Disease

Coronary microcirculation may be affected by both structural damage and functional alteration (Table 30.3). Microvascular obstruction occurring in the setting of myocardial infarction, despite optimal recanalization of culprit epicardial coronary artery, namely, "no-reflow phenomenon," is the most severe form of coronary microvascular impairment. Its pathophysiology relies on distal embolization of atherothrombotic debris, leukocyte plugging, platelet aggregation, extravascular edema, and vasospasm [7]. About 50 % of patients with microvascular obstruction in the acute phase of myocardial infarction display recovery of myocardial perfusion over time [8]. Reversible alterations in the coronary microcirculation have been described soon after coronary angioplasty [9]. Nonetheless, a reduced vasodilator response can be found also in normal, non-infarct-related coronary arteries early after an acute myocardial infarction [10].

The functional impairment of coronary microcirculation appears as reduction in the coronary flow reserve, in the absence of epicardial stenosis. A reduced vasodilator response has been observed in non-stenosed coronary arteries of patients with single-vessel disease [11]: abnormalities of small distal coronary vessels may

Table 30.3 The pathophysiological and clinical spectrum of microvascular disease

	Alterations	Causes
Structural	Luminal obstruction	Microembolization in ACS or after revascularization
		Infiltrative heart disease (e.g., Anderson–Fabry cardiomyopathy)
	Vascular wall infiltration	
	Vascular remodeling	HCM, arterial hypertension
		Aortic stenosis, arterial hypertension
	Vascular rarefaction	
		Aortic stenosis, arterial hypertension
	Perivascular fibrosis	
		Systemic sclerosis
Functional	Endothelial dysfunction	Smoking, hyperlipidemia, diabetes
	Dysfunction of smooth muscle cell	HCM, arterial hypertension
	Autonomic dysfunction	Coronary recanalization
Extravascular	Extravascular compression	Aortic stenosis, HCM, arterial hypertension, acute transplant rejection
	Reduction in diastolic perfusion time	Aortic stenosis

Adapted from Camici and Crea [1]

ACS acute coronary syndrome, *HCM* hypertrophic cardiomyopathy

contribute to determine an altered coronary flow reserve in patients with ischemic heart disease, regardless of atherosclerotic coronary stenoses, and may at least partially account for the elusive link between the anatomical severity of coronary stenoses and clinical symptoms [1]. In patients with normal epicardial coronary arteries and some cardiac disease, such as dilated cardiomyopathy [12], hypertrophic cardiomyopathy [13], left ventricular hypertrophy due to hypertension, and aortic stenosis [14], the reduced coronary flow reserve is often independent of the degree of left ventricular hypertrophy, and the typical behavior of microvascular disease during stress testing is the frequent induction of chest pain, ST segment depression, and perfusion abnormalities without regional or global wall motion changes (Fig. 30.2).

The sequence of events is therefore strikingly different from the classic ischemic cascade found during stress testing in the presence of a coronary stenosis (Table 30.4). The alternative ischemic cascade is illustrated in Fig. 30.3 and is derived from pragmatic clinical experience [15].

Many findings in cardiac syndrome X are not readily understandable, but seem important [16]. The very same ischemic nature of chest pain and ST segment depression in cardiac syndrome X patients remains uncertain [17–20]. According to the ischemic theory, it has been supposed that in these patients focal ischemia in small myocardial regions scattered throughout the myocardium and caused by prearteriolar dysfunction might explain the paradox of angina and ST segment depression provoked by physical or pharmacological stress [21]. The site of abnormally

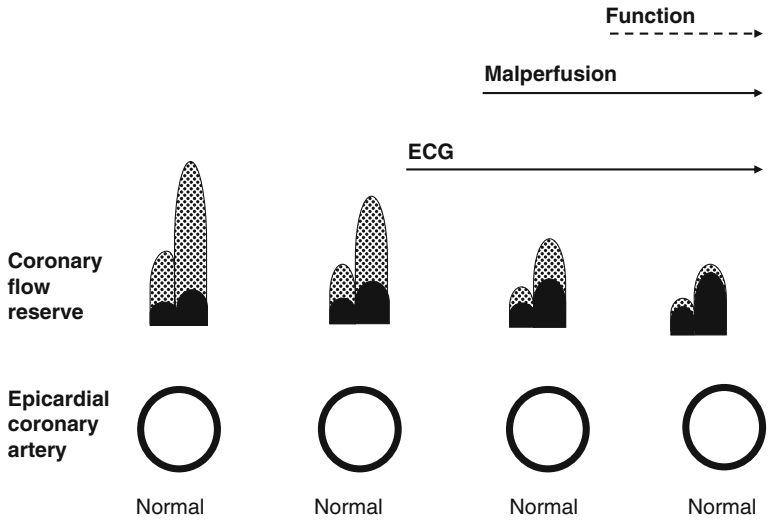

Fig. 30.2 The features of microvascular disease consist of normal epicardial coronary arteries (even when observed by intravascular ultrasound: *lower row*) and reduced coronary flow reserve (by Doppler tracing showing a spectrum of coronary hyperemic responses, from normal, *left*, to abolished, *far right*). Chest pain and ECG changes are frequent during stress, especially when flow reserve is reduced, whereas echocardiography changes (*dashed lines*) are only very rarely observed (Modified from Picano et al. [15])

Table 30.4 Classic and alternative cascade during stress testing

	Classic	Alternative
Clinical models	Coronary stenosis	Microvascular disease
Epicardial coronary anatomy	Stenotic	Normal
Coronary flow reserve	Depressed	Depressed
Stress: chest pain	Present	Present
Stress: ST depression	Present	Present
Stress: dyssynergy	Present	Usually absent
Experimental model	Yes	No

elevated resistances (in patients with reduced coronary flow reserve) might be intramural, upstream from the endocardium–epicardium branching point, which is not visualized by coronary angiography [22] (Fig. 30.4).

Thus, the abnormal resistance to flow would result in maximal dilation of subendocardial arterioles in rest condition, because of the concomitant higher metabolic demand of the subendocardium. In response to pharmacological or metabolic stimuli, such as dipyridamole or pacing or exercise, subendocardial arterioles would be unable to dilate further, whereas subepicardial arterioles would normally dilate. Thus, a decrease in pressure downstream from the site of increased resistance would occur, with reduction of flow to the subendocardium. The evidence that, despite ischemic-like stress-induced chest pain and ST segment changes [2], left ventricular

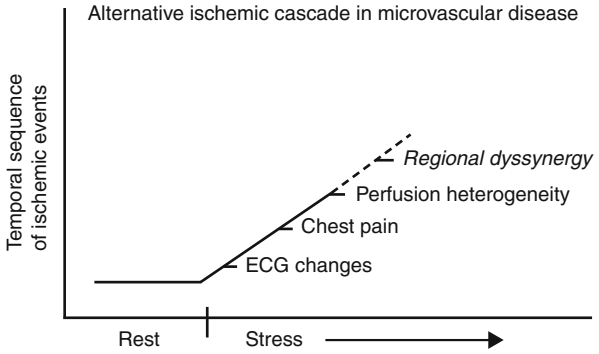

Fig. 30.3 In the model of microvascular disease (reduction in coronary flow reserve with normal epicardial arteries), such as that found in syndrome X or left ventricular hypertrophy, anginal pain and ST segment changes usually appear in the absence of any detectable wall dysfunction (Modified from Picano et al. [15])

function remains normal during stress echocardiography in cardiac syndrome X patients (see below) is not incompatible with true myocardial ischemia: indeed, it is well known that the presence or absence of abnormal wall motion is related to the amount of ischemic subendocardial tissue, with minor degrees of transmural involvement or patchy myocardial ischemia less likely to produce regional dysfunction [15].

Pathophysiology of coronary microvascular impairment in tako-tsubo cardiomyopathy has been recently proven. Indeed, it has been demonstrated by several imaging tools that microcirculatory impairment tends to resolve over time in tako-tsubo cardiomyopathy natural course, thus paralleling spontaneous recovery of myocardial contractile function. A transient and spontaneously reversible constriction of coronary microcirculation has been postulated as a potential common pathogenetic mechanism, since extent of both perfusion defect and regional myocardial dysfunction in the acute phase of tako-tsubo cardiomyopathy transiently decreases during adenosine infusion, promptly returning to baseline values after cessation of the infusion. This is in sharp contrast to what is observed in patients with myocardial infarction, in whom, no significant change in myocardial perfusion and function can be elicited by adenosine challenge [6].

30.3 Stress Echo in Microvascular Disease

Currently, coronary microcirculation cannot be directly imaged in vivo in humans. Spatial resolution of coronary angiography allows only visualization of the coronary artery major branches, characterized by a diameter greater than 300 μm. Beyond invasive assessment of blood flow by intracoronary Doppler systems, most information about the structure and function of coronary microcirculation has to be indirectly derived by noninvasive imaging techniques, such as positron emission tomography (PET), cardiovascular magnetic resonance (CMR), and

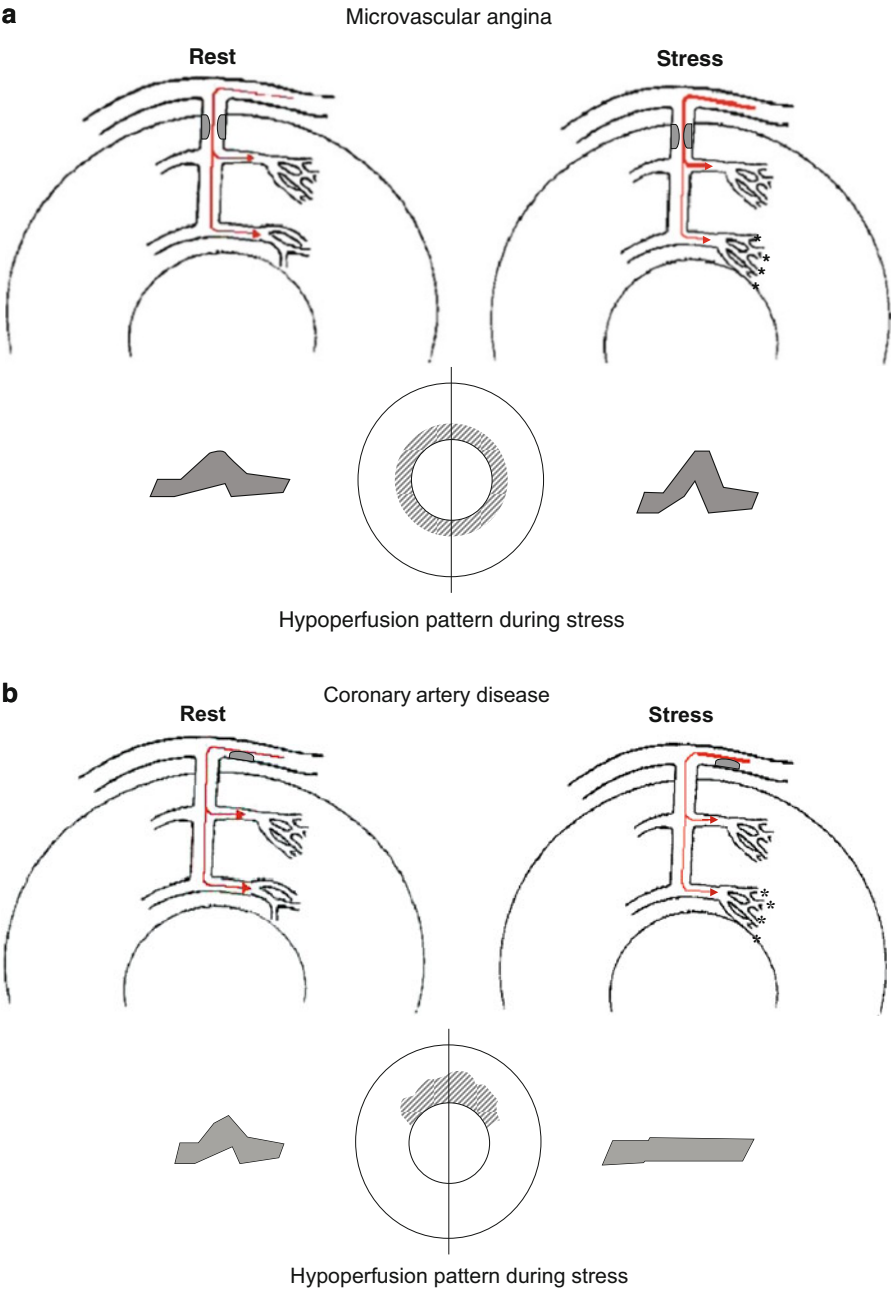

Fig. 30.4 Schematic representation of transmural coronary hemodynamics (*upper panels*), regional wall motion thickening (*lower panels*), and myocardial ischemia transmural distribution (*middle panels*) in syndrome X (**a**) and in epicardial stenosis (**b**). Induced myocardial hypoperfusion is more horizontally diffuse in syndrome X and more transmurally extended in CAD: only in the latter case of critical mass of ischemic myocardium is reached (Redrawn and modified from the original hypothesis of Epstein and Cannon [22])

echocardiography. Basing on the concept that "ischemia is a reduction in myocardial blood flow sufficient to cause a decrease in myocardial contraction" [23], these tools provide assessment of myocardial perfusion and function under rest and stress conditions. Several qualitative and quantitative measures of blood flowing through the coronary circulation have been validated to describe the function of the microvasculature in patients with normal coronary angiograms. Particularly, three ultrasound methods are currently used to explore coronary microcirculation. Evaluation of global and regional left ventricular contractile function during rest and stress echo offers the opportunity to identify any inducible wall motion abnormalities, while vasodilatory challenge of epicardial coronary artery blood flow by transthoracic Doppler echocardiography allows testing the coronary flow reserve. Wall motion can be easily assessed with all stresses (exercise, dobutamine, dipyridamole), whereas the evaluation of coronary flow is best performed with vasodilators (dipyridamole or adenosine). The rationale for such approach relies on the evidence that, while in patients with coronary artery disease, the extent of the reduction in coronary/myocardial blood flow and flow reserve is directly, albeit only grossly, related to the severity of stenosis, and in subjects with angiographically normal arteries, it is a marker of microvascular dysfunction. Interestingly, with last-generation ultrasound technology and advanced expertise, dual imaging (function and flow) stress echocardiography provides simultaneous insight into the regional and global left ventricular function and coronary flow reserve. Both of them are necessary for the diagnostic and prognostic characterization of the heterogeneous population of patients with chest pain and angiographically normal coronary arteries [15]. Finally, myocardial contrast echocardiography (MCE), by using second-generation ultrasound contrast agents, clearly depicts any potential perfusion abnormalities, both at rest and during stress. Similarly to PET and CMR, MCE is capable to identify reduction of myocardial blood flow due to microvascular disease irrespectively or in addition to wall motion abnormalities (Fig. 30.5). In that, it is more sensitive than standard stress echo, although any perfusion defect occurring in left ventricular segments with preserved wall motion needs to be carefully differentiated by artifacts [24].

Patients with microvascular disease may show different findings on stress echocardiography:

1. Absence of wall motion abnormalities and normal coronary artery flow reserve
2. Absence of wall motion abnormalities and reduced coronary flow reserve
3. Inducible wall motion abnormalities and reduced coronary flow reserve

The finding of reduced coronary flow reserve without any wall motion abnormality does not rule out the relationship between microvascular disease and myocardial ischemia. Indeed, in such patients a reduction in myocardial blood flow, suggestive of ischemia, can be clearly appreciated by cardiac imaging perfusion techniques, even when left ventricular contractile function remains normal during stress. Such phenomenon can be explained by the evidence that the appreciation of a regional dysfunction by two-dimensional echocardiography requires a critical ischemic

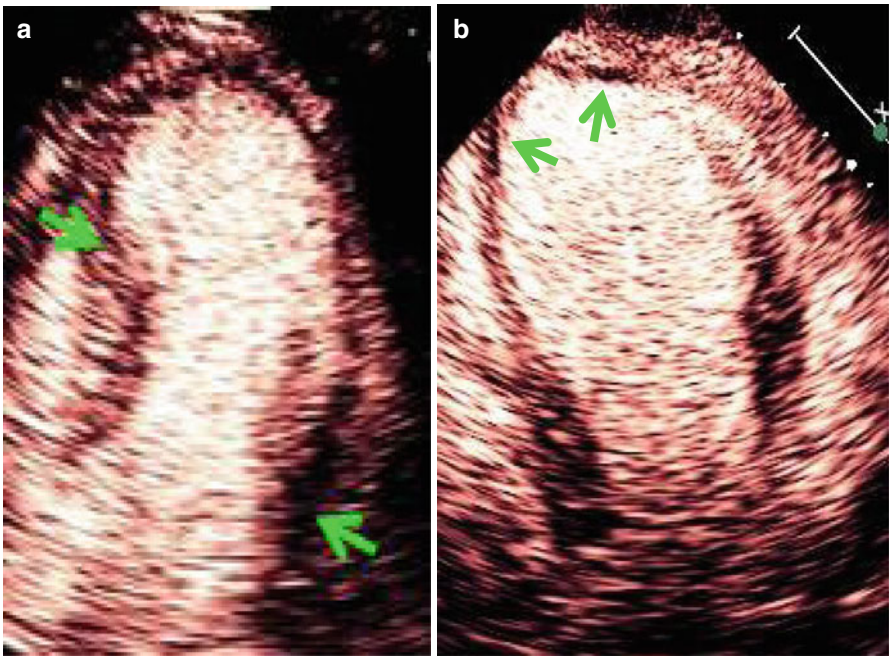

Fig. 30.5 Myocardial contrast echocardiography images in 4-chamber view in a patient with multivessel coronary artery disease (**a**) and in a patient with Churg–Strauss syndrome. In (**a**), a diffuse subendocardial perfusion defect occurring at peak of dipyridamole stress echo with contrast is clearly seen (between *arrows*), extending within several myocardial segments. In (**b**), two areas of subendocardial and near-transmural patchy perfusion defect can be appreciated (*arrows*) at rest, which is consistent with the widespread microvascular damage of such syndrome

mass of at least 20 % of transmural wall thickness and about 5 % of the total myocardial mass [25–27] and that, for minimal flow reductions, abnormalities of regional systolic function are subtle and certainly below the threshold of detection by echocardiography. Indeed, even under ideal imaging conditions, a subendocardial infarction can be accompanied in 20 % of cases by a perfectly normal/hyperkinetic regional and global wall thickening [28]. Moreover, regional thickening and motion express radial function, which can be still normal when longitudinal and/or circumferential function is clearly impaired during less severe ischemia: it has been recently shown by myocardial velocity imaging and speckle tracking mode in experimental models of stress-induced ischemia [29–31].

In patients with left ventricular hypertrophy or young athletes, experiencing symptoms such as chest pain or syncope typically during exercise [32–34], and in patients with cardiac syndrome X (see below), a significant (>50 mmHg) intraventricular gradient (Fig. 30.6) during stress echocardiography has been observed with increasing frequency. These patients display resting echocardiography within normal limits and

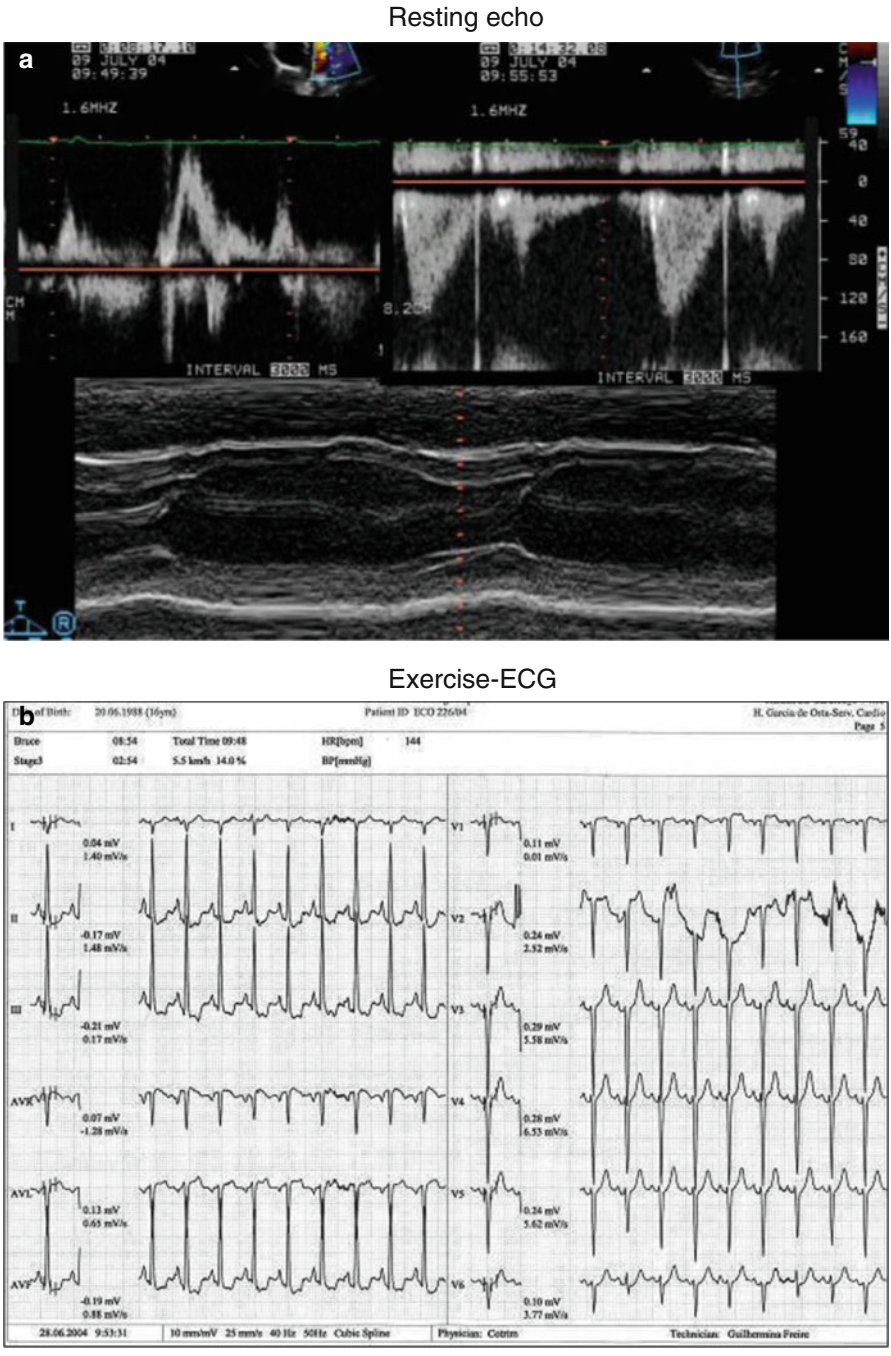

Fig. 30.6 (**a**) Normal echocardiogram without left ventricular hypertrophy. (**b**) Exercise test with alteration in ST segment in DII, DIII, and AF. (**c**) At peak exercise, systolic anterior movement of mitral valve and significant intraventricular gradient was detected (Courtesy of Cotrim et al. [34])

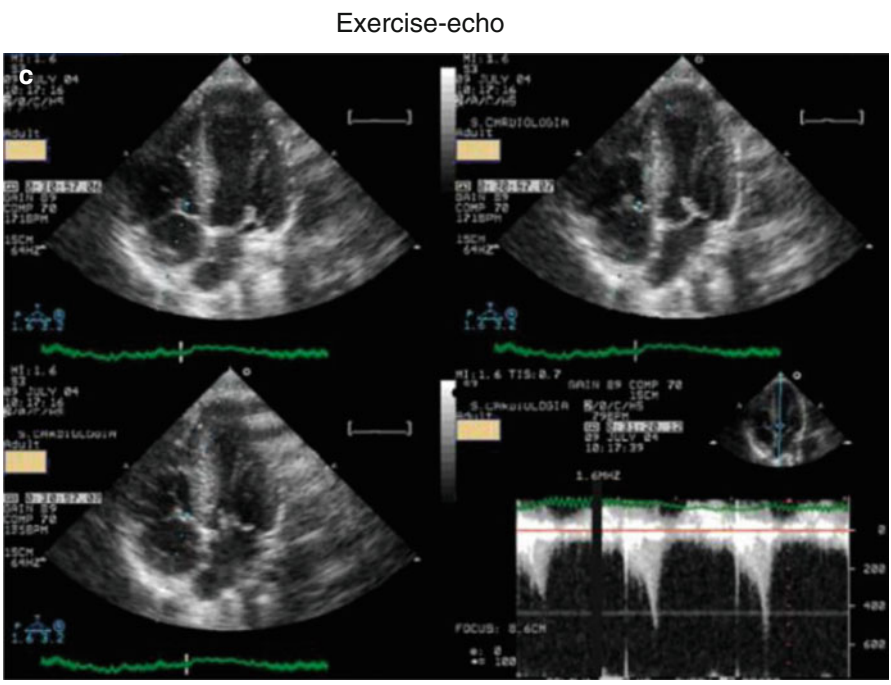

Fig. 30.6 (continued)

a normal coronary flow reserve, but exercise induces ST segment depression. Although such abnormalities during exercise do not represent a contraindication for participation in competitive sports, according to the recommendations of the 36th Bethesda Conference [35] and the European Society of Cardiology [36], it has been suggested that, in the presence of a history of chest pain or syncope during exercise, the athletes should be advised to suspend sports activity [34]. This subgroup of patients might especially benefit from β-blocker therapy, which determines an inconstant benefit in the general population of patients with microvascular angina [17]. A similar left ventricular outflow tract obstruction has been described during dobutamine infusion in patients with chest pain that develop significantly higher intraventricular gradients [37–39]. Not surprisingly, treatment with the β-blockers bisoprolol resulted in a reduction of angina score, as well as normalization of intraventricular flow velocities [39].

30.3.1 Stress Echo in Cardiac Syndrome X

There are three main findings during stress echocardiography in cardiac syndrome X: (1) regional and global left ventricular hyperkinesia (but regional wall motion abnormalities are described in roughly 10 % of patients), (2) reduced coronary flow reserve on mid-distal left anterior descending coronary arteries in about 20 % of patients (but reserve is normal in the majority of patients), and (3) stress-induced intraventricular pressure gradient (in approximately 5–10 % of patients).

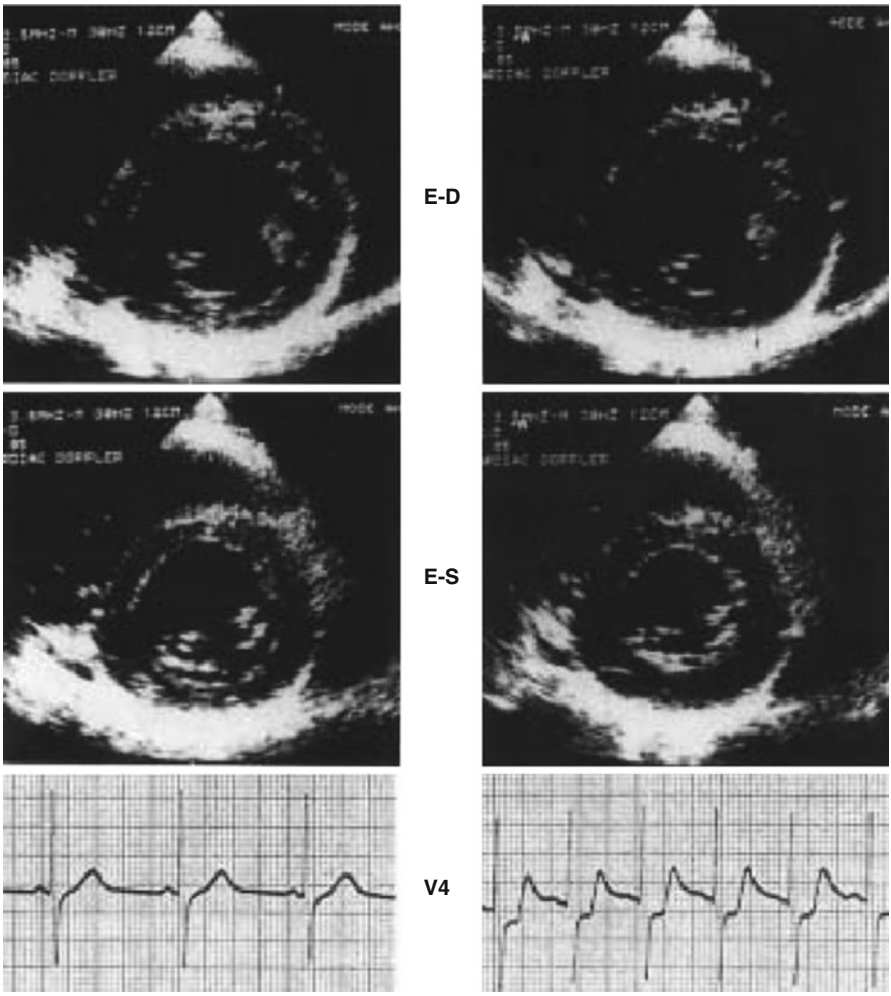

Fig. 30.7 Parasternal short-axis section of the left ventricle at the papillary muscle level under basal conditions (*left*) and after dipyridamole infusion (*right*). Despite ST segment depression induced by dipyridamole, regional asynergy is not detectable. E-D end-diastole, E-S end-systole. This patient had a positive exercise electrocardiography test for both chest pain and ST segment depression. Coronary angiography showed a normal coronary artery tree (Modified from Picano et al. [40])

In cardiac syndrome X, the peculiar pattern during stress echocardiography is the regional and global left ventricular hyperkinesia (Fig. 30.7) with ST segment depression and chest pain, consistently observed during dipyridamole [40], exercise [41], and dobutamine [42, 43].

The stress-induced hyperkinesis is coherent with the original report by Arbogast and Bourassa in 1973 with pacing left ventriculography [5]. Although the left ventricle is hyperdynamic during stress, perfusion changes are often found with perfusion scans [44]. CMR may show subendocardial perfusion defect during stress and

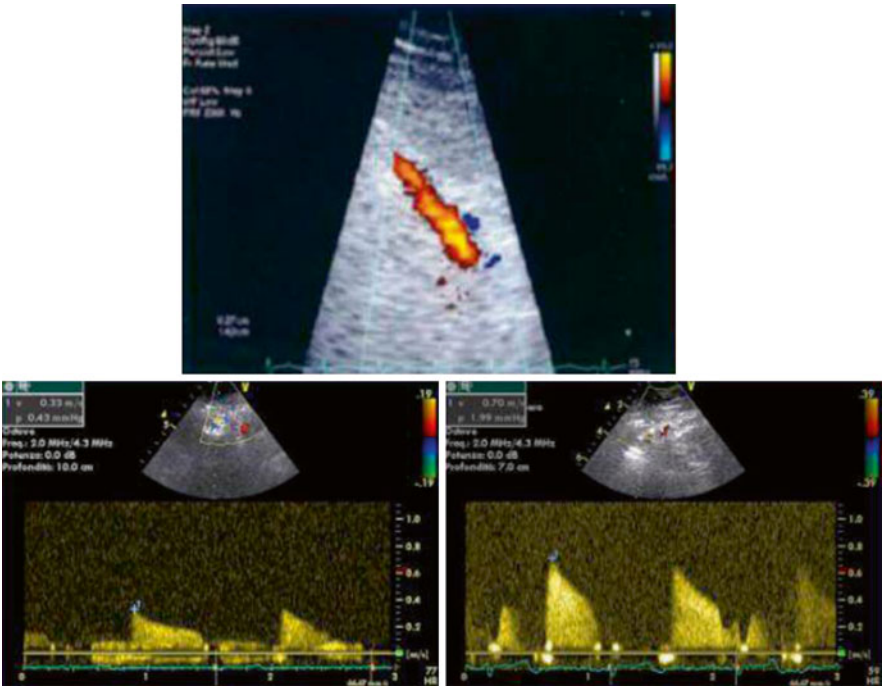

Fig. 30.8 Example of coronary arteries assessment in patients with normal coronary arteries. Visualization of coronary flow in the mid-distal portion of the left anterior descending artery using color Doppler flow mapping in the upper panel. Peak flow diastolic velocity was 33 cm s − 1 under basal conditions (*lower left panel*) and 70 cm s − 1 after dipyridamole infusion (*lower right panel*), with a normal coronary flow reserve value (2.1) (Courtesy of Dr. Fausto Rigo)

metabolic abnormalities consistent with ischemia in at least 30 % of cases [17–20]. Coronary flow reserve can be measured during Doppler transthoracic vasodilator stress echocardiography on mid-distal left anterior descending coronary artery, semi-simultaneously with wall motion imaging. It can be normal (Fig. 30.8) or impaired (Fig. 30.9): a reduced (<2.0) coronary flow reserve can be found in one out of five syndrome X patients, in the absence of wall motion abnormalities [44, 45].

30.3.2 Stress Echo in Tako-Tsubo Cardiomyopathy

Stress echocardiography reveals unique findings in tako-tsubo cardiomyopathy: (1) resolution of wall motion abnormalities and perfusion defect by vasodilatory challenge; (2) a reduced coronary flow reserve, which spontaneously normalizes over time; and (3) intraventricular pressure gradient during dobutamine administration.

During the acute phase of the syndrome, vasodilatory challenge by intravenous administration of adenosine typically determines a dramatic improvement of global

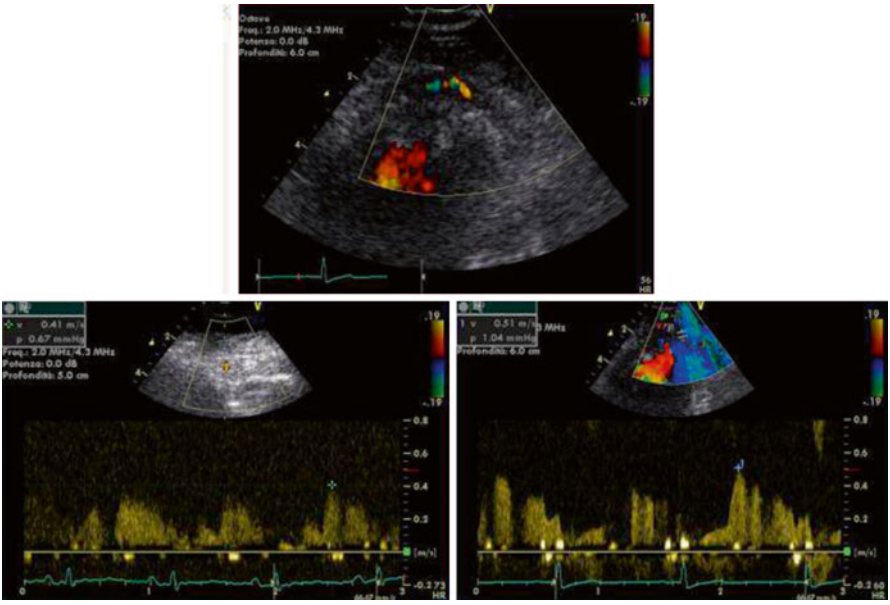

Fig. 30.9 Example of coronary flow reserve assessment in patients with abnormal CFR. Visualization of coronary flow in the mid-distal portion of left anterior descending artery using color Doppler flow mapping in the *upper panel*. Peak flow diastolic velocity was 41 cm s − 1 under basal conditions (*lower left panel*) and 51 cm s − 1 after dipyridamole infusion (*lower right panel*), with an abnormal coronary flow reserve value (1.2) (Courtesy of Dr. Fausto Rigo)

and regional left ventricular function associated to recovery of myocardial perfusion, probably thanks to resolution of the coronary microvascular constriction state. Such response disappears after stopping vasodilatory challenge. Moreover, a reduced coronary flow reserve, assessed by transthoracic Doppler and dipyridamole stress echocardiography at the level of both anterior descending and right coronary arteries, is typically found during the acute phase of the syndrome. Usually, it ranges between 1.6 and 2.6 [46, 47] and rises up to 3.2 at follow-up [48]. Interestingly, the hyperemic coronary flow velocity and the coronary flow reserve significantly correlate with indexes of left ventricular systolic function, but not with measures of diastolic function, thus underlying absence of any role of the diastolic compressive forces to the coronary microcirculation in this setting [48]. Finally, in susceptible patients, dobutamine stress echocardiography has been demonstrated to induce contractile dysfunction of the left ventricular apex, as it spontaneously occurs in the acute phase of tako-tsubo cardiomyopathy [49]. Wall motion abnormalities involving the apical and anteroseptal myocardial segments at peak dobutamine infusion have been reported, together with hypercontractility of the basal myocardial segments, determining near-cavity obliteration and increased left ventricular diastolic pressure [50]. Actually, the typical clinical setting of tako-tsubo cardiomyopathy

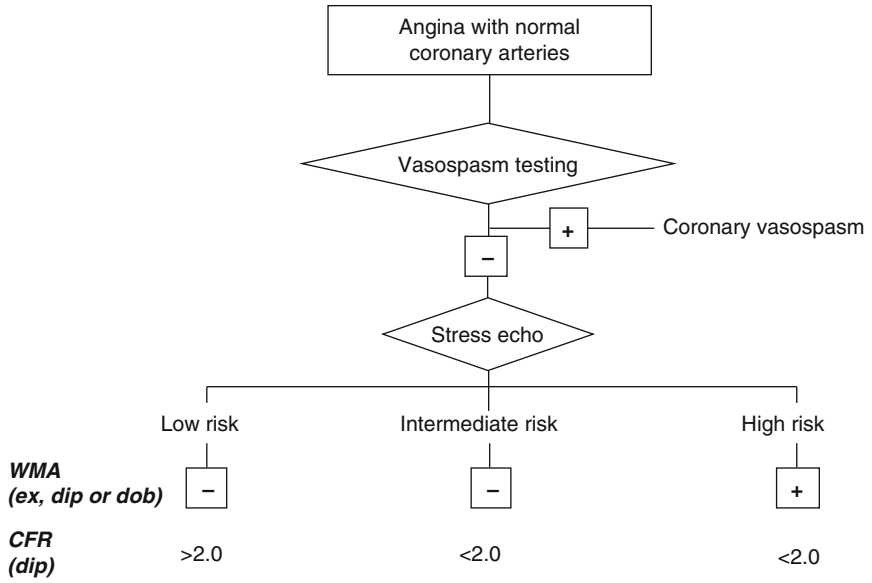

Fig. 30.10 The role of stress echocardiography in the diagnostic flowchart of patients with chest pain and normal coronary arteries

can be also elicited by the intravenous administration of therapeutic doses of catecholamines and beta-receptor agonists [51]. Apical akinesis has been observed in 33 % of patients and midventricular akinesis in 22 % of patients undergoing dobutamine administration and in 44 % of patients receiving epinephrine infusion [52].

30.4 Clinical Impact of Stress Echo: Diagnostic Flowchart and Prognosis

Stress echocardiography can play a key role in the diagnostic process of cardiac diseases characterized by coronary microvascular impairment (Fig. 30.10). Moreover, it allows to identify different pathophysiological mechanisms underlying angina with normal coronary arteries and related prognosis.

First, not all the patients with a history of chest pain, normal resting function, and normal coronary arteries have microvascular disease [1]. In fact, at least two other broad categories can contribute to the finding of normal coronary arteries: variant angina, which can certainly be overlooked if not considered, and a noncardiac origin of chest pain, as can be found in anxiety, psychotic disorders, and esophageal disease. Table 30.5 reports several clues that can aid in the often difficult recognition of these three noncardiac conditions. Thus, in patients with angina even at rest and highly variable exercise tolerance, associated with palpitations and syncope and ongoing therapy with Methergine, 5-fluorouracil, or sumatriptan, with marked seasonal and circadian variation, worsening in springtime, in early morning, and with

Table 30.5 Clues for the recognition of noncardiac conditions

	Microvascular disease	Variant angina	Noncardiac chest pain
Pathogenesis	Small-vessel alteration	Epicardial artery spasm	Anxiety, esophageal spasm, etc.
Chest pain pattern	On effort, emotion, at rest	At night, with palpitations and/or lipotimia	Nitrate sensitive or resistant, lasting second to hours
	Nitrate resistant	Lasting up to 10 min, nitrate sensitive	Localized or retrosternal
Resting LV function	Normal	Usually normal	Normal
Ergonovine test	Negative	Positive	Negative
Exercise stress test	Positive	Negative or positive	Negative
Stress test			
Chest pain	Yes	No	No or yes
ST segment	Yes	No	No
Perfusion changes	Frequent	No	Usually no
Echocardiographic changes	No	No	No
Coronary angiography	Normal	Normal (irregularities frequent)	Normal
ICUS	Frequently normal	Alterations on spasm site	Normal
Therapy	Trial and error	Nitrates and Ca^{2+} blockers	None

ICUS intracoronary ultrasound, *LV* left ventricle

β-blockers, a stress for induction of coronary vasospasm (with ergometrine or hyperventilation) is firstly required [53].

After ruling out coronary vasospasm, stress echocardiography can be performed to further characterize pathophysiology of angina with normal coronary arteries and to stratify patient prognosis. Prognostic value of microvascular disease is quite different to that of coronary artery disease. While severity and extent of coronary artery disease have been proven to inversely relate to patient survival, chest pain with the angiographic label of normal coronary arteries is generally considered to identify a prognostically benign subset [54, 55]. Indeed, prognosis of patients with microvascular disease, as a group, is good, but displays some heterogeneity, which is related to the stress echo findings. Thus, patients may be classified at low risk when no wall motion abnormalities can be provoked and coronary artery flow reserve is normal. The prognosis of these patients was found to be excellent (<0.5 % hard event rate per year) [56]. At the other end of the spectrum, patients showing stress-induced regional wall motion abnormalities are considered at high risk. In these patients, the event rate was threefold higher [56]. Between the two extremes, about 20 % of patients without wall motion abnormalities show a reduced coronary flow reserve (<2.0), with an intermediate hard event rate [57]. Such patients are

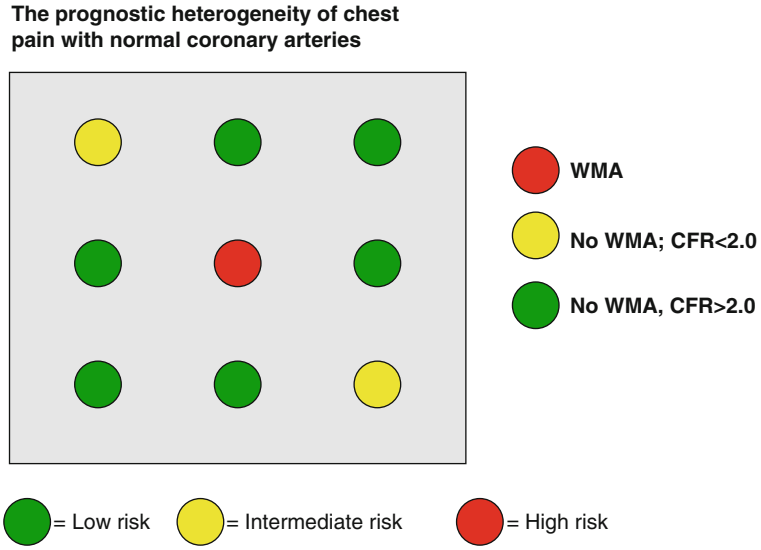

Fig. 30.11 The prognostic heterogeneity of patients with chest pain and angiographically normal coronary arteries. Although the prognosis as a group is good, there is considerable heterogeneity. Prognosis is less good in patients (one out of nine) with inducible wall motion abnormalities and intermediate in patients (2 out of 9) with reduced coronary flow velocity reserve without inducible regional wall motion abnormalities. The prognosis is consistently excellent in patients without wall motion abnormalities and with normal coronary flow velocity reserve

known to be at intermediate risk (see Fig. 27.1). Stratification can be schematically represented as in Fig. 30.11: out of nine patients with identical clinical and angiographic presentation and supposedly good prognosis, six have excellent, two have good, and one has a poor prognosis. These results are coherent with a recent meta-analysis [58] showing that patients with chest pain and angiographically nonsignificant coronary artery stenoses may have a prognosis that is not as benign as commonly thought. In fact, even in the absence of true ischemia associated with stress-induced wall motion abnormalities, coronary endothelial dysfunction, presence of left ventricular hypertrophy, and evidence of coronary microvascular dysfunction have been linked to adverse outcome [59]. More definitive data on this crucial issue are in progress. A prospective study based on Eastern Denmark will include 2000 women with angina and normal coronary arteries studied with coronary flow reserve by Doppler of the left anterior descending coronary artery and followed up for 5 years for cardiovascular outcomes [60].

Among patients at low risk, special subsets – to be systematically looked for in symptomatic athletes – at probably higher risk are those developing a significant intraventricular gradient during exercise or dobutamine. In them, sports activity can be theoretically at greater risk and β-blockers might be warranted, possibly with a more consistent therapeutic benefit that in the overall population, although certainly more data are needed at this point.

Thus, stress echocardiography helps identify the pathophysiological heterogeneity hidden behind apparently similar clinical, stress electrocardiographic, and

angiographic presentations. The patient with known or suspected microvascular disease will benefit from the versatility of resting and stress echocardiography. In the screening phase, resting transthoracic echocardiography is helpful to rule out possible causes of angina with normal coronary arteries: left ventricular hypertrophy with or without valvular heart disease, mitral valve prolapse, regional or global left ventricular dysfunction, and left ventricular outflow tract obstruction. Following the initial screening, identification of wall motion, coronary flow reserve, and dynamic intraventricular obstruction may be carried out in the same time by stress echocardiography. A refined diagnostic and prognostic characterization of the different subsets will eventually allow targeting specific therapies on strictly selected patients, more likely to benefit from a tailored approach than with blind carpet bombing on the basis of nonspecific clinical and angiographic criteria.

30.5 Current Guidelines

Current ESC guidelines on the management of stable coronary artery disease recommend to perform stress echo in verifying the presence of inducible wall motion abnormalities in association to angina and ischemic ECG changes. Thus, in every patient with sufficiently typical chest pain in whom, despite abnormalities of the ECG and/or stress test results indicative of myocardial ischemia, coronary angiography fails to show fixed or dynamic obstructions in epicardial coronary arteries, the existence of primary coronary microvascular disease should be suspected. In such patients, stress echo usually shows absence of regional wall motion abnormalities in conjunction with angina and ST changes, whereas a reduction in coronary flow reserve on the anterior descending coronary artery territory can be elicited by vasodilator challenge [61]. A coronary flow reserve <2.0 strongly suggests coronary microvascular disease. If such criteria are satisfied, more invasive investigations can usually be avoided (Table 30.6).

Table 30.6 Cardiac stress imaging and invasive investigations in patients with suspected coronary microvascular disease

	A	M	R	Class	Level	Ref
Exercise or pharmacological echocardiography should be considered in order to establish whether regional wall motion abnormalities occur in conjunction with angina and ST changes	√			IIa	C	ESC 2013
Transthoracic Doppler echocardiography of the LAD with measurement of diastolic coronary flow velocity following intravenous vasodilators and at rest may be considered for noninvasive measurement of coronary flow reserve		√		IIb	C	ESC 2013
Intracoronary acetylcholine and adenosine with Doppler measurements may be considered during coronary arteriography, if the arteriogram visually normal, to assess endothelium-dependent and non-endothelium-dependent coronary flow reserve and detect microvascular/epicardial coronary vasospasm			√	IIb	C	ESC 2013

A appropriate, *M* may be appropriate, *R* rarely appropriate

Table of Contents Video Companion

See stress echo primer, case 7 and case 10

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Stress Echocardiography in Hypertension

31

Jesus Peteiro and Eugenio Picano

31.1 Background

Uncontrolled and prolonged elevation of blood pressure can lead to a variety of changes in the myocardial structure, coronary vasculature, and conduction system of the heart. These changes can lead to the development of left ventricular hypertrophy, coronary artery disease, various conduction system diseases, and systolic or diastolic dysfunction of the myocardium, which manifest clinically as angina or myocardial infarction, cardiac arrhythmias (especially atrial fibrillation), and congestive heart failure. Patients with angina have a high prevalence of hypertension. Hypertension is an established risk factor for the development of coronary artery disease, almost doubling the risk [1]. Transthoracic echocardiography is especially helpful for an initial risk stratification and identifies four key variables of recognized prognostic value [2]: (1) left ventricular hypertrophy, especially of the concentric type; (2) left atrial dilatation, often occurring in the absence of valvular heart disease or systolic dysfunction and may correlate with the severity of diastolic dysfunction; (3) diastolic dysfunction, common in hypertension, and usually but not invariably accompanied by left ventricular hypertrophy [3]; and (4) systolic dysfunction (Table 31.1).

Stress echocardiography adds critically important pathophysiologic, diagnostic, and prognostic information to the information provided by resting transthoracic echocardiography.

31.2 Pathophysiology

Arterial hypertension can provoke a reduction in coronary flow reserve through several mechanisms which may overlap in the individual patient: coronary artery disease, left ventricular hypertrophy, and microvascular disease [4] (Fig. 31.1). Abnormal coronary flow reserve has been demonstrated in patients with essential hypertension, despite the presence of angiographically normal arteries and the

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Table 31.1 Rest and stress echocardiography for risk stratification in hypertensive subjects with normal resting left ventricular function

	Higher risk	Lower risk
Resting echocardiography		
LVH (g m^{-2})	>125	<125
LA (mm^2)	>4.5	<4.5
DD (grade)	2–3	0–1
RWT	>0.45	<0.45
Stress echocardiography		
WMA	Yes	No
CFR	<2.0	>2.0

CFR coronary flow reserve, *DD* diastolic dysfunction (from 0 = absent to 3 = severe), *LA* left atrial volume (in apical biplane view), *LVH* left ventricular hypertrophy (by ASE-cube method), *RWT* relative wall thickness, *WMA* wall motion abnormalities

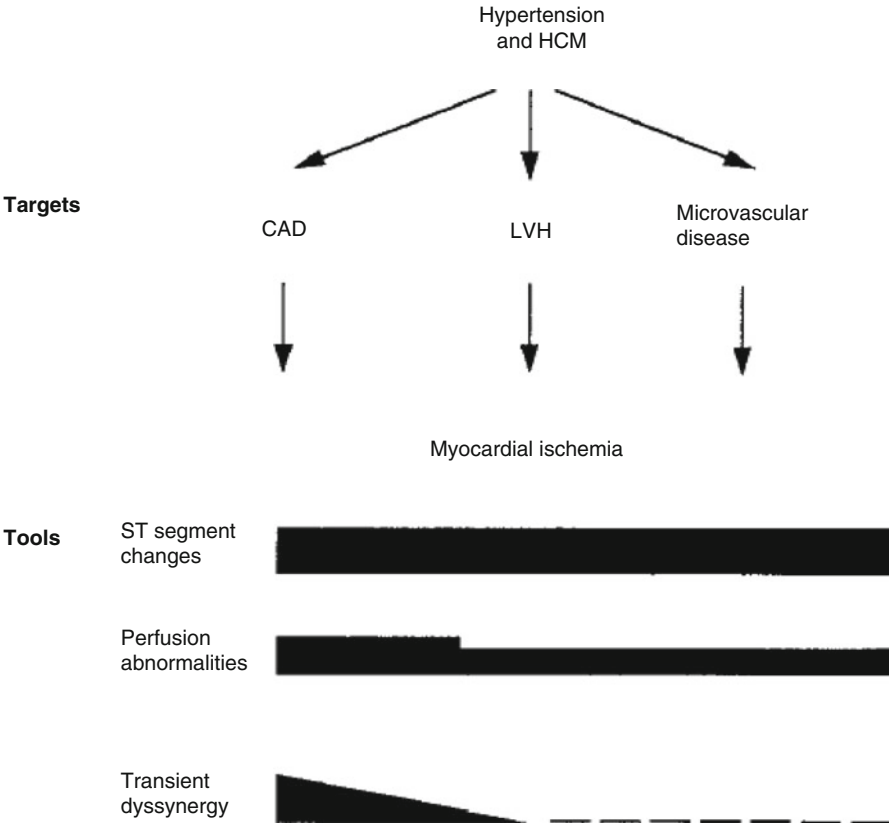


Fig. 31.1 Three main targets of hypertension: coronary artery disease (*CAD*), left ventricular hypertrophy (*LVH*), and microvascular disease. All three of these conditions can provoke stress-induced ST segment depression and perfusion abnormalities, but only CAD evokes transient dyssynergy (Modified from Lucarini et al. [9])

absence of left ventricular hypertrophy [5]. This observation has been attributed to the remodeling of both vascular and extravascular structures and to coronary hemodynamic alterations. The former includes remodeling of intramural arterioles and interstitial fibrosis and leads to a decreased density of vessels in the coronary microvasculature, whereas the latter is characterized by increased extravascular compressive forces and elevated systolic and diastolic wall stress and impaired relaxation. Coronary microvascular dysfunction in patients with hypertension is not necessarily related to the presence or degree of left ventricular hypertrophy [6, 7].

31.3 Diagnosis of Coronary Artery Disease

The noninvasive diagnosis of coronary artery disease in hypertensive individuals is particularly challenging for the cardiologist, since the coexistence of hypertension dramatically lowers the specificity of exercise electrocardiography and perfusion scintigraphy [8, 9]. Experience with diagnostic tests in these patients led to the frustrating conclusion in the prestress echocardiographic era that "no noninvasive screening test has been found to adequately discriminate between hypertensive patients with and without associated atherosclerosis" [10]. Furthermore, all exercise-dependent tests also show a markedly lowered feasibility in hypertensive patients; severe hypertension during the resting condition is a contraindication to exercise testing, and even in mild to moderate hypertension, the first step of exercise can induce an exaggerated hypertensive response that limits effort tolerance [10]. Stress echocardiography tests have proved to have a higher specificity than ECG [11, 12] or perfusion stress testing [13, 14], with a similar sensitivity (Fig. 31.2). In addition, pharmacological stresses have a significantly higher feasibility than exercise stress testing [11], especially with vasodilator testing, which does not evoke the often limiting hypertensive response that can be associated with dobutamine stress [15] (Fig. 31.3). An exaggerated systolic blood pressure rise has been considered a cause of wall motion abnormalities during exercise in the absence of coronary lesions in old studies that evaluated exclusively patients submitted to angiography [16, 17]. However, recent studies evaluating higher number of patients and without being subject to test verification bias have found that patients with exaggerated systolic blood pressure response are not more likely to have false-positive results than those with normal pressure responses [18, 19]. For cases of premature cessation of exercise due to an exaggerated systolic blood pressure, dipyridamole stress echocardiography might be considered since there is little or no systolic blood pressure rise during this stress [20].

Apart from symptoms that might suggest ischemia, hypertensive patients, particularly those with left ventricular hypertrophy, frequently complain of dyspnea that can be the result of either coronary artery disease, diastolic dysfunction, or a noncardiac disease. A diastolic stress test with exercise [21] is useful in this condition to rule out ischemia and to correlate dyspnea with parameters that suggest high filling pressures, such as an increased ratio of early diastolic transmitral velocity to early diastolic tissue Doppler velocity (E/e′) [21, 22] or the change of a normal LV inflow pattern or a pattern of altered relaxation to a pseudonormalized pattern during exercise [23]. An E/e′ ratio >13–15 is considered abnormal [21, 24].

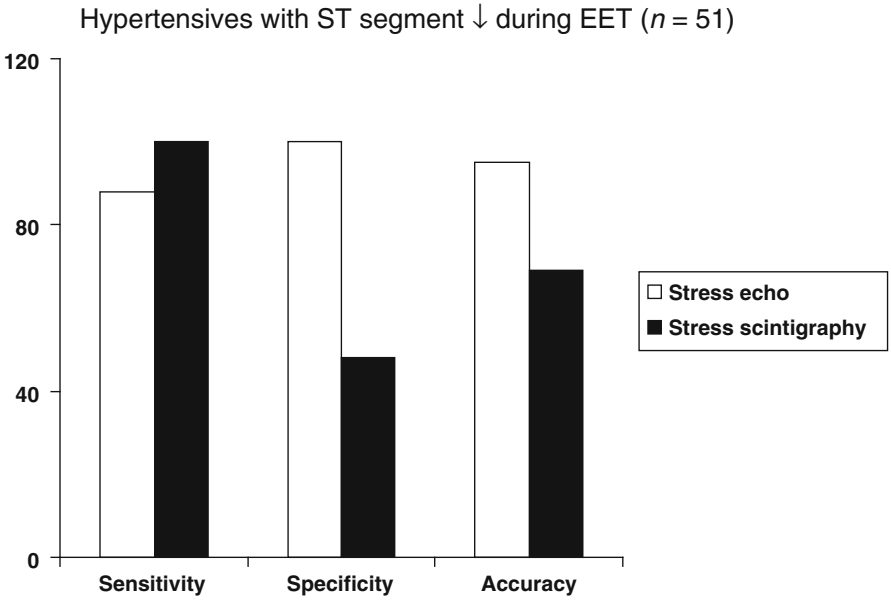


Fig. 31.2 Histogram showing sensitivity, specificity and accuracy of dipyridamole stress test with atropine (*white bars*) and exercise thallium perfusion scintigraphy (*black bars*) for coronary artery disease detection in hypertensive patients with chest pain and positive exercise test. *EET* exercise electrocardiography test (Modified from Astarita et al. [14])

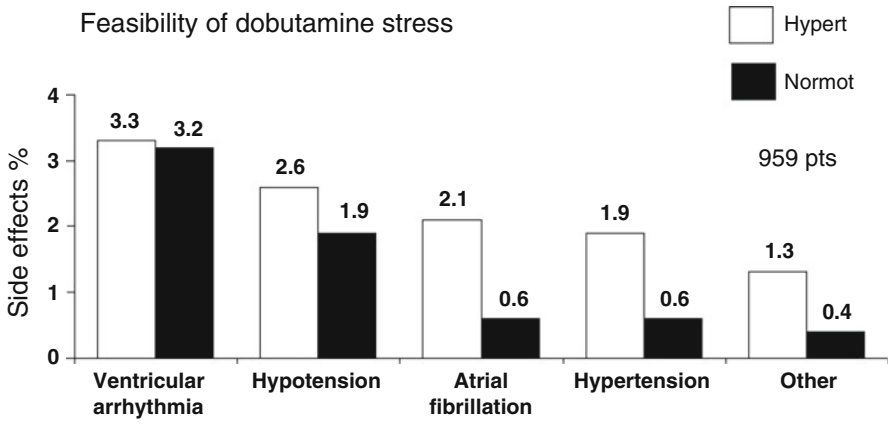
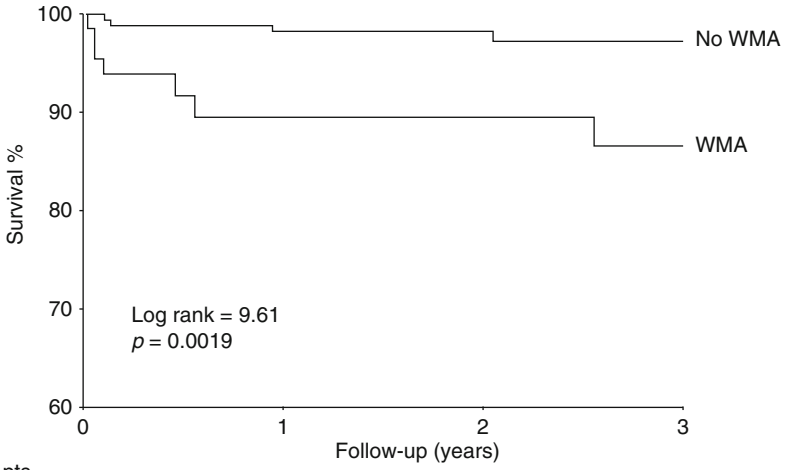


Fig. 31.3 Safety and tolerability profile of dobutamine stress testing in a large cohort of normotensive (*black bars*) and hypertensive patients (*white bars*): all side effects are more frequent in hypertensive subjects (Modified from Cortigiani et al. [15])

31.4 Prognostic Stratification

During stress, we have three signals of potential value in hypertensive patients: ST segment depression, wall motion abnormalities, and coronary flow reserve. The pathophysiological significance of stress-induced, ischemic-like electrocardiographic changes remains uncertain [25]. This stress pattern is often found in these patients with normal coronary arteries and hyperkinetic wall motion. The electrocardiographic changes may merely represent nonspecific, innocent alterations or may reflect true subendocardial hypoperfusion. Such ischemic-like electrocardiographic changes occurring with angiographically normal coronary arteries have been associated with a reduced coronary flow reserve [26], a higher incidence of spontaneously occurring or stress-induced ventricular arrhythmias [27], higher values of left ventricular mass index, and when left ventricular mass is normal, more pronounced structural and functional changes in systemic arterioles [28]. Regression of structural changes of systemic arterioles achieved with any form of antihypertensive therapy is paralleled by the electrocardiographic negativity of a previously positive ECG stress test result [29, 30].

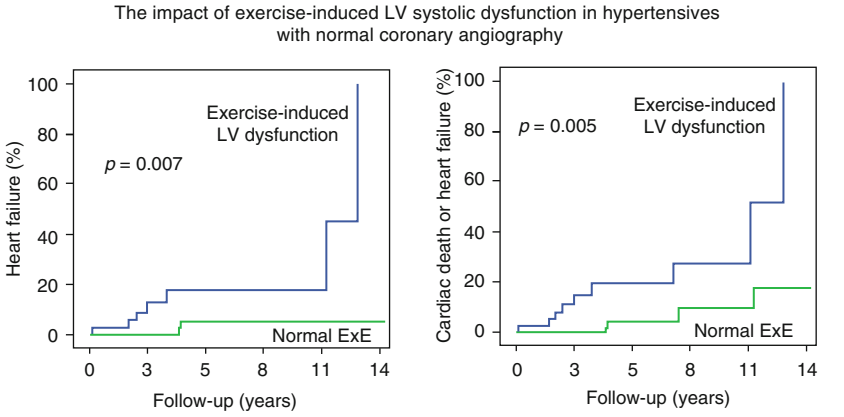
As with microvascular angina, resting and stress echocardiography can be very helpful for risk stratification in patients with chest pain and angiographically normal coronary arteries. The prognostic value of stress-induced wall motion abnormalities is strong and extensively documented. Hypertensive patients with inducible wall motion abnormalities (with or without underlying coronary artery disease) are at higher risk than those without [31–35] (Fig. 31.4). The prognosis is worse when the stress-induced dysfunction is present on the top of a resting regional wall motion abnormality [34]. In one study of hypertensive patients with normal coronary



Number of pts				
(no WMA)	185	147	104	78
(WMA)	72	38	32	26

Fig. 31.4 The prognostic value of inducible wall motion abnormalities (*WMA*) in hypertensive patients (Modified from Cortigiani et al. [31])

angiography, those with exercise-induced wall motion abnormalities leading to a decrease in LV ejection fraction had five times higher cardiac mortality and almost seven times higher cardiac failure during follow-up than those with a normal exercise echocardiogram [35] (Fig. 31.5). Within the subset of hypertensive patients with no wall motion abnormalities, patients with reduced coronary flow reserve assessed with transthoracic echocardiography are at intermediate risk (Fig. 31.6),



	Hazard ratio (IC 95 %) non-adjusted	Hazard ratio (IC 95 %) adjusted
All-cause mortality	3.35 (1.09 –10.31)	2.36 (0.71–7.86)
Cardiac death	5.64 (1.08–29.35)	5.02 (0.84–29.93)
Heart failure	8.91 (1.80 – 44.17)	6.91 (1.28 – 37.36)
Cardiac death or heart failure	5.70 (1.71 – 19.04)	4.48 (1.24 – 16.04)

Fig. 31.5 The prognostic value of LV systolic dysfunction during exercise echocardiography in hypertensive patients with normal coronary angiography (Modified from Prada-Delgado et al. [35])

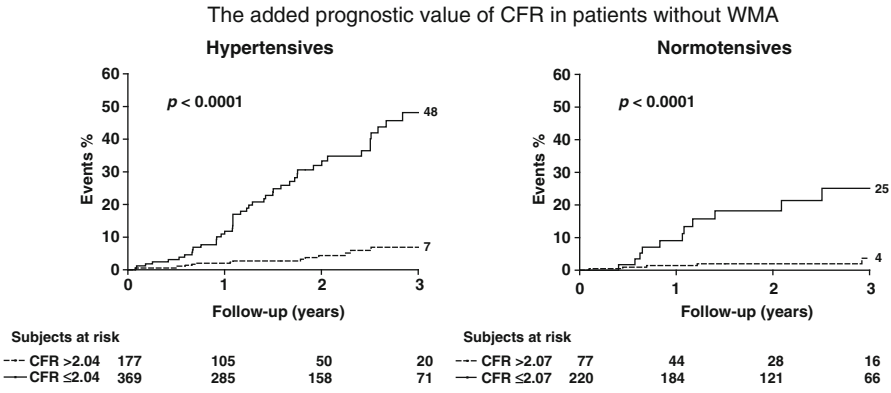


Fig. 31.6 The prognostic value of reduced coronary flow reserve (*CFR*) in hypertensives (*left panel*) and normotensives (*right panel*) with reduced coronary flow reserve (Modified from Cortigiani et al. [36])

and patients with neither wall motion abnormalities nor coronary flow reserve reduction are at the lowest risk [36] (Fig. 31.7).

When compared to other stress imaging techniques with comparable prognostic value, such as myocardial perfusion scintigraphy, stress echocardiography has four clear advantages: lower cost (approximately 1:3) compared with perfusion scintigraphy [37]; higher specificity (which is important to avoid a number of useless coronary angiographies) [13, 14], also maintained in challenging subsets such as patients with right bundle branch block [38]; additive prognostic value over other parameters obtained during resting echo, prior to exercise, such as left ventricular hypertrophy [39] (Fig. 31.8); and most importantly, lack of radiation exposure [40]. Powerful

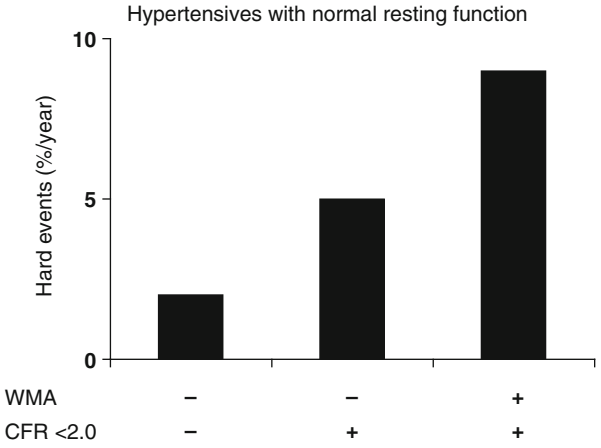


Fig. 31.7 Risk stratification in hypertensive patients based on the simple parameters of wall motion abnormalities (*WMA*) and reduction in coronary flow reserve (*CFR* <2.0). Both parameters can be identified during a single stress echocardiography test ("two birds with one stone"), more easily with a vasodilator stress

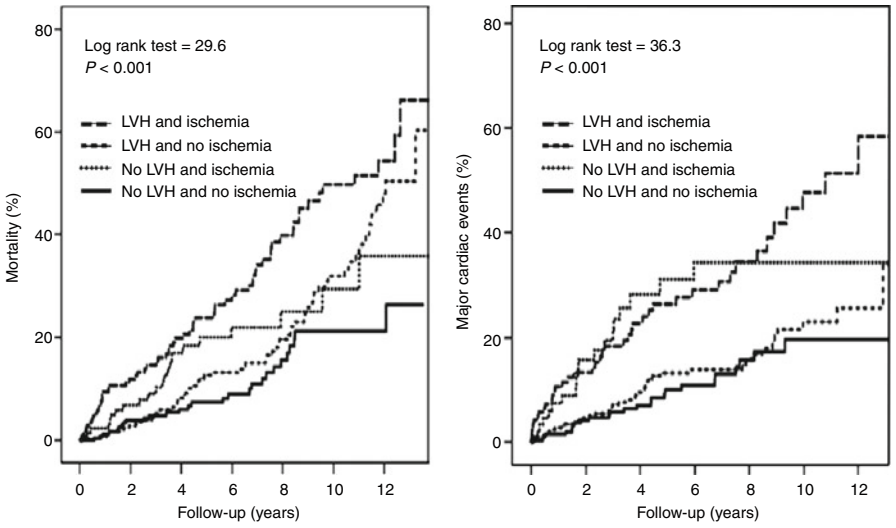


Fig. 31.8 Overall mortality and major cardiac event survival curves according to the presence of left ventricular hypertrophy on rest echocardiography and ischemia on exercise echocardiography. Note how the worst outcome occurs in patients with both LV hypertrophy and ischemia (Modified from Peteiro et al. [39])

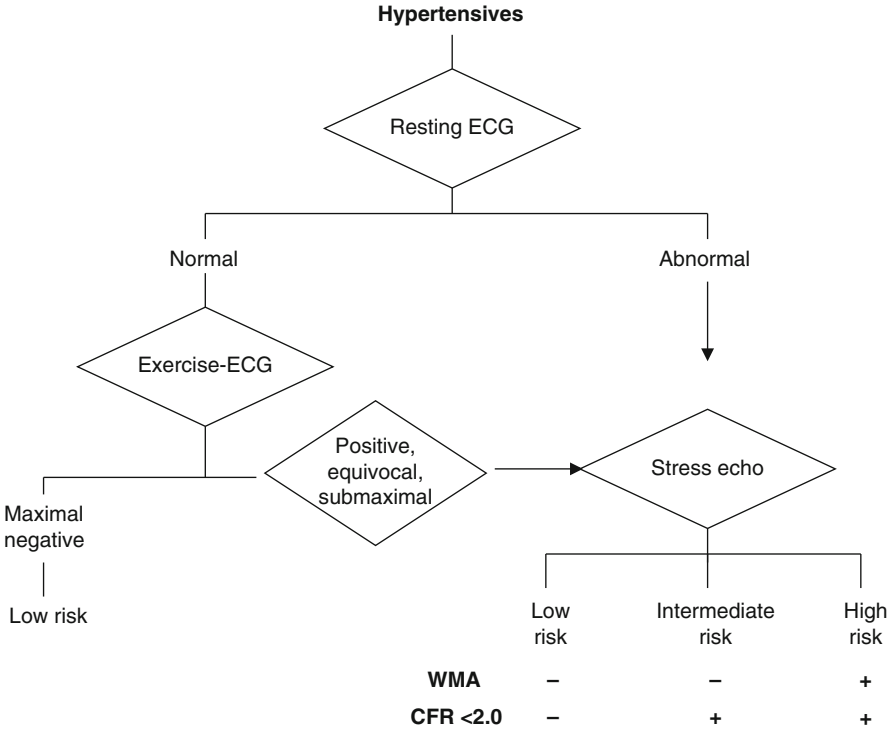


Fig. 31.9 The proposed diagnostic algorithm in hypertensive patients. Exercise electrocardiography remains the most informative first-line test, due to the wealth of information (blood pressure response, arrhythmias, exercise tolerance) provided beyond ST segment changes. The negative predictive value is high in patients with interpretable and normal ECG at rest. In patients with abnormal or equivocal stress ECG findings, and in patients with resting ECG abnormalities, a stress imaging test (rest and stress echocardiography) is indicated as a gatekeeper to coronary angiography

prognostic stratification and efficient diagnosis based on the integrated use of exercise ECG and rest and stress echocardiography (Fig. 31.9) can be achieved in hypertensives.

31.5 Pitfalls

The main pitfalls for stress echo in hypertensives are a reduction in feasibility of stress testing due to limiting excessive blood pressure rise with exercise or increase in frequency of limiting side effects such as atrial arrhythmias with dobutamine. The diagnostic markers suffer from a reduction in specificity, more modest with wall motion abnormalities (which may occur especially in the apical region with excessive blood pressure rise) and more pronounced with perfusion changes, since reduction in coronary flow reserve may occur independently of coronary artery stenoses due to left ventricular hypertrophy and/or microvascular disease.

Table 31.2 Main stress imaging indication in hypertension

	A	M	R	Class	Level	Ref.
Whenever history suggests ischemia, a stress ECG is recommended, and if positive or ambiguous, an imaging stress test (stress echo, stress cardiac magnetic resonance, or nuclear scintigraphy) is recommended	√			I	C	ESC (2013) [41]
Stress imaging in patients able to exercise and with interpretable ECG			√	II	C	ESC (2013) [41]

A appropriate, *M* may be appropriate, *R* rarely appropriate

31.6 Clinical Guidelines

European Society of Hypertension and European Society of Cardiology Guidelines 2013 recognize that the diagnosis of myocardial ischemia is particularly challenging because hypertension lowers the specificity of exercise electrocardiography and perfusion scintigraphy [41]. An exercise test without significant ECG changes has an acceptable negative predictive value in patients without strong symptoms indicative of obstructive CAD. When the exercise ECG is positive or uninterpretable/ambiguous, an imaging test of inducible ischemia (such as stress echo) is warranted for the diagnosis of myocardial ischemia (Table 31.2). Stress-induced wall motion abnormalities are more specific for angiographically assessed coronary artery stenosis, whereas perfusion abnormalities are frequently found with angiographically normal coronary arteries associated with left ventricular hypertrophy and/or microvascular disease. The use of dual echocardiography imaging of regional wall motion and transthoracic Doppler-derived coronary flow reserve on the left anterior descending coronary artery has recently been suggested to distinguish obstructive CAD (reduced coronary flow reserve plus inducible wall motion abnormalities) from isolated coronary microvascular damage (reduced coronary reserve without wall motion abnormalities) [37].

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Stress Echocardiography in Diabetes

32

Lauro Cortigiani and Eugenio Picano

Coronary artery disease is the leading cause of mortality and morbidity in patients with diabetes. Approximately one-half of deaths are attributed to coronary artery disease in diabetic patients, whose risk of myocardial infarction or cardiac death is two- to fourfold greater than in nondiabetic patients [1]. Moreover, cardiac events are as frequent in diabetic patients without evidence of coronary artery disease as in nondiabetic patients with known coronary artery disease [2]. Recent studies with electron beam computed tomography have shown that subclinical atherosclerosis is common in patients with diabetes, and studies with myocardial perfusion scintigraphy (with single-photon emission tomography) or stress echocardiography have shown that 25–50 % of asymptomatic diabetic patients have ischemia during exercise or pharmacological stress and that a substantial proportion of these patients go on to develop major cardiovascular events within several years [2, 3]. The increased risk associated with diabetes calls for effective prevention and risk stratification strategies to optimize therapeutic interventions [3]. Clearly, asymptomatic diabetic patients include a subset of individuals at high risk of cardiovascular disease who would benefit from improved risk stratification beyond that possible with risk factor scoring systems alone [4]. Exercise testing is of limited value in the diabetic population because exercise capacity is often impaired by peripheral vascular [5] or neuropathic disease [6]. Furthermore, test specificity on electrocardiographic criteria is less than ideal because of the high prevalence of hypertension and microvascular disease [7]. Stress imaging and in particular stress echocardiography can play a key role in the optimal identification of the high-risk diabetic subset, also minimizing the economic and biologic costs of diagnostic screening, since stress echocardiography costs three times less than a perfusion scintigraphy and is a radiation-free technique without long-term oncogenic risks [8].

32.1 Pathophysiology

Diabetes mellitus can provoke cardiac damage at four levels: coronary macrovascular disease, autonomic cardiomyopathy, diabetic cardiomyopathy, and coronary

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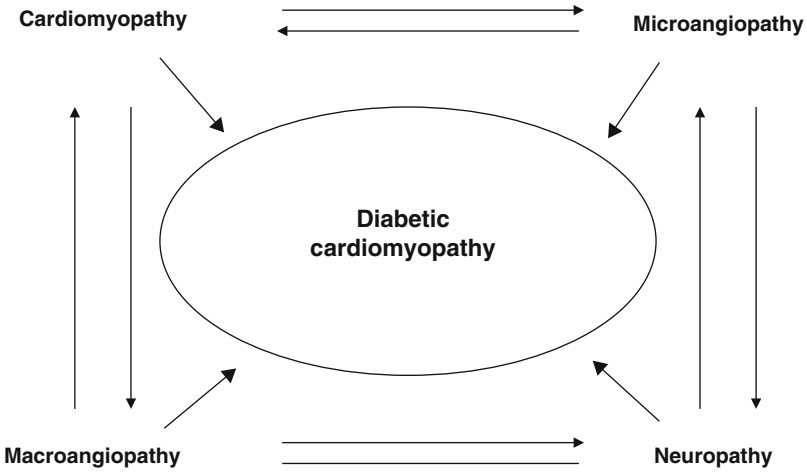

Fig. 32.1 The four aspects of damage in the diabetic heart: autonomic neuropathy, diabetic cardiomyopathy, coronary microangiopathy, and coronary macroangiopathy. The four pathways – albeit pathogenetically distinct – cross talk. For instance, microangiopathy may codetermine neuropathy – through vasa nervorum involvement – and, at the coronary level, may impair coronary flow reserve, amplifying the impact of an epicardial coronary artery stenosis

microvascular disease (Fig. 32.1). These syndromes are rarely found in isolated form in individual patients, but more often overlap and potentiate each other. In particular, diabetes mellitus induces coronary structural [9] and functional [10, 11] microvascular abnormalities, which are associated with coronary endothelial dysfunction and impairment in coronary flow reserve, even in the absence of epicardial coronary artery disease [12]. In young subjects with uncomplicated diabetes, there is a marked coronary microvascular dysfunction in response to adenosine infusion (primarily reflecting abnormal endothelium-independent vasodilation) and to the cold pressor test (primarily reflecting endothelium-dependent vasodilation) [13].

32.2 Diagnosis of Coronary Artery Disease

The coronary microangiopathy component can amplify the effects of coronary macroangiopathy, which is a major complication of diabetes. Coronary, cerebral, and peripheral vascular diseases are the causes of death in 75 % of adult diabetic subjects. The coexistence of epicardial coronary artery stenosis with microangiopathy can explain the low specificity of perfusion imaging compared to stress echocardiography in the detection of coronary artery disease in asymptomatic (and symptomatic) diabetic patients [14–21]. In fact, the typical behavior of microvascular disease during stress testing is the frequent induction of ST segment depression and perfusion abnormalities, with true reduction in coronary flow reserve without regional or global wall motion changes [8]. In practical terms, this means that in patients with normal baseline ECG results, the negative predictive value of a

maximal exercise ECG is satisfactory, but in all patients with positive or ambiguous ECG and/or chest pain findings, a stress echocardiography test is warranted. In diabetic patients, stress echocardiography has shown a higher specificity than perfusion imaging but suffers from a higher rate of false-positive results, possibly due to the coexistence of cardiomyopathy in many patients [21].

32.3 Prognostic Stratification

Risk stratification of diabetic patients is a major objective for the clinical cardiologist, given their increased risk for coronary artery disease [1]. Resting echocardiography is already important for this purpose, since there is a distinct "cardiomyopathy cascade" (Fig. 32.2) with higher risk levels – and higher degrees of cardiomyopathic involvement – identified by left atrial dilatation [22], diastolic dysfunction [23], and impaired longitudinal function [24], which may all coexist with normal ejection fraction [25].

Stress echocardiography has shown powerful risk stratification capabilities in diabetics. In patients with overt resting ischemic cardiomyopathy, the presence of myocardial viability recognized by dobutamine echocardiography independently predicts improved outcome following revascularization in nondiabetics as well as in diabetic patients following revascularization [26]. Also in patients with normal resting left ventricular function, a clear refinement of prognosis can be obtained with stress

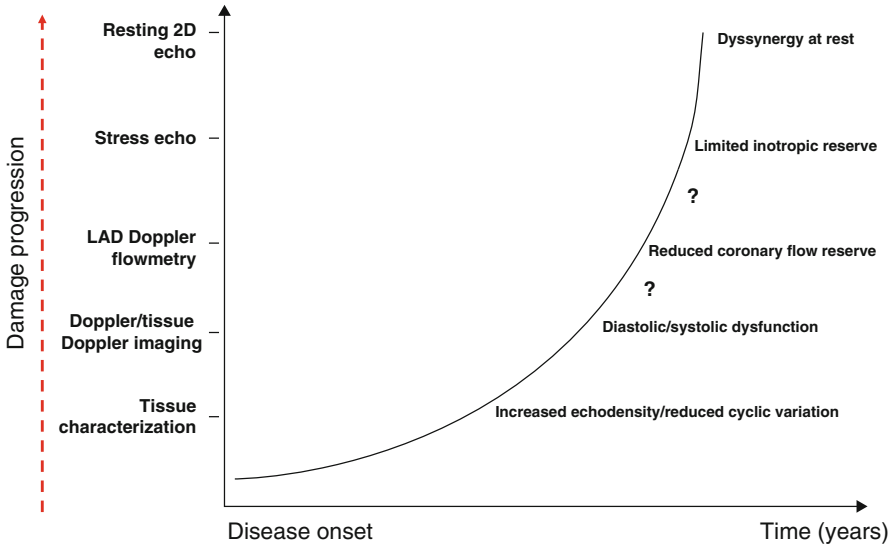

Fig. 32.2 Cardiomyopathy cascade. In the sequence of events, changes in diastolic function and alterations in longitudinal function of the left ventricle (such as reduction in mitral annulus plane systolic excursion by *M*-mode or reduction in systolic velocity by myocardial tissue Doppler or strain rate imaging) precede by years or decades the reduction of ejection fraction (From Picano [25])

echocardiography, first and foremost on the basis of classical wall motion abnormalities [27–35], which place the patients in a high-risk subset for cardiovascular events (Fig. 32.3). The incremental prognostic information provided by stress echocardiography is highest in patients with intermediate-to-high threshold positive exercise electrocardiography test results [34]. However, in diabetic patients – differently from nondiabetic subjects – a negative test result based solely on wall motion criteria is associated with less benign outcome in the presence of diabetes [33] (Fig. 32.3).

In these patients, coronary flow reserve evaluated simultaneously with wall motion during vasodilation stress testing by transthoracic Doppler echocardiography adds independent prognostic information [36] (Fig. 32.4).

In particular, a normal coronary flow reserve is associated with tighter glycemic control [37] and better long-term event-free survival in unselected diabetic patients

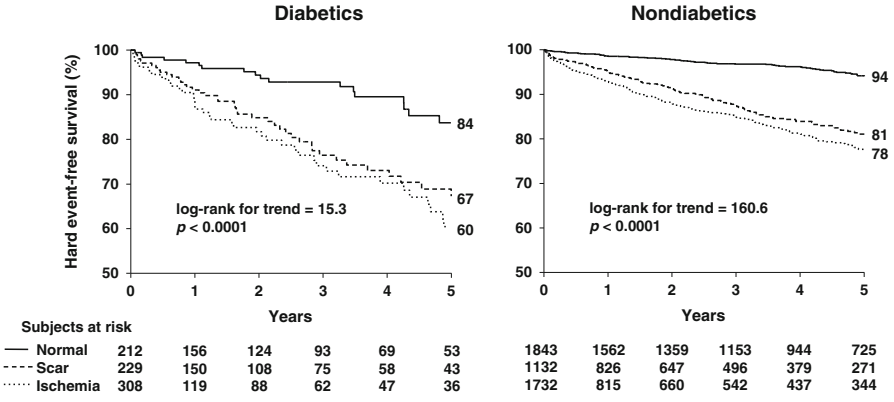

Fig. 32.3 Kaplan-Meier event-free survival curves in diabetics (*left*) and nondiabetics (*right*). In patients without scarring and inducible wall motion abnormalities, the prognosis is excellent in nondiabetics but is still poor in diabetics in whom a better stratification is needed (From Cortigiani et al. [33])

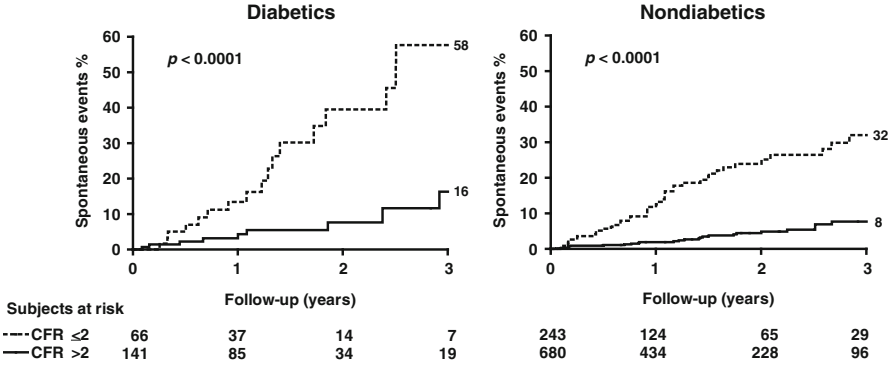

Fig. 32.4 Kaplan-Meier survival curve event rate for diabetic and nondiabetic patients with coronary flow reserve (*CFR*) >2 or ≤2 and negative stress echocardiography by wall motion criteria (From Cortigiani et al. [36])

[38] as well as in diabetic patients with angiographically normal coronary arteries [39]. Explanations for reduced coronary flow reserve in the absence of stress-induced wall motion abnormalities include mild-to-moderate epicardial coronary artery stenosis, severe epicardial artery stenosis in the presence of anti-ischemic therapy, and severe microvascular coronary disease in the presence of patent epicardial coronary arteries [36]. Further stratification in patients with negative wall motion response is more challenging to carry out with coronary flow reserve than with dobutamine or exercise stress. The identification of a lower-risk subset can be achieved with these stresses, evaluating contractile reserve at peak stress with the pressure-volume relationship (see Chap. 4). The lower contractile reserve is associated with a higher rate of events in spite of wall motion negativity [40].

32.4 The Diagnostic Flowchart in Diabetics

The general diagnostic flowchart in diabetics (both symptomatic and intermediate-to-high-risk asymptomatic) can be summarized as in Fig. 32.5. After the exercise stress test, a stress imaging test is often warranted. The recognized finding that 10–15 % of asymptomatic diabetics indeed have coronary artery disease has led to

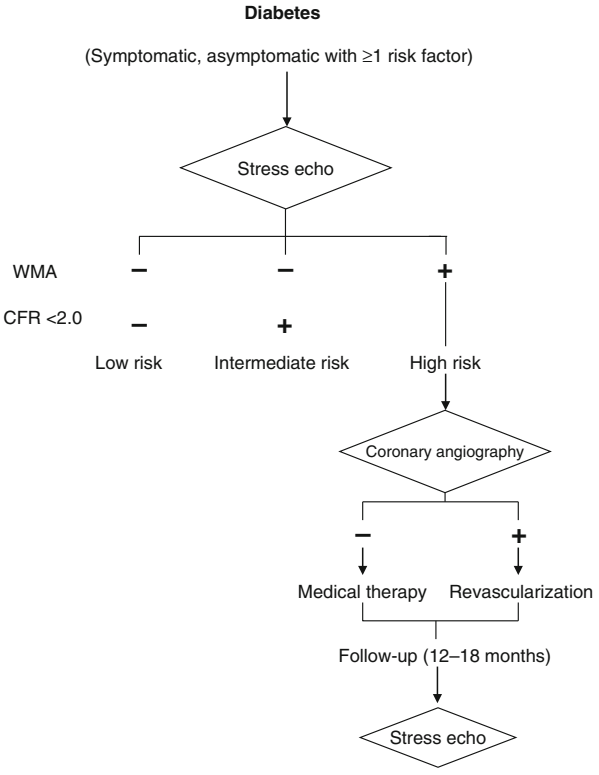

Fig. 32.5 The diagnostic flowchart in diabetics for recognition of coronary artery disease

proposing stress imaging for a more effective risk stratification [41, 42]. However, the economic and long-term risk burden is especially important due to recent accumulation of suggestive evidence that percutaneous coronary revascularization may not provide additive benefits to intensive medical management in patients with stable coronary artery disease [4]. Therefore, we currently recommend that testing for atherosclerosis or ischemia be reserved for those in whom medical treatment goals cannot be met and for selected individuals in whom there is strong clinical suspicion of very-high-risk coronary artery disease [4]. Even in these individuals, techniques with substantial radiation exposure – albeit recommended by authorities – such as myocardial scintigraphy or cardiac computed tomography should be used with great wisdom and prudence, and stress echocardiography is by far a more sustainable option [8].

32.5 Pitfalls

Exercise capacity is frequently impaired in people with diabetes due to the high prevalence of obesity, sedentary lifestyle, peripheral neuropathy (both sensory and motor), and vascular disease [43]. For those unable to perform an exercise test, pharmacological stress testing may be required.

32.6 Clinical Guidelines

The main appropriate, possibly appropriate, and rarely appropriate indications for stress echocardiography in diabetics are summarized in Table 32.1 [43, 44].

Table 32.1 Clinical guidelines for the use of stress echo in diabetics

	A	M	R	Class	Level	Ref.
People with diabetes should undergo investigation for CAD by exercise ECG stress testing as the initial step in the presence of typical or atypical symptoms (e.g., unexplained dyspnea, chest discomfort). In these patients, SE as a first-line test is inappropriate			√	EC		[43]
Signs or symptoms of associated disease (peripheral arterial disease, carotid bruits, transient ischemic attacks, stroke, etc.)		√		IIb	C	[44]
Stress echo should be used in individuals with diabetes in whom resting ECG abnormalities preclude the use of exercise ECG stress testing or in those who are unable to exercise	√			EC		[43]

EC expert consensus. Adapted from Ref. [43, 44]

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Stress Echocardiography in Dilated Cardiomyopathy

33

Marco Guazzi and Eugenio Picano

Heart failure is a progressive, lethal syndrome characterized by accelerating deterioration [1]. Its estimated prevalence in the USA is around 2.0 %, with an increased prevalence of 6–10 % in patients over 65 years of age [2]. The prognosis of heart failure is uniformly poor if the underlying problem cannot be rectified; half of all patients carrying a diagnosis of heart failure will die within 4 years, and in patients with severe heart failure, more than 50 % will die within 1 year [2]. The actual rate of deterioration is highly variable and depends on the nature and causes of the overload, the age of the patient, and many other factors (Fig. 33.1). Following a period of asymptomatic left ventricular dysfunction that can last more than a decade, survival after the onset of significant symptoms averages about 5 years [3]. Stress echocardiography has a role in initial and advanced stages (Fig. 33.2). In formulating the 2001 document, also endorsed in the 2005 document, the ACC/AHA guidelines developed a new approach to the classification of heart failure, identifying four stages: stage A (at high risk but without structural heart disease, e.g., hypertension), stage B (structural heart disease but without signs and symptoms of heart failure, e.g., previous myocardial infarction or asymptomatic valvular heart disease), stage C (structural heart disease with current or prior symptoms of heart failure), and stage D (refractory heart failure requiring specialized interventions). According to this staging approach, which is conceptually similar to that achieved by staging in other diseases such as cancer, patients would be expected either not to advance at all or to advance from one stage to the next, unless progression of the disease was slowed or stopped by treatment. The recent realization that therapies aimed at symptomatic heart failure may improve outcomes in patients with asymptomatic left ventricular dysfunction has increased the importance of recognizing and treating patients with the asymptomatic stage A and B condition, possibly even more frequent than overt heart failure. In the early stage, in patients with normal left ventricular function, a reduced inotropic reserve can unmask initial damage. In advanced stages, stress echocardiography complements resting echocardiography, identifying a heterogeneous prognostic profile that underlies a similar resting echocardiographic pattern (Table 33.1).

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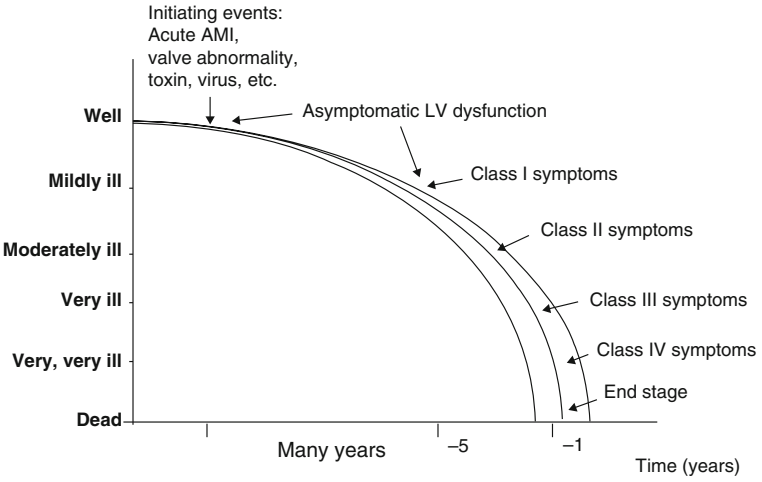

Fig. 33.1 The natural history of cardiomyopathy (Modified from Katz [3])

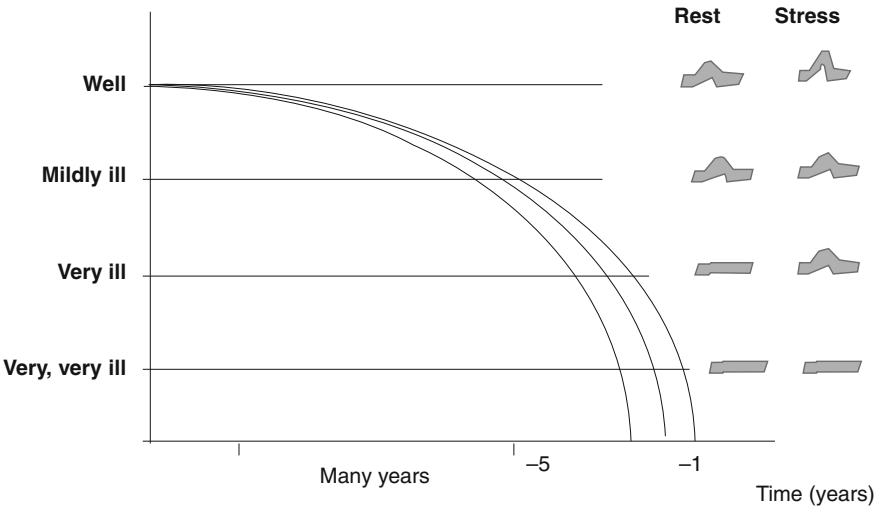

Fig. 33.2 The role of stress echocardiography in prognostic titration of cardiomyopathy. At an early stage, baseline function is normal but inotropic reserve is depressed. At an advanced stage, the baseline function is depressed but there is inotropic reserve. At a very advanced stage, the resting function is depressed and the inotropic response is abolished

Table 33.1 Stress echocardiography response and the four stages of dilated cardiomyopathy

Disease class (ACC/AHA)	Stage of disease	Resting global function (EF)	Longitudinal function	Stress function	Coronary flow reserve
A	Absent	Normal	Normal	Normal	Normal
B	Initial	Normal	Abnormal	Blunted hyperkinesia	↓ →
C	Overt	Abnormal	Very abnormal	Functional recovery	↓
D	Advanced	Abnormal	Very abnormal	No functional recovery	↓↓

EF ejection fraction

33.1 Incipient or Latent Cardiomyopathy

Some patients are exposed to potentially cardiotoxic conditions, such as chemotherapy in cancer or iron overload in thalassemia. The clinical natural history of these conditions is characterized by a very short interval between the onset of cardiac symptoms and end-stage cardiac failure. The detection of preclinical cardiac involvement can be important in order to start more aggressive therapy. There are two possible and not mutually exclusive approaches for the early detection of incipient myocardial damage when ejection fraction is still normal. The first possibility is to assess longitudinal function, impaired at an earlier stage of disease than ejection fraction, which may remain normal due to supernormal compensatory radial function. The selective early impairment of longitudinal global function can be easily measured with *M*-mode mitral annulus plane systolic excursion or with myocardial velocity imaging, as decreased systolic S wave velocity of basal (septal and/or lateral) segments with tissue Doppler and/or strain rate imaging. The early reduction in longitudinal function, with normal ejection fraction, has been described in several conditions, from systemic sclerosis [4] to diabetic [5] or hypertensive [6] cardiomyopathy.

The second approach is to assess the segmental and global contractile reserve during inotropic challenge. The rationale of applying stress echocardiography in these conditions is that structural impairments of the myocardial wall can be subtle enough so as not to impair resting systolic function but severe enough to blunt or even exhaust the contractile response to the inotropic stimulation. At low doses ($\leq$10 μg kg^{-1} per min), dobutamine selectively stimulates β-1 myocardial receptors, determining a mild, sustained inotropic stimulation with little if any effect on either systemic hemodynamic parameters or loading conditions. With these low dobutamine doses, the lower basal wall shows a blunted increase in percent systolic thickening, or in peak systolic velocity on myocardial velocity imaging, which helps detect early damage. The blunted regional cardiac contractile reserve (Fig. 33.2) has also proved useful in detecting subtle forms of cardiac involvement in several diseases, such as doxorubicin chemotherapy [7], thalassemia [8], diabetic [9], or hypertrophic cardiomyopathy [10].

In all these conditions, the reduction in myocardial contractile reserve – best observed with dobutamine stress – is also accompanied by impaired coronary flow reserve, best detected today by vasodilator stress combined with pulsed Doppler of the mid-distal left anterior descending coronary artery [11]. The reduction of coronary flow reserve at a very early clinical stage, when symptoms are absent or minimal and left ventricular ejection fraction is normal at baseline [12], has been described in several clinical conditions such as systemic sclerosis [13] and diabetic [14] or hypertensive [15] heart disease. Contractile reserve focuses on the myocytes, whereas coronary flow reserve assessed the coronary microcirculation. Both impaired contractile reserve and decreased coronary flow reserve are therefore very early and possibly diagnostically relevant markers of initial cardiomyopathy, at a stage when any form of intervention (lifestyle or drugs) is more likely to be efficacious (Table 33.1).

33.2 Dilated Cardiomyopathy

Dilated cardiomyopathy is a condition that predominantly affects ventricular systolic function. Nevertheless, indices of global systolic dysfunction as measured at rest are inadequate for depicting the severity of the disease and are poorly correlated with symptoms, exercise capacity, and prognosis [16]. In contrast, the assessment of contractile reserve during stress, rather than baseline indices, is an important means of quantifying the degree of cardiac impairment and refining prognostic prediction [17]. In general, all of the 12 available studies on several hundred patients have shown a beneficial effect of a preserved inotropic response on prognosis, although disparate methodology, selection criteria (including both idiopathic and ischemic dilated cardiomyopathy), and prognostic end point were utilized [18–30]. The contractile reserve can be identified through wall motion index improvement (greater than 0.20) or with a reduction of end-systolic volume during stress. A specific application has been proposed in patients with long-lasting atrial fibrillation and dilated cardiomyopathy. Atrial fibrillation can cause a reversible form of dilated cardiomyopathy, with restoration of normal left ventricular function after cardioversion to sinus rhythm. The distinction between idiopathic dilated cardiomyopathy and tachycardiomyopathy is important because restoration of sinus rhythm leads to a significant improvement in left ventricular function only in the latter case [19].

The dobutamine infusion protocol is similar to the one followed in patients with ischemic heart disease but without atropine administration. In patients with dilated cardiomyopathy and heart failure, a lack of increase in left ventricular function is associated with higher mortality (Fig. 33.3). However, limiting minor side effects occur in about 10–20 % of these patients, who have a depressed ejection fraction and are more vulnerable to an arrhythmic side effect of the drug. In patients with contraindications to or submaximal, nondiagnostic dobutamine stress echocardiography, alternative tests may offer comparable information. Dipyridamole may elicit a prognostically meaningful increase in function, comparable to that provided with the more arrhythmogenic dobutamine [31]. With dipyridamole, the prognostic information is further expanded by the assessment of coronary flow reserve on the left anterior descending artery (Fig. 33.4) and, when possible, the posterior

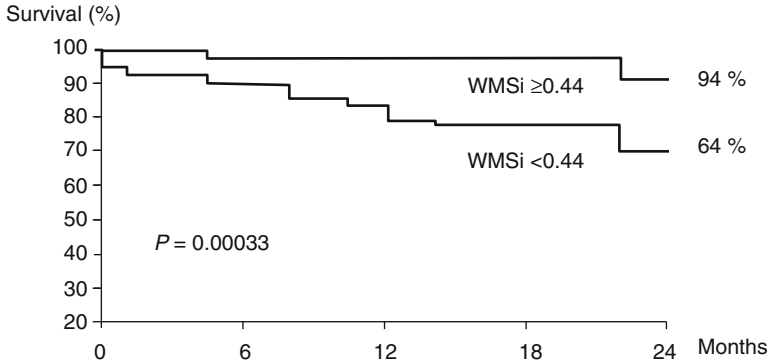

Fig. 33.3 Kaplan–Meier survival curves in patients with dilated cardiomyopathy separated on the basis of preserved (Δ WMSI >0.44) or impaired (Δ WMSI <0.44) left ventricular contractile reserve during dobutamine stress (Modified from Pratali et al. [24])

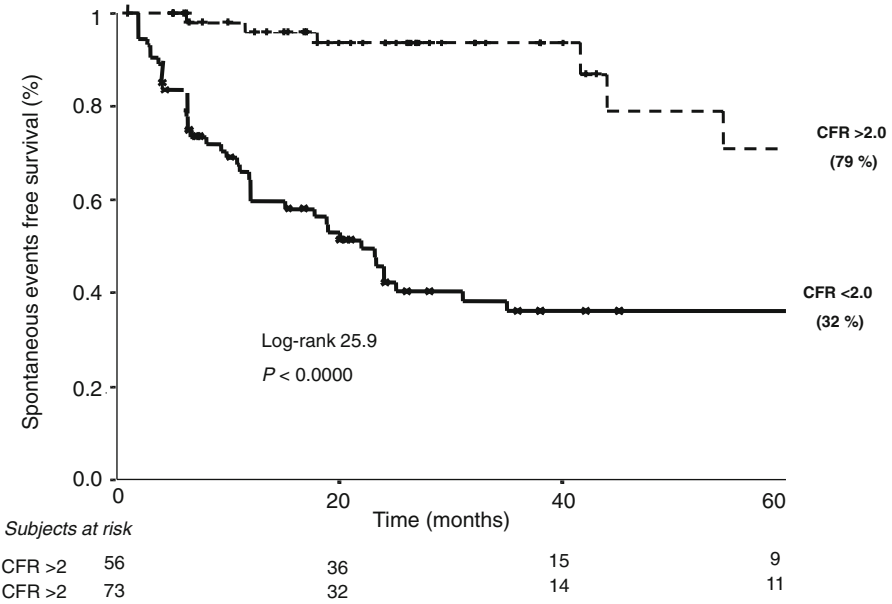

Fig. 33.4 Kaplan–Meier survival curves in patients with dilated cardiomyopathy separated on the basis of normal (CFR >2.0) or depressed (CFR <2.0) coronary flow reserve (Modified from Rigo et al. [32])

descending right coronary artery. The prognosis is worse in patients with depressed coronary flow reserve assessed on LAD with pulsed Doppler [32] or in the entire left ventricle with perfusion myocardial contrast echocardiography [33]. The prognostic information derived from stress echocardiography can be added on the top of the versatility of data provided by resting transthoracic echocardiography. Ejection fraction remains the cornerstone of prognostic assessment, and the risk of death increases hyperbolically with the reduction in ejection fraction (see Fig. 22.1 in

Table 33.2 Prognosis in dilated cardiomyopathy: key parameters beyond ejection fraction

	M-mode	2D	Color	CW	PWD/TDI	Lung
TAPSE	√					
LVESV, LAVI		√				
MI			√			
PASP				√		
E/e′					√	
B-lines						√

PASP pulmonary artery systolic pressure, *TDI* tissue Doppler imaging, *TAPSE* tricuspid annular plane systolic excursion, *ULC* ultrasound lung comets

Chap. 22). Nevertheless, for any given ejection fraction, prognosis can change dramatically with a few variables that can be easily obtained by a comprehensive resting echo and can be incorporated in an integrated echo score which provides additional information over standard, nonimaging, echo scores [34, 35]. A reduced tricuspid annulus plane systolic excursion and increased pulmonary artery systolic pressure may further worsen the prognostic outlook (Table 33.2), dominated by the "deadly quartet": (1) dilated (end-systolic volume >90 mL m^{-2}) left ventricle, (2) severe mitral insufficiency, (3) diastolic restrictive pattern (or E/e value >15), and (4) increased extravascular lung water detectable as B-lines on lung ultrasound [36–39].

All these parameters evaluate prognostically critical aspects of cardiopulmonary hemodynamics beyond myocardial ischemia and regional function, ranging from diastolic function to valvular competence to pulmonary and hemodynamic congestion and cardiac remodeling. These parameters can change dramatically during stress, and a dynamic assessment with stress echo likely provides a more accurate stratification than resting evaluation, as strongly suggested by initial experiences. If lung water or mitral insufficiency or end-systolic volume [40–42] acutely and markedly increases during exercise, the patient is more likely to suffer unfavorable events in the short-term.

33.3 Differentiation Between Ischemic and Nonischemic Dilated Cardiomyopathy

The detection of coronary artery disease in a patient with global left ventricular dysfunction and dilatation has important therapeutic and prognostic implications. The diagnosis of ischemic cardiomyopathy may either be straightforward or impossible on a clinical basis. At one end of the clinical spectrum, the ischemic etiology is obvious when an unequivocal history of ischemic heart disease and infarction can be collected. As a rule, several episodes of myocardial necrosis have progressively reduced pump function. After repeated infarctions, marked global dysfunction ensues, and anginal symptoms are reduced and progressively replaced by dyspnea. At the other end of the clinical spectrum, ischemic cardiomyopathy can be

Table 33.3 Differential diagnosis of dilated cardiomyopathy

	Ischemic	Nonischemic
History of infarction	Yes/no	No
Resting regional abnormality	Yes/no	No/yes
Stress inducible abnormalities	Yes/no	No/yes
CMR	Subendocardial transmural scar	Patchy, subepicardial fibrosis
MSCT	Severe CAD	Normal

CAD coronary artery disease, *CMR* cardiac magnetic resonance, *MSCT* multislice computed tomography

completely superimposable on an idiopathic form with signs and symptoms of congestive heart failure. Dyspnea can be an angina equivalent, and on the other hand, angina may be present in idiopathic and absent in ischemic cardiomyopathy. Several noninvasive clues to this differentiation have been proposed (Table 33.3). Ischemic patients more frequently show akinetic segments and a more elliptical shape at resting echocardiography, a smaller and less compromised right ventricle, and larger stress-induced defects during perfusion imaging, with scintigraphy or echocardiography. Encouraging results have also been reported with dobutamine stress echocardiography. Of particular value are the biphasic response in at least two segments and/or the extensive ischemic response [43, 44]. However, all stress-imaging clues concerning the distinction between ischemic and idiopathic cardiomyopathy cannot always be considered clinically significant, although they have been reported to be statistically significant in some studies. Cardiomyopathy is one of the most frequent sources of false-positive ischemic response, and no wall motion abnormalities can be evoked in an ischemic cardiomyopathy when fibrosis is extensive. Cardiovascular magnetic resonance can be more helpful, identifying a subendocardial–transmural regional pattern in ischemia as opposed to a patchy, diffuse scar pattern in nonischemic dilated cardiomyopathy. Coronary angiography (or its noninvasive counterpart of multislice computed tomography) is quite often the only way to firmly establish the differential diagnosis between ischemic and idiopathic cardiomyopathy [45].

In these patients, the role of stress echocardiography is mainly focused on prognostic stratification. The presence of significant (four or more left ventricular segments) contractile reserve is associated with a better prognosis and greater functional recovery with either medical therapy or cardiac resynchronization therapy or (in coronary artery disease patients) revascularization [46].

33.4 Stress Echo and Cardiac Resynchronization Therapy

Cardiac resynchronization therapy (CRT) is an established technique in patients with end-stage heart failure. Current selection criteria include New York Heart Association class III or IV heart failure, left ventricular ejection fraction of 35 % or less, and wide QRS complex (>120 ms). The majority of patients selected according to these criteria respond well to CRT, but 30 % (by echocardiographic criteria) do

not respond. The most frequently used clinical marker is the improvement of one grade or more in NYHA class; the most frequently used echocardiographic marker is an antiremodeling effect defined as a reduction of 15 % or more in left ventricular end-systolic volume [47]. In the majority of patients, there is full agreement between clinical and echocardiographic response, but 25 % of patients show discordant results, more often with clinical but not echocardiographic response. The large number of nonresponders for a costly, risky, and demanding therapy such as CRT led researchers to look for better selection criteria (Figs. 33.5 and 33.6).

Newer echocardiographic techniques to evaluate LV dyssynchrony have been described in the post-PROSPECT [48], after the demonstration that complex, tedious, and time-consuming TDI-based parameters assessing LV dyssynchrony added nothing to clinical and ECG stratification [49]. All these promising indices – including those derived from real-time 3D and 2D-derived speckle tracking analysis – will be used with a healthy degree of skepticism until they have been subjected to further assessment and conclusive validation [50]. Recently, disappointment with the mechanical dyssynchrony approach led several investigators to integrate the electrical approach with a more functional approach. In fact, it is probably unrealistic to expect a response to CRT if there is not enough muscle to be resynchronized.

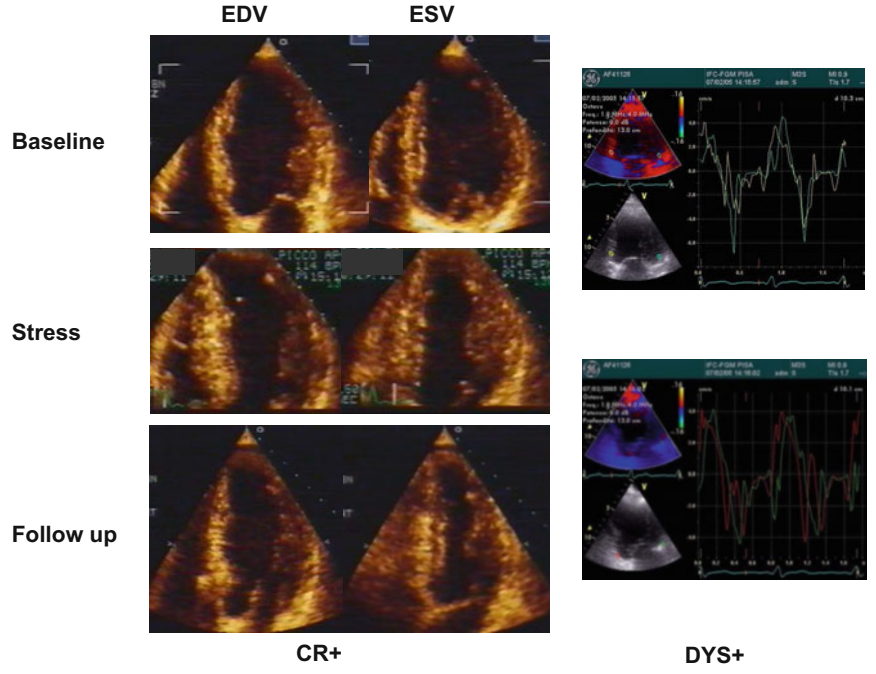

Fig. 33.5 An example of a CRT responder. Echocardiographic four-chamber view at rest, at peak stress and at follow-up of a patient with contractile reserve (*CR+*) (*left*) and tissue Doppler criteria of intraventricular dyssynchrony (*Rest DYS+*) (*right*). *EDV* end-diastolic volume, *ESV* end-systolic volume (Modified from Ciampi et al. [52])

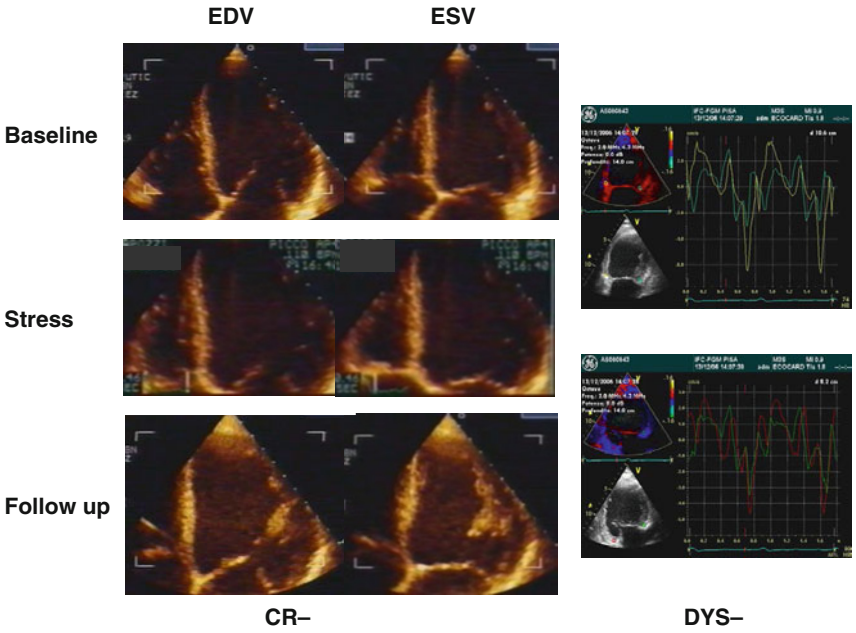

Fig. 33.6 An example of a CRT nonresponder. Echocardiographic four-chamber view at rest, at peak stress, and at follow-up of a patient without contractile reserve (*CR–*) (*left*) without tissue Doppler criteria of intraventricular dyssynchrony (*Rest DYS–*) (*right*) (Modified from Ciampi et al. [52])

In other words, it is unlikely that home comfort will benefit from a brand-new electric system if there are no walls and no ceiling left. Indeed, this so-called functional approach appears to be much more gratifying in selecting candidates for CRT. In patients with depressed ejection fraction, the lack of a substantial (five segments or more) viability response to dobutamine stress echocardiography is invariably associated with a lack of response to CRT [51–58], as shown concordantly by seven studies (three of them multicentric) collecting over 600 patients (Table 33.4). The improvement is most likely in patients with contractile reserve and lack of severe diastolic dysfunction at rest.

The beneficial effect of electrical therapy in heart failure patients, with or without CAD, requires the presence of a critical mass of target tissue. Also, this shift in diagnostic forms from electrical synchronicity to functional reserve dramatically simplifies the screening of the CRT candidate; stress echocardiography is simpler, much faster, and more reproducible than CRT criteria. Echocardiographic evaluation of dyssynchrony may add something to the risk stratification, but only in patients with viability. This approach can be made even simpler and more quantitative in CRT, when the single most important stress echocardiographic parameter is variation in end-systolic volume, which today can be estimated even more accurately with RT3D. This stress echocardiography-driven approach to selection of CRT responders is now mature and ready for large-scale validation (Figs. 33.7 and 33.8).

Table 33.4 Contractile reserve and improvement after CRT

Author	Journal, year	Study design	Number of pts	Dob dose (mcg)	Cutoff
Munin et al. [58]	*Echocardiog*, 2014	Single center	52	40	EF >7 %
Mizia-Stec et al. [57]	*Int J Cardiol*, 2014	Prospective, multicenter, observational	129	20	>0.20 WMSI
Gasparini et al. [56]	*Am Heart J*, 2012	Prospective, multicenter, observational	221	40	ESV decrease >10 %
Altman et al. [55]	*Am J Cardiol*, 2011	Single center	31	10	EF >20 %
Chaudhry et al. [54]	*J Am Soc Echocardiogr*, 2011	Single center	54	20	WMSI >5 segments
Sénéchal et al. [53]	*Echocardiography*, 2010	Single center	59	20	Stroke volume >15 %
Ciampi et al. [52]	*Eur J Heart Fail*, 2009	Multicenter	69	40	WMSI >0.20
Da Costa et al. [51]	*Heart Rhythm*, 2006	Single center	71	10	EF >25 % increase

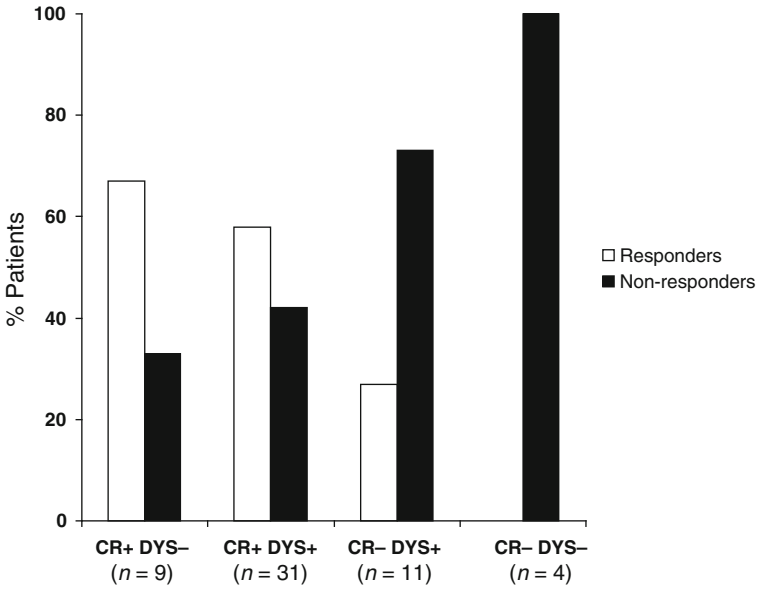

Fig. 33.7 Responders to cardiac resynchronization therapy are selected on the basis of contractile reserve more efficiently than with dyssynchrony (Modified from Ciampi et al. [52])

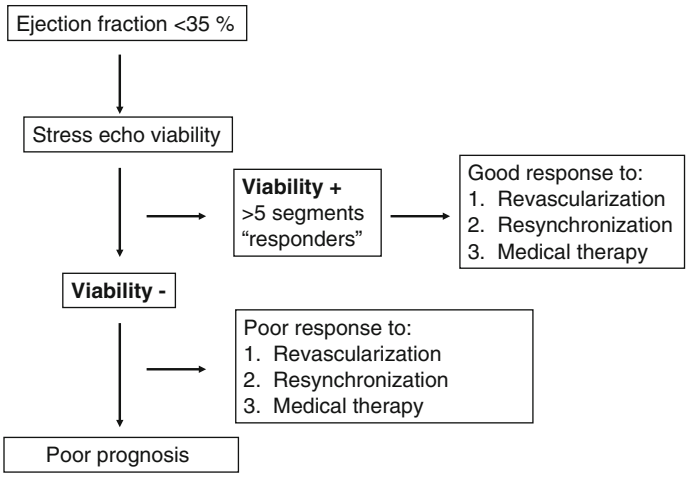

Fig. 33.8 The importance of being viable in patients with depressed ejection fraction. Whatever the underlying disease, response to therapy is dependent upon underlying presence of myocardial viability. The type of therapy obviously depends on the underlying etiology: coronary revascularization in coronary artery disease, aortic valve replacement in low-flow, low-gradient aortic stenosis, and cardiac resynchronization therapy in nonischemic cardiomyopathy (Modified from Ciampi et al. [46])

It is important to emphasize that the prognostic benefit associated with contractile reserve in CRT can also be observed in these patients left under medical therapy, especially with beta-blockers [59–63].

33.5 Stress Echo and Cardiopulmonary Exercise Testing

The most typical clinical manifestation of stable HF is exercise intolerance with fatigue and dyspnea as incurring symptoms for low levels of exercise. Despite advances in technologies related to diagnostic testing and the popularity of imaging techniques, assessment of exercise responses provides a critical enhancement of the clinical decision-making of these patients. Specifically, exercise gas exchange analysis by cardiopulmonary exercise testing (CPET) is a precise and reproducible technique to detect exercise performance that has many clinical applications out of the peculiar pathophysiological-based information including diagnosis, evaluation of therapy, risk stratification, and guide to physical activity [64]. The two most studied and clinically relevant CPET variables are oxygen consumption (VO_2) at peak exercise and the rate of increase in minute ventilation to carbon dioxide production (VE/VCO_2) slope reflective of ventilation efficiency. Peak VO_2 has been historically viewed as the gold standard noninvasive parameter to ascertain the need of heart transplantation [65], while VE/VCO_2 slope has become more popular across recent years for a similar or even greater prognostic ability [66] and the advantage of being

effort independent. Both peak VO_2 and VE/VCO_2 slopes have driven clinical practice through the Weber [67] and Ventilatory Class (VC) classifications [66], respectively. Recently, attention has been paid for an additional meaningful parameter, i.e., the exercise oscillatory ventilation identified as a cyclic pattern in VE and gas kinetics that resembles, in some instances, the occurrence of Cheyne–Stokes respiration during sleep [68]. Because these markers emerged as particularly powerful prognostic indicators, risk stratification algorithms have been built using these three indicators under a score format [69, 70]. Consistently, most recent guidelines on CPET have incorporated the information derived from any single variable in an integrated analysis under a color-coded risk table analysis that simply and comprehensively applies to the final test report in daily practice [64].

Despite its established clinical uses, CPET has the intrinsic limitation that it does not provide measures of cardiac contractile state and relaxation as well as of right ventricular functional adaptation to incremental exercise. Even more the test does not allow to dissect the relative contribution of dynamic mitral and tricuspid valve incompetence to the observed abnormal CPET phenotypes. Assessment of these determinants is of special relevance in the functional evaluation of HF patients and makes a strong rationale for combining exercise echocardiography with CPET as an area of intriguing and growing development.

Approximately 50 % of patients with CAD or dilated cardiomyopathy develop chronic secondary mitral regurgitation (SMR) which is a complex entity often underappreciated [71]. SMR may exhibit a wide range of severity that confers an adverse prognosis which is worse with increasing severity [72]. There are several mechanisms and key events in the pathogenesis of SMR that can be summarized in a distortion of normal LV geometry, both regional and global, with subsequent displacement of papillary muscle to apex and lateral wall that in turn make the chordae tendineae away from the line of coaptation and lead to deformation of mitral valve. The consequent imbalance between tethering (apical displacement of mitral leaflets) and closing forces (forces developed by LV during systolic contraction which contribute to valve closure) yields to valve regurgitation [73]. Alterations in mitral annulus size and shape contribute to the development of SMR as an adjunctive mechanism.

SMR is dynamic and, therefore, influenced by loading conditions, and echocardiography specifically points to the study of exercise-induced MR and its hemodynamic consequences [74].

End-systolic sphericity index and wall motion score index are significantly related to ERO changes [75], as well as a relationship has been documented between MR jet area/left atrial area increase during exercise and LV shape (reduction of LV major to minor axis ratio) [76]. An important relationship has also been demonstrated between exercise mitral deformation and LV sphericity index, assessed with both two- (2D) and three-dimensional (3D) echocardiography and dyssynchrony [77]. CRT reduces the dynamic component of SMR during exercise in both synchronized and nonsynchronized LV [78].

The relationship between exercise-induced MR and impaired functional capacity is clearly established. In patients with asymptomatic or mild symptomatic patients with idiopathic dilated cardiomyopathy, an increase in ERO, determined by enlarged tenting area, affected functional capacity and emerged as the strongest independent determinant of exercise duration [76]. Patients with exercise-induced MR have lower peak VO_2 and higher VE/VCO_2 slope [79]. Interestingly, the relationship between exercise-induced MR and peak VO is reinforced by the performance improvement observed after CRT therapy [80, 81].

Preliminary findings from our group obtained in 102 patients with dilated cardiomyopathy with peak exercise-induced MR of different entity showed a progressive incremental distribution in ERO severity according to Weber and VC functional classes. Taking a peak ERO >20 mm^2 as a significant cutoff, it was found a high average ERO even in the lowest VC classes (I and II) compared to Weber class A and B, suggesting that the degree of ventilation inefficiency may better reflect the severity of underlying exercise-induced MR [82] (Fig. 33.9).

MR is a well-recognized determinant of pulmonary hypertension (PH) in HF populations which portends an unfavorable prognosis especially when right ventricular (RV) to pulmonary circulation (PC) uncoupling coexists [83]. There is recent renewed interest on the role of RV to PC uncoupling in the natural history of HF [84], and its investigation during exercise through a combined stress echo/CPET assessment seems another meaningful new application. A simplification of RV to PC coupling measure may noninvasively be obtained by looking at the relationship between systolic pulmonary pressure (PASP) changes and tricuspid annular plane systolic excursion (TAPSE), and a RV to PC uncoupling phenotype is tightly related to a worse ventilatory efficiency during exercise [85] (Fig. 33.10).

Upcoming studies will clarify how much a combined stress echo/CPET approach will be of help to improve our understanding on the pathophysiological mechanisms and clinical course of patients with failing hearts.

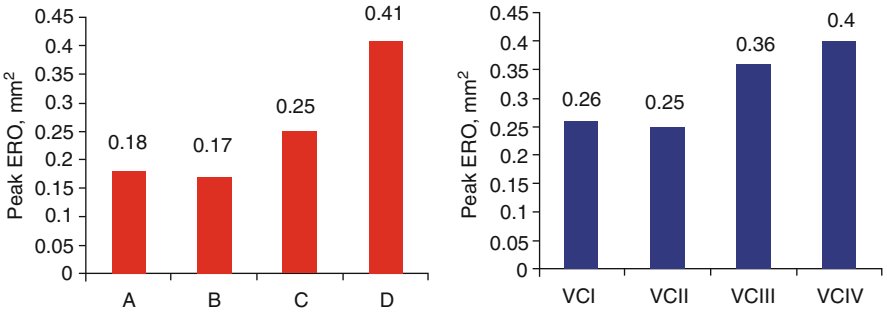

Fig. 33.9 Peak ERO distribution according to Weber (*A*) and VC (*B*) classes (Modified from Generati et al. [82])

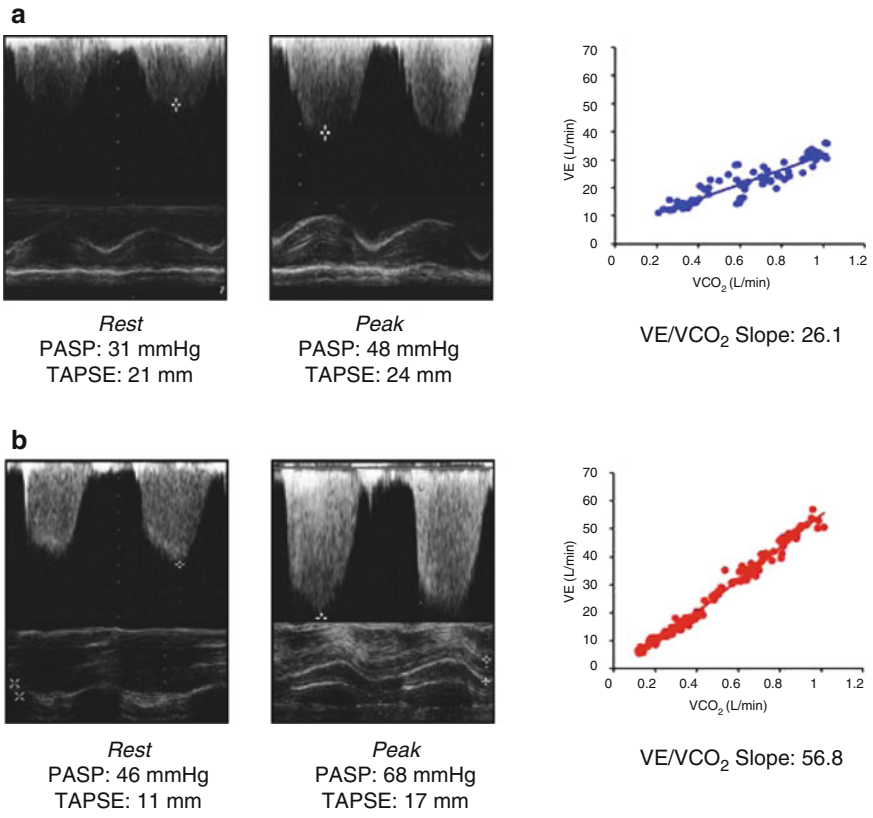

Fig. 33.10 Example of HF patients with no MR, preserved RV to PC coupling, and normal exercise ventilation efficiency (**a**) and a subject (**b**) with impaired RV to PC coupling and severely compromised ventilation (Modified from Borghi-Silva et al. [85])

33.6 Pitfalls of Stress Echo in Dilated Cardiomyopathy

The accuracy of imaging stress testing for ischemia may be diminished in patients with severe left ventricular dysfunction and remodeling, thus making the test less useful for its intended purpose. This is one of the possible explanations of the counterintuitive finding that in CAD patients with severe LV dysfunction, inducible myocardial ischemia does not identify patients with more severe prognosis or those with greater benefit from CABG over medical therapy [86]. The usual focus of SE is the change in regional wall motion (viability and ischemia), but several studies have shown a dissociation between myocardial ischemia, evidence of viability, and subsequent adverse events, which are more likely due to heart failure than the underlying coronary atherosclerosis per se [87]. Probably SE should focus more on prognosis-changing cardiovascular hemodynamic response (from B-lines to diastolic function) to integrate the time-honored information on wall motion. Finally, the risk of life-threatening complications during pharmacological stress (especially

Table 33.5 Indications to resting TTE and stress echo in DC

	Rest TTE	SE	COR	LOE
Newly suspected heart failure	A		I	C
Viability assessment is reasonable before revascularization in CAD		**A**	**IIa**	**C**
Routine repeat measurement	**R**		**III**	**B**

From Ref. [89]

COR indicates class of recommendation, *LOE* level of evidence

dobutamine) is higher in the presence of resting left ventricular dysfunction [88]. This is an additional reason to use exercise whenever possible as the stress of choice in these patients. It is safer and more informative on cardiovascular hemodynamic changes than pharmacological stresses.

33.7 Clinical Guidelines

The main appropriate and inappropriate indications to rest and stress echo in heart failure are summarized in Table 33.5, following the latest recommendations of ACCF/AHA [89]. ESC guidelines also assign a class of recommendation IIa (level of evidence C) to stress echo in patients thought to have CAD and who are considered suitable for coronary revascularization, to determine whether there is reversible myocardial ischemia and viable myocardium [90].

Table of Contents Video Companion

See in the section illustrative cases: case numbers 29, 30, and 31 (by Maria Joao Andrade, MD, Carnaxide, Lisbon, Portugal).
See also in the section selected presentations: B-lines, in and out the stress echo lab.
Springer Extra Materials available at http://extras.springer.com/2015/978-3-319-20957-9

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Stress Echocardiography in Hypertrophic Cardiomyopathy

34

Iacopo Olivotto, Stefano Nistri, and Eugenio Picano

34.1 Background

Hypertrophic cardiomyopathy (HCM) is the most common monogenic disease of the myocardium, with a 1:500 prevalence in the general population worldwide, although often misdiagnosed or neglected [1–6]. HCM is defined by the presence of increased left ventricular (LV) wall thickness ≥15 mm by any imaging modality in one or more LV myocardial segments that is not solely explained by abnormal loading conditions and occurs in the absence of other detectable causes [2, 3, 6]. A lower threshold for LV thickness (i.e., ≥13 mm) is adopted in first-degree relatives of patients with unequivocal disease. Clinical diagnosis is customarily made with two-dimensional echocardiography by detection of increased LV wall thickness, usually in the presence of a small LV cavity, after suspicion has been raised by the clinical profile or as a part of screening [2, 3]. In most patients, HCM is caused by mutations in genes encoding contractile proteins of the cardiac sarcomere, Z-disk, and intracellular calcium handling pathways [4–9]. A minority of cases are caused by inherited metabolic and neuromuscular diseases, which are most common in pediatric cohorts, or so-called phenocopies such as amyloidosis or Fabry disease. In over one-third of patients, however, the genetic basis of the disease remains unresolved [6, 7]. To date, hundreds of different mutations have been associated with HCM (>90 % affecting myosin-binding protein C, beta-myosin heavy chain, and troponin T), and many families exhibit "private" mutations which have not been previously described. Adding to the genetic complexity of the disease is the fact that many of these variants, suspected to cause disease, do not meet the requirements for pathogenicity and are necessarily classified as "variants of unknown significance" (VUS) [7]. Despite over two decades of research in the field, attempts to correlate genotype with phenotype, disease severity, and outcome have yielded inconsistent and overall disappointing results, although some clinically relevant associations have been observed [8].

HCM is often characterized by a stable and uneventful clinical course and may be diagnosed late in life [2, 3, 5, 6]. However, about 50 % of patients experience symptoms related to effort or meals, 25 % develop atrial fibrillation, and 15 %

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progress toward LV dysfunction and heart failure, including 5 % ultimately developing end-stage disease (Fig. 34.1). In addition, the condition is associated with a 0.5–1 % annual risk of sudden cardiac death [10]. Prior history of cardiac arrest is an obvious indicator of risk representing a clear-cut indication for the ICD [2, 3]. In primary prevention, however, arrhythmic risk prediction proves extremely challenging, due to the low event rate and low positive predictive accuracy of risk factors identified to date. Current recommendations include individual multiparametric assessment comprising age, family history of sudden death, unexplained syncope, multiple-repetitive non-sustained ventricular tachycardia, elevated LV outflow gradients (at rest or during Valsalva maneuver), massive LV hypertrophy, abnormal pressure response to exercise, and complex genotype [2, 3, 5, 10].

Resting echocardiography provides a wealth of information in HCM patients [11] and adds to clinical risk stratification by identifying additional markers of risk such as massive LV hypertrophy (>30 mm), intraventricular obstruction (>30 mmHg), progressive wall thinning and declining systolic function over serial evaluations, and the presence of LV apical aneurysms [2, 3, 11]. Left atrial dilation and restrictive LV filling pattern may also help to identify high-risk subsets [12–19]. Recently, extensive intramyocardial fibrosis identified by CMR as late gadolinium enhancement has proven of some utility in predicting cardiovascular mortality, heart failure-related end points, and sudden cardiac death [19, 20] (Fig. 34.2).

Despite the wealth of clinical and pathophysiological information provided by genetic testing, clinical evaluation, and multiparametric imaging in resting conditions, stress echocardiography remains an essential step in patients with HCM, in order to assess a number of relevant features including functional capacity, presence and extent of provokable obstruction, myocardial ischemia, exercise-induced arrhythmias, coronary flow reserve, and blood pressure response to exercise (Table 34.1). All these informations represent a substantial contribution to clinical management and risk stratification [11, 20–34].

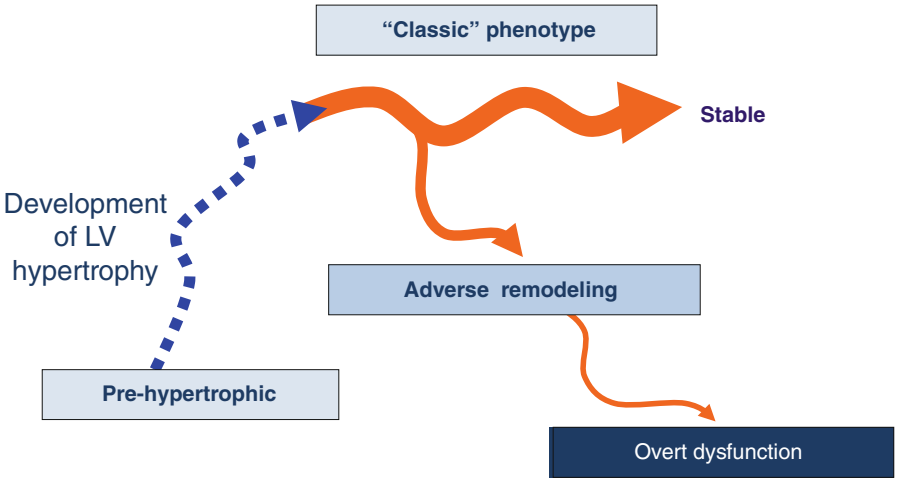

Fig. 34.1 Stages of hypertrophic cardiomyopathy. Thickness of the *orange lines* reflects prevalence of each stage in HCM cohorts. Prevalence of non-hypertrophic HCM is unknown (From Olivotto et al. [10])

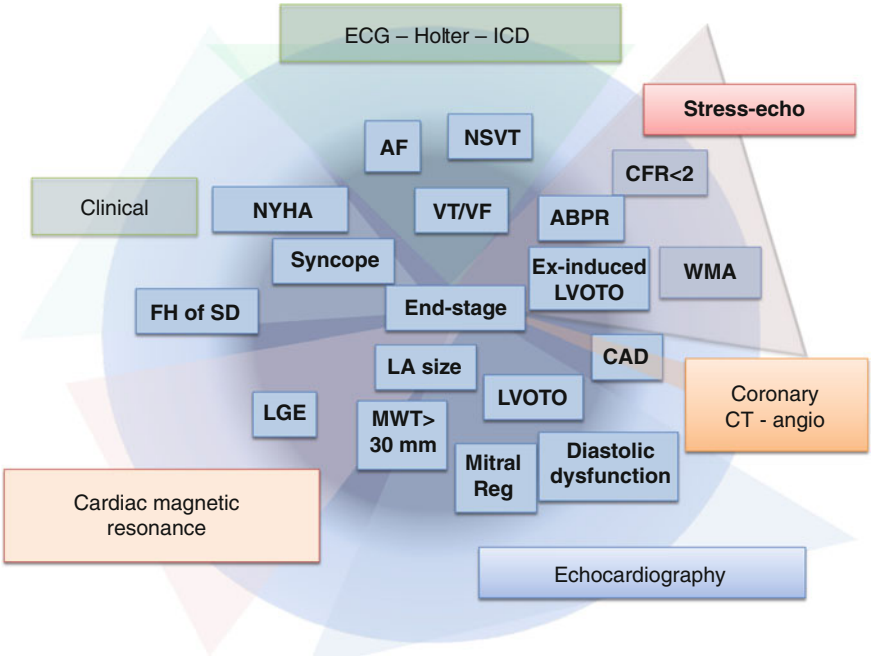

Fig. 34.2 Contribution of stress echocardiography to risk stratification in hypertrophic cardiomyopathy. All listed features have been shown or suspected to predict adverse outcome in HCM. *Abbreviations*: *ABPR* abnormal blood pressure response to exercise, *AF* atrial fibrillation, *CAD* coronary artery disease, *CFR* coronary flow reserve, *FH* family history, *ICD* implantable cardioverter defibrillator, *LA* left atrial, *LGE* late gadolinium enhancement, *LVOT obstruction* left ventricular outflow tract obstruction, *NYHA* New York Heart Association functional class, *MWT* maximum wall thickness, *NSVT* non-sustained ventricular tachycardia, *WMA* wall motion abnormalities, *Reg* regurgitation, *SD* sudden death, *VT/VF* ventricular tachycardia/fibrillation

Table 34.1 Clinically relevant information derived from stress echocardiography in HCM

Evaluation of SAM LVOT gradients and functional mitral regurgitation
Assessment of blood pressure response to exercise
Evaluation of exercise-induced arrhythmias
Exclusion of chronotropic incompetence (in patients treated with AV node blockers)
Tailored lifestyle recommendations and indications for appropriate level of activity, including clearance for noncompetitive sports in active individuals
Functional evaluation in end-stage disease (associated with VO2 measurement)
Exclusion/assessment of mid-ventricular obstruction
Exclusion/assessment of right ventricular outflow obstruction
Assessment of heart rate recovery
Evaluation of clinical relevance of coronary myocardial bridging
Exclusion/assessment of associated conditions including atherosclerotic coronary artery disease

34.2 Pathophysiology

Clinical and hemodynamic response to exercise or pharmacological stress in HCM is complex, resulting from the interplay of diastolic dysfunction, microvascular ischemia, dynamic obstruction, and functional mitral regurgitation. Symptoms and signs of myocardial ischemia are often found in patients with HCM, in the presence of angiographically normal coronary arteries, reflecting microvascular disease exacerbated by left ventricular hypertrophy and dynamic obstruction (Fig. 34.3) [33–37]. Nevertheless, typical angina on effort associated with ECG changes and wall motion abnormalities may suggest epicardial coronary artery stenosis or, in younger patients, tunneling of the LAD [31, 38, 39].

Myocardial ischemia is primarily due to extensive remodeling of the intramural coronary arterioles and blunted coronary artery reserve, occurring not only in the hypertrophied septum but also in the less hypertrophied left ventricular free wall [35, 36]. However, intrinsic molecular abnormalities of the cardiomyocyte, such as enhanced late sodium current leading to cytoplasmic calcium overload, have been shown to play an important role by increasing oxygen demand [40]. Microvascular ischemia is believed to contribute to the most severe manifestations of HCM including ventricular arrhythmias, sudden death, and progressive left ventricular

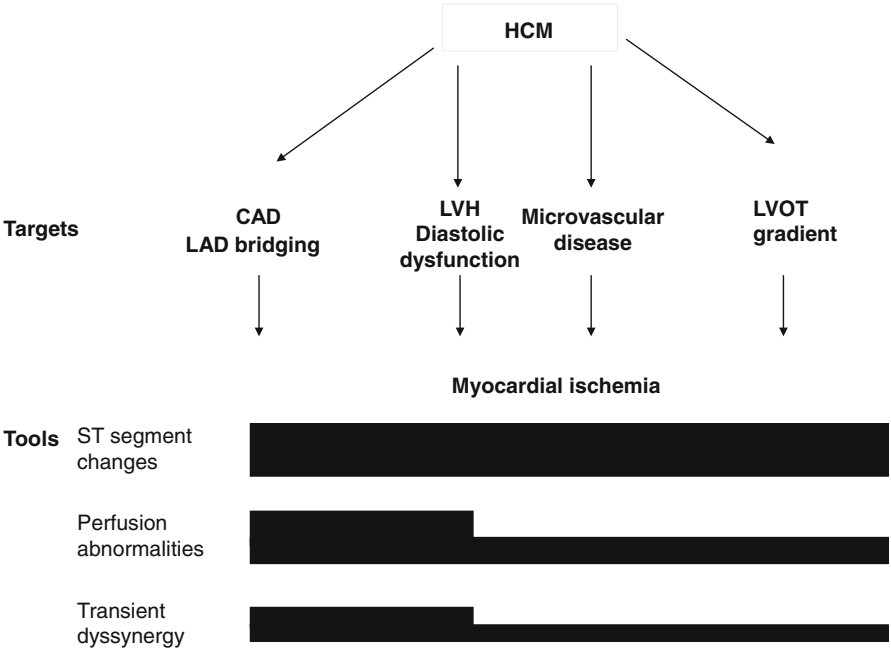

Fig. 34.3 The four main pathways to myocardial ischemia in hypertrophic cardiomyopathy (HCM): epicardial coronary artery disease (CAD), left ventricular hypertrophy, microvascular disease, and intraventricular dynamic obstruction. All four mechanisms may induce a reduction in coronary flow reserve; wall motion abnormalities are less likely—but still present—with non-CAD pathways

remodeling, and the degree of microvascular dysfunction is an independent predictor of long-term deterioration and death from cardiovascular causes [36, 37]. As in other models of microvascular disease, such as cardiac syndrome X or arterial hypertension [36, 41], ST segment changes and perfusion abnormalities are frequently elicited during stress in HCM patients, representing reduced flow reserve and true subendocardial underperfusion [35]. However, inducible wall motion abnormalities are rare and remain a more specific hallmark of epicardial coronary artery disease [31], with clear adverse prognostic meaning [42]. The concomitant presence of CAD, particularly when severe, identifies a subset of potential candidates for revascularization who are at particularly high risk of severe outcomes [38]. Of note, the absence of wall motion abnormalities does not necessarily contradict the ischemic nature of chest pain and ST segment depression in HCM patients. Rather, because of the largely subendocardial nature of ischemia, as well as the considerable LV wall thickness, the degrees of transmural involvement are less likely to reach the critical mass of ischemic tissue needed to determine wall motion and thickening abnormalities [41].

Intraventricular obstruction is an additional mechanism of ischemia, determining a disproportionate increase in oxygen demand and reduction in subendocardial flow supply due to increased extravascular resistances [25, 35, 36]. Most HCM patients have the propensity to develop intraventricular gradients under resting or physiologically provokable conditions. Such dynamic obstruction generally occurs at the LV outflow, produced by systolic anterior motion of the mitral valve causing ventricular septal contact [25, 43–45]. LV outflow obstruction is a pathophysiological conspiracy caused by the concomitance of marked mitral leaflet elongation, hyper-contractile small or normal-sized LV, abnormally positioned papillary muscles, small LVOT dimensions, and abnormally directed anterograde flow in systole due to septal hypertrophy, leading to systolic anterior motion (SAM) of the mitral valve (Fig. 34.4) [43–45].

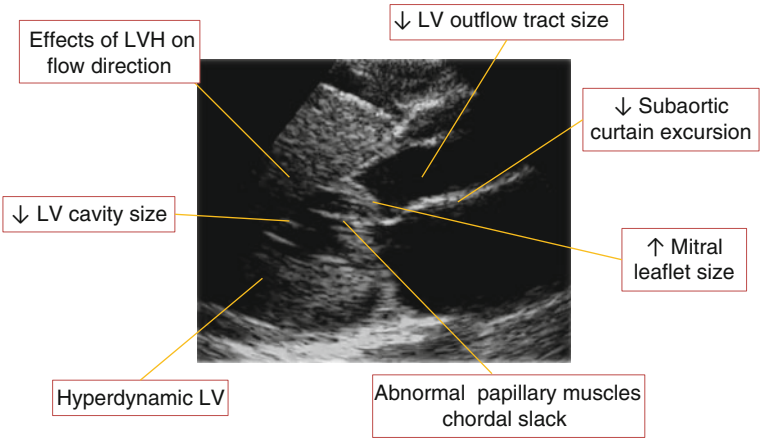

Fig. 34.4 LVOT obstruction is a pathophysiological conspiracy in HCM, resulting from the interplay of a constellation of different features, highlighted in the figure. *LV* left ventricle, *LVH* left ventricular hypertrophy

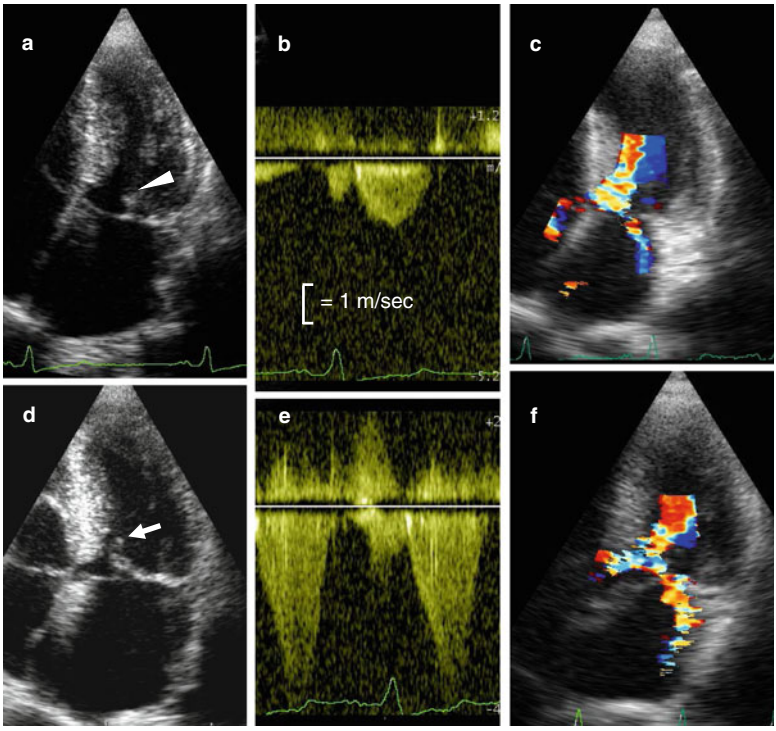

Fig. 34.5 Exercise-induced obstruction in patients with HC. (**a**) Apical five-chamber long-axis view at end systole with only mild systolic anterior motion (SAM) (*arrowhead*), (**b**) continuous-wave Doppler image showing normal LV outflow tract velocity (1.8 m/s), and (**c**) SAM-related posteriorly directed mild mitral regurgitation jet, all images obtained at rest. (**d**) SAM with septal contact (*arrow*), (**e**) corresponding continuous-wave Doppler velocity of 5 m/s (i.e., 100-mmHg gradient), and (**f**) substantial increase in magnitude of functional, laterally directed mitral regurgitation, all obtained at peak exercise in identical view (From Nistri et al. [48])

SAM is in turn associated with variable degrees of functional (SAM-related) mitral regurgitation, due to loss of leaflet coaptation, which is mid-to-late systolic and inferolaterally oriented. In the elderly, posterior mitral annulus calcification, anteroposition of the mitral apparatus, and sigmoid septal morphology with decreased septal-aortic angle increases the likelihood of SAM and obstruction, which may develop in previously unobstructed patients [43]. Due to its dynamic nature, the severity of SAM-related mitral regurgitation varies with the degree of LVOT obstruction, may increase significantly during effort, and represents a main determinant of symptoms (Fig. 34.5) [1–3, 5, 6].

Finally, dynamic obstruction may occur at different sites besides the LVOT, including the LV mid-ventricle (due to interposition and septal contact of the anterior papillary muscle) and the RVOT (due to a sphincter-like mechanism occurring at the level of the crista supraventricularis) [43]. Fixed, anatomic obstruction due to sub-aortic membranes should be carefully excluded. Each of these mechanisms should be systemically assessed, since management strategies may differ, particularly when

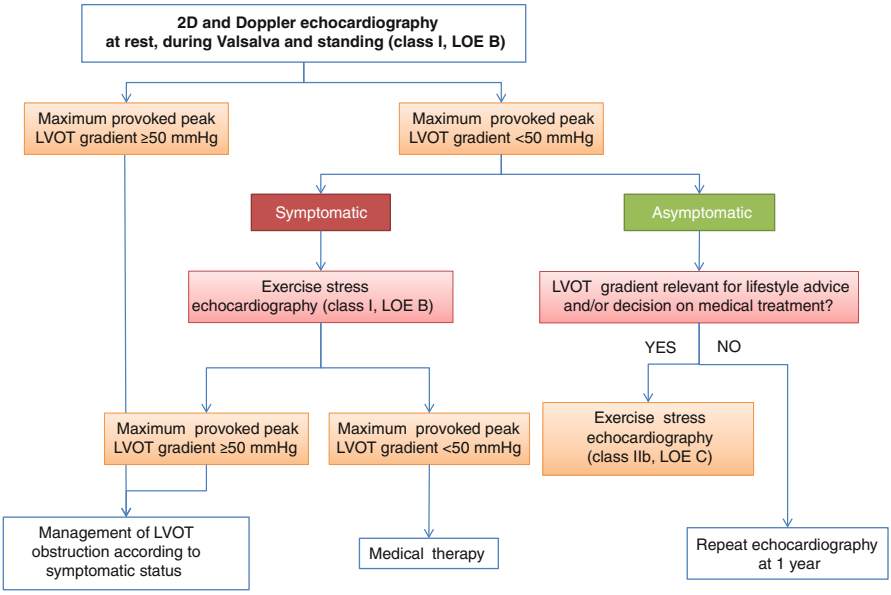

Fig. 34.6 Protocol for the assessment and treatment of left ventricular outflow tract obstruction from the 2014 European Society of Cardiology guidelines on diagnosis and management of hypertrophic cardiomyopathy. *LOE* level of evidence, *LVOT* left ventricular outflow tract (Modified from Elliott et al. [2])

interventions aimed at relieving LVOT obstruction are considered [2, 3]. Dynamic assessment of LVOT obstruction (at rest and during bedside maneuvers and exercise) holds important prognostic information and plays a pivotal role for the assessment of symptoms [2, 3]. The recent ESC guidelines on diagnosis and management of HCM provided a Class I recommendation for two-dimensional and Doppler echocardiography during a Valsalva maneuver in the sitting and semi-supine position—and then on standing if no gradient is provoked—in all HCM patients [2].

By convention, LVOT obstruction is defined as an instantaneous peak Doppler LV outflow tract pressure gradient ≥30 mmHg at rest or during physiological provocation (i.e., Valsalva maneuver, standing, and isotonic exercise). A gradient of ≥50 mmHg is usually considered the threshold at which LVOT obstruction becomes hemodynamically important and invasive treatment may be appropriate [2, 3]. Up to one-third of patients have obstruction at rest (peak instantaneous gradient >30 mmHg); another one-third have labile, physiologically provoked gradient (<30 mmHg at rest and physiologically provoked gradient >30 mmHg); and only one-third have true nonobstructive forms (rest and physiologically provoked gradient <30 mmHg) [25]. Provokable gradients may characteristically peak after cessation of exercise, due to the effects of the ensuing fall in peripheral resistance (Fig. 34.6).

Of note, while not all patients with HCM have LVOT gradients, it is also true that not all subjects with stress-induced gradients have HCM. Significant gradients can be observed during exercise or dobutamine stress in patients with syndrome X or hypertension, athletes, takotsubo syndrome, congenital heart diseases following

cardiac valve surgery, or acute myocardial infarction and can be precipitated by dehydration, reduction in preload and LV cavity size, and/or increase in LV contractility [46, 47].

34.3 Clinical Indications of Stress Exercise

Stress testing is very safe in HCM patients, even in the presence of resting LVOT obstruction [26, 27]. As a general rule, exercise testing is preferable to pharmacological stress in HCM patients, due to the high prevalence of false-positive findings in the latter, in terms of provokable obstruction, as well as the uncertain relevance of pharmacologically induced gradients to physiological conditions and patients' symptoms [2, 25]. The 2014 ESC guidelines suggest that "exercise stress echocardiography is recommended in *symptomatic* patients if bedside manoeuvres fail to induce LVOT obstruction ≥50 mmHg" [Class I, level of evidence (LOE) B] (Fig. 34.7) [2].

However, stress echocardiography, particularly when based on physiological exercise, provides useful information in virtually all HCM patients and is offered routinely at our centers unless the acoustic window is poor or the individual is clinically unstable or unable to exercise. In subjects with unfavorable profile and congestive symptoms, exercise echocardiography may provide essential clues with regard to arrhythmic risk, disease progression, presence of comorbidity, response to

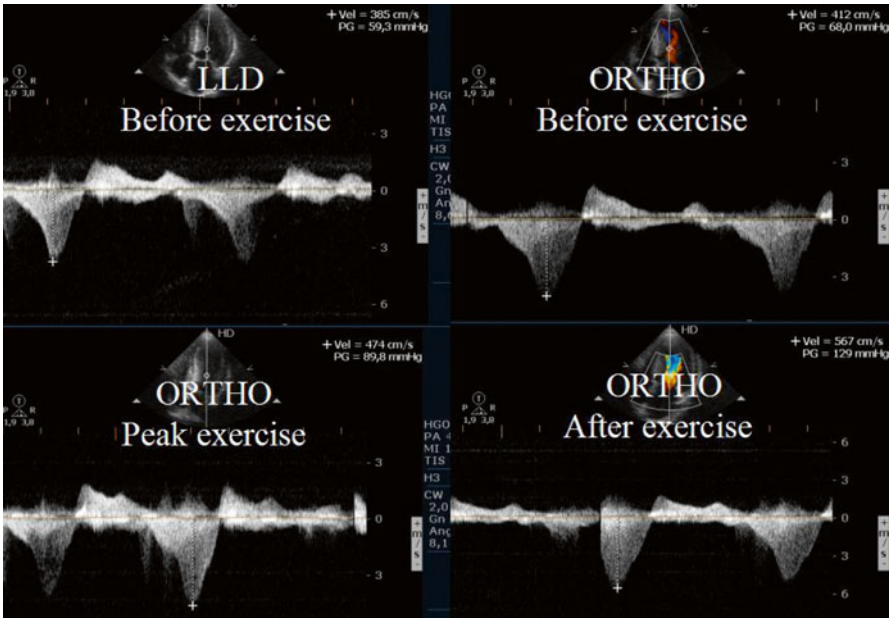

Fig. 34.7 Left ventricular outflow tract peak gradient during exercise in a symptomatic athlete. The gradient is more obvious in orthostatic position at peak exercise (*right upper panel*, 136 mmHg after 12 min of exercise) and early recovery phase (*left lower* and *middle panels*, 159 mmHg) and immediately disappears in the left lateral decubitus position after exercise (*right lower panel*) (From Dimitrow et al. [47])

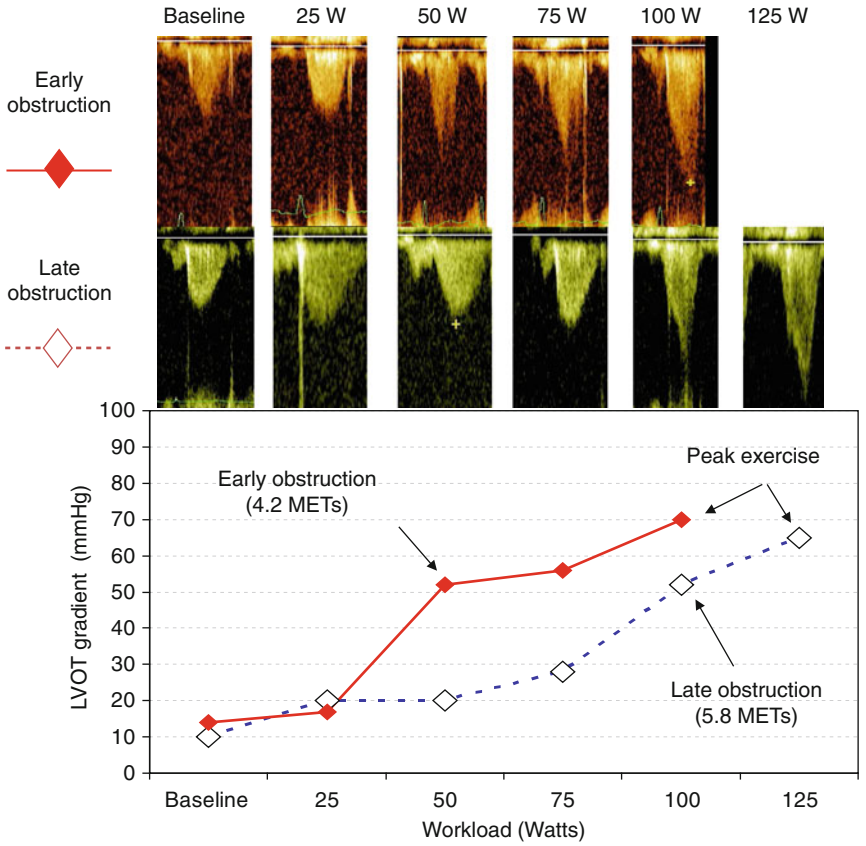

Fig. 34.8 Patterns of gradient provocation with exercise. In a 45-year-old patient with early obstruction (*solid line* and *red squares*), a 55-mmHg inducible gradient was measured at 50 W (4.2 METs). Exercise was terminated at 100 W (5.8 METs) because of dyspnea associated with a peak upright gradient of 70 mmHg; the peak post-exercise supine gradient was 87 mmHg. In a 47-year-old patient with late obstruction (*broken line* and *white squares*), a 52-mmHg gradient was induced at 100 W (5.8 METs). Exercise was terminated at 125 W (78.5 METs) because of fatigue when the gradient had increased to 65 mmHg; peak post-exercise supine gradient was 85 mmHg (From Dimitrow et al. [47])

treatment, and potential indication to advanced options such as transplant. Provokable obstruction, in patients who are nonobstructive at rest, may be useful in predicting symptomatic progression and outcome [26–28].

In *asymptomatic*, active HCM patients who are nonobstructive at rest and have none of the established risk factors, a negative stress echocardiography serves the purpose of confirming a favorable clinical profile and provides reassurance with regard to physical activity and other lifestyle issues such as pregnancy (Table 34.1). Exercise echocardiography proves very useful in this context to provide tailored advice regarding safe levels of exertion (depending on the workload at which SAM develops; Fig. 34.8) [48], as well as response to pharmacological or invasive treatment in reducing incidence and severity of exercise-induced LVOT gradients (Fig. 34.9) [49].

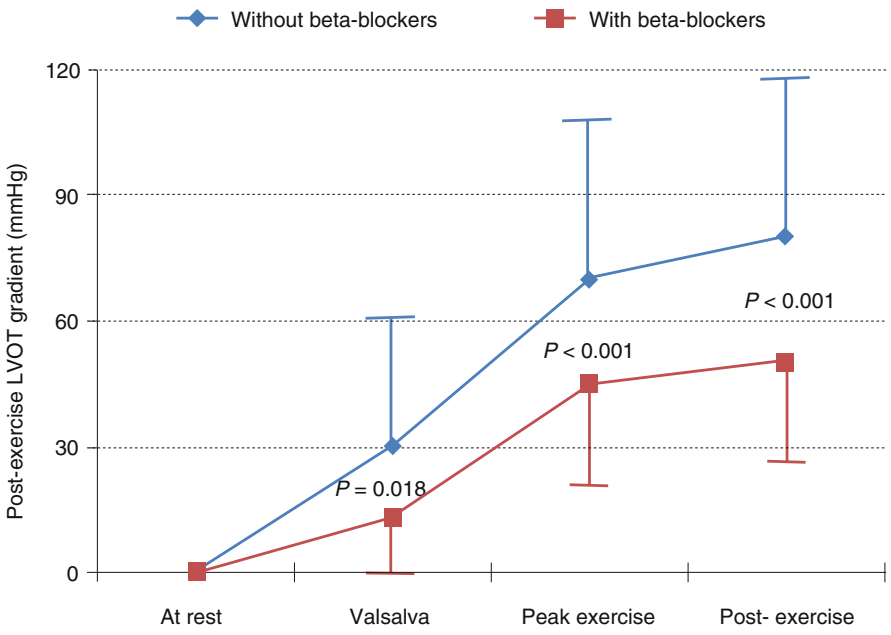

Fig. 34.9 Left ventricular outflow tract (*LVOT*) gradients at rest, with Valsalva maneuver, at peak exercise and post-exercise, at initial exercise echo (*solid blue line*) and on beta-blockers (*dotted red line*). *Squares* and *vertical lines* indicate mean and SD at each step for the 27 study patients (From Nistri et al. [49])

Furthermore, HCM patients who self-report as being asymptomatic often exhibit significant exercise limitation, to which they have grown accustomed, requiring appropriate investigation [10]. The ESC guidelines suggest that exercise echocardiography may be considered also in asymptomatic patients with a resting or provoked—during Valsalva maneuver in the standing, sitting, or semi-supine positions—peak LVOT gradient of <50 mmHg, when the presence of an LVOT gradient is relevant to lifestyle advice and decisions on medical treatment (Class IIb, LOE C). As an alternative, nitrate challenge should be considered in patients who cannot perform physiological exercise [2].

34.4 Interpretation of Findings

Based on the specific pathophysiological background, stress echocardiography is the key in identifying a number of markers of risk in HCM patients (Table 34.1), including: (1) de novo provocation or exacerbation of dynamic LVOT pressure gradients, (2) blood pressure response to exercise, (3) exercise-induced arrhythmias, (4) transient regional wall motion abnormalities, (5) heart rate recovery, and (6) reduction in coronary flow reserve.

As previously discussed, dynamic obstruction occurring at the LVOT and/or mid-ventricular level is common in active HCM patients and is a main

determinant of exercise limitation and symptoms [2, 3, 10, 25, 48]. Remarkably, severe provokable obstruction, occasionally leading to surgical myectomy or alcohol septal ablation, may be unsuspected at routine echocardiographic evaluation, due to total lack of SAM in resting conditions [25]. Thus, in the absence of adequate evaluations by exercise echocardiography, the cause of symptoms may be misinterpreted and an opportunity for effective treatment missed. An exercise-induced gradient greater than 50 mmHg is generally considered of "surgical" interest when associated with drug refractory symptoms [2, 3]. Dynamic gradients increase during effort and may persist or even increase during (early) recovery, following a fall in systemic resistance [30, 48]. However, a subset has been recently described in which a paradoxical reduction in gradient is observed with effort, associated with preserved functional tolerance and favorable clinical profile [50] (Fig. 34.10).

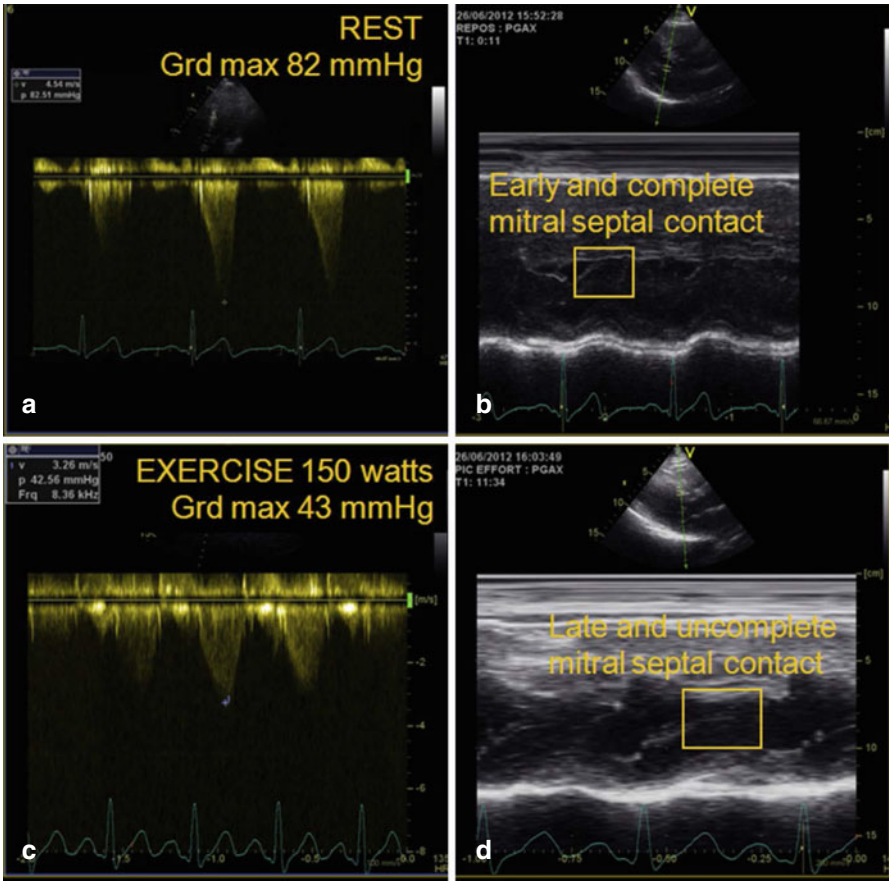

Fig. 34.10 Paradox LVOT obstruction response to exercise. In this asymptomatic HCM patient with resting obstruction of 82 mmHg (**a**, **b**), a decrease to 43 mmHg was observed during exercise, resulting in excellent exercise tolerance (150 W) (**c**, **d**) (From Lafitte et al. [50])

Several factors influence the impact of provokable obstruction on functional capacity and symptoms, including precocity of gradient onset, degree of associated mitral regurgitation, time from last meal or alcohol consumption, and concomitant presence of mid-ventricular obstruction [2, 3, 5, 43, 48]. Of note, β-blockade is capable of blunting provokable obstruction and improving exercise capacity in HCM patients [49].

Abnormal blood pressure response (ABPR) to exercise is defined as exercise-induced hypotension (any decrease in systolic blood pressure below baseline in the absence of an initial rise with exercise, or a sustained decrease of >20 mmHg during exercise following an initial rise) or failure to increase blood pressure (a systolic blood pressure rise of less than 20 mmHg from baseline) [51–54]. ABPR is observed up to one-quarter of HCM patients and is believed to identify hemodynamic instability secondary to LVOT obstruction, diastolic dysfunction, microvascular ischemia, and inappropriate peripheral vasodilatation, representing an independent predictor of sudden cardiac death [51–54]. Whether therapeutic interventions such as surgical myectomy, alcohol septal ablation, or pharmacological therapy may consistently resolve ABPR and whether this in turn may translate into a survival benefit is as yet unresolved. Exercise-induced hypotension is an indication for interruption of stress testing and may require positioning the patient in the supine or Trendelenburg position when symptomatic.

Exercise-induced ventricular arrhythmias are uncommon in HCM patients but, when present, predict major arrhythmic events. In a large study of 1380 patients referred to a cardiomyopathy clinic in London, only 27 had NSVT, and three had ventricular fibrillation during exercise. In multivariable analysis, exercise NSVT/VF was independently associated with a threefold independent increased risk of sudden death or appropriate ICD discharge [55]. The clinical relevance of ventricular arrhythmias in HCM is inversely related to age and should be considered with particular suspicion in the pediatric/adolescent age group [15].

For the purposes of noninvasive identification of concomitant coronary artery disease, wall motion abnormalities in HCM patients are equally sensitive and substantially more specific than perfusion abnormalities and ST segment depression but may suffer from false-positive responses especially in the presence of marked hypertrophy and with exercise and dobutamine stress [31, 34]. Stress echocardiography based on wall motion abnormalities is therefore more convenient than perfusion-based testing, as patients with inducible wall motion abnormalities will have the greatest benefit from an ischemia-driven revascularization. After ruling out wall motion abnormalities (and therefore functionally significant underlying coronary artery disease), stress echocardiography may offer invaluable information regarding coronary flow reserve and underlying microvascular disease [32, 33]. With a last-generation "two birds with one stone" protocol, both function and coronary flow reserve can be caught with a single stress (accelerated, fast high-dose dipyridamole). A reduced coronary flow reserve and/or flow maldistribution during stress identify a relatively higher-risk subgroup, even in the absence of inducible wall motion abnormalities [32, 33]. Stress-induced ischemic-like electrocardiographic changes, in the absence of wall motion abnormalities, may also be related to syncope and/or subsequent LV dilatation in adult patients with HCM and normal

coronary arteries [31]. Of note, in survivors of cardiac arrest and in patients with sustained ventricular tachyarrhythmias or severe angina, the ESC guidelines recommend performing coronary angiography (Class I, LOE C) irrespective and independent of stress echo results. Furthermore, invasive or CT coronary angiography should be considered in patients with typical exertional chest pain (Canadian Cardiovascular Society Class <3) and an intermediate pretest probability of atherosclerotic coronary artery disease (Class IIa, LOE C). Finally, invasive or CT coronary angiography should be considered in adult patients before invasive septal reduction therapy (Class IIa, LOE C) [2].

Heart rate recovery (HRR) following exercise is a product of vagal reactivation and sympathetic withdrawal [56]. Impairment of HRR after cardiopulmonary exercise testing is associated with increased risk of cardiovascular outcomes and all-cause mortality in the general population [57]. In a recent study, patients with HCM showed lower HRR compared to normal controls, after normalization to peak heart rate. Heart rate at 3 min following cessation of exercise significantly correlated with peak left ventricular outflow tract gradient and remained a significant predictor of HRR after multivariable analysis [58]. Whether the degree of HRR impairment, likely reflecting sympathetic predominance, may predict adverse outcome in HCM patients remains unresolved.

Overall, stress echocardiography has great potential for noninvasive detection of CAD and microvascular disease, which might be combined with the more established assessment of LVOT gradient, mitral insufficiency, and diastolic function to titrate risk in HCM patients, ranging anywhere between low risk (no gradient, no wall motion, normal coronary flow reserve, no mitral insufficiency) and high risk (significant gradient, inducible wall motion abnormalities, reduced flow reserve, severe mitral insufficiency), with all intermediate responses. Larger evidence bases are needed at this point to translate the scientific potential into a solid clinical flowchart.

34.5 Stress Echo in Genotype-Positive, Phenotype-Negative Subjects

Genetic counseling is recommended in all patients when HCM cannot be explained solely by a non-genetic cause, to enable cascade genetic testing of their relatives [2]. Relatives of HCM probands in whom causative mutations have been detected may display no or minimal phenotype. Recent studies suggest a benign clinical course for most clinically unaffected mutation carriers. Moreover, the clinical significance of mild, "early" morphological, and functional abnormalities detected in these individuals is uncertain but probably minor in most cases [2, 9, 59]. In one study, dynamic echocardiographic evaluation elicited latent obstruction in genotype-positive, phenotype-negative subjects [60]. Similar to HCM patients with overt phenotype, the highest and sometimes only significant gradients occurred at immediate recovery in the upright position [60]. The most plausible explanation for the development of obstruction in the absence of hypertrophy lies with the abnormally increased mitral valve leaflet dimensions, now recognized as a primary feature of

the disease [61, 62]. These structural abnormalities of the mitral valve may be related to developmental mechanisms involving the pro-epicardium [63].

34.6 Technical Issues and Pitfalls

In the vast majority of HCM patients, stress testing can be performed safely, including those with elevated LVOT gradients at rest who are normotensive and have no history of hemodynamic instability on effort. In fact, while HCM has long been considered a relative contraindication to stress testing, it is now well established that echocardiography during physiological exercise has minimal risk when performed in a controlled, supervised environment [2, 26, 27]. Nevertheless, in a subset of HCM patients, stress testing is not feasible or advisable, due to the inability to exercise, severe congestive symptoms (NYHA Class $\geq$ III), hemodynamic instability associated with elevated LVOT gradients at rest, known effort-induced arrhythmias, or severe comorbidities [20]. Conversely, acoustic window quality is rarely a problem, given the young mean age of patients with HCM.

Since many factors may affect LVOT gradient evaluation, a standardized approach is essential in order to have meaningful and comparable results across different laboratories. Indeed, different exercise modalities have been described in the literature, including semi-supine ergometer, treadmill (with image acquisition either during exercise or at peak and supine immediately after exertion), and upright bicycle, with imaging during exercise, at peak upright and immediately after exertion, upright, and supine. The semi-supine exercise is a reasonable alternative, although cardiac symptoms in these patients are noted most commonly when they are in the erect position, during or immediately after exertion, as already noted in the early description of the disease [1]. Substantial agreement between the magnitude of outflow gradients measured at the final step of the exercise test in the upright position and those gradients obtained in the supine position immediately following cessation of exercise has been reported, with post-exercise supine gradients overestimating somewhat the upright gradients on the average of 5 mmHg for the study group [48]. In the same study, moreover, with real-time monitoring of LV outflow tract velocities during physiologic exercise, the timing of onset of obstruction was shown to dictate the degree to which exercise capacity was impaired in HCM patients with provokable gradients [48]. Consistently, it has been suggested that the most effective way to unmask a labile gradient is to perform echo monitoring while exercising in the upright position and immediately post-exercise in upright. This approach can be applied not only to HCM but also to other groups, such as athletes [47], in whom after an inconclusive exercise ECG, the test of choice is exercise echo. In fact, owing to radiation exposure and the young age of most athletes, the use of cardiac CT and nuclear cardiology should be restricted to athletes with unclear stress echo or CMR [64]. There are, however, relatively few data comparing the different protocols. As such, the ESC guidelines suggest that "laboratories should develop and validate their own protocol and ensure that staff are properly trained in the procedure." A protocol proposal is shown in Fig. 34.11: care should be given to assessing degree of obstruction, mitral regurgitation, diastolic dysfunction, wall motion

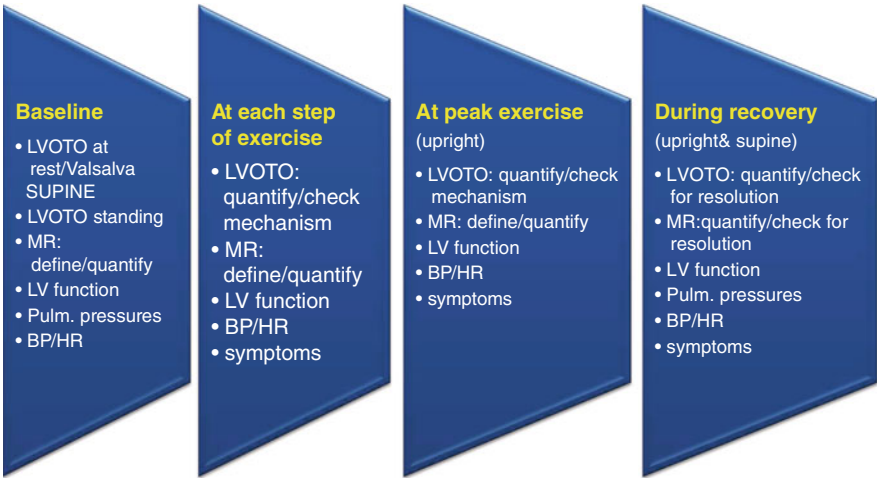

Fig. 34.11 Proposed protocol for exercise echocardiography in HCM (upright bicycle or treadmill). *BP* arterial blood pressure, *HR* heart rate, *LVOT obstruction* left ventricular outflow tract obstruction, *MR* mitral regurgitation

abnormalities, and pulmonary pressures at each step [65]. A frequent pitfall during effort involves the possibility of sampling MR instead of LVOT. Therefore, the utmost care should be employed to avoid this source of misinterpretation [25].

Table of Contents Video Companion

See illustrative case number 41, by Carlos Cotrim, MD, Lisbon, Portugal. Springer Extra Materials available at http://extras.springer.com/2015/978-3-319-20957-9

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Stress Echocardiography After Cardiac Transplantation

35

Leyla Elif Sade and Eugenio Picano

35.1 Background

Cardiac transplantation is an increasingly important treatment for end-stage cardiac disease, but rejection continues to be a major complication [1]. Rejection can be either acute or chronic (Table 35.1). Acute rejection is a major problem in the first year following cardiac transplantation. It is characterized by subtle or overt myocardial dysfunction, with normal epicardial coronary arteries. However, the coronary flow reserve, a pathophysiological hallmark of microvascular disease (as has been described in other situations such as syndrome X or hypertension with normal coronary arteries [2, 3]), may be impaired, particularly in severe rejections [4, 5]. In particular, during acute cardiac rejection, the reversible reduction of coronary reserve could be the result of the limitation of vasodilatation due to functional abnormalities such as metabolically or immunologically related decreased responsiveness of the vascular wall to vasodilator stimuli or to structural abnormalities, such as interstitial edema or cellular infiltration [4]. Immunosuppressive treatment can resolve structural and functional abnormalities and restore the normal coronary flow reserve [4].

Cardiac allograft vasculopathy (CAV) is the chronic manifestation of rejection and is a major factor limiting long-term prognosis after heart transplantation [1]. In several respects, the disease differs from atherosclerotic coronary artery disease. The mechanism is thought to be immune mediated. Higher coronary flow velocities at rest together with blunted hyperemic flow responses are detected in patients with CAV [6, 7]. After transplantation, there is an increase in microvascular resistance due to changes in myogenic tonus and intimal thickening [8, 9]. Patients with increased resistance develop greater decreases in fractional flow reserve and increases in plaque volume [8, 10]. In addition, CAV is characterized by endothelial dysfunction and smooth muscle cell proliferation in the intima [11], and there is characteristic inappropriate negative remodeling with progressive diffuse intimal thickening that leads to loss of luminal caliber, which decreases vascular compliance [12]. More focal, localized stenosis can also develop [13, 14] even without warning angina due to denervation. Small-vessel disease is also common and contributes to the reduction in

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Table 35.1 Heart transplant rejection

	Acute	Chronic
Pathological changes	Edema, cellular infiltrates, myocyte damage	Diffuse coronary artery wall thickening (with focal stenosis)
Diagnostic gold standard	Endomyocardial biopsy	Intracoronary ultrasound (coronary angiography)
Reversibility upon treatment	Yes	No
Rest echocardiography	Increase wall thickness/texture/ decrease in ejection fraction	Segmental abnormalities, decreased systolic thickening
Coronary flow reserve	May be reduced	Reduced
Stress echocardiography	May be abnormal	Abnormal

coronary flow reserve [15–17] and unfavorable outcome [18, 19]. The disease may develop rapidly within months and the clinical diagnosis of CAV is difficult with several noninvasive techniques [20–24]. Annual coronary angiography remains the most common approach to monitoring the development and progression of CAV. Nevertheless, mild degrees of CAV may remain undetected by angiography [13, 25]. Using intravascular ultrasound (IVUS), which is considered the reference standard for diagnosing CAV, up to 75 % of all heart transplantation patients have some evidence of CAV at 1 year, but only 10–20 % by angiography [26].

Pharmacological stress echocardiography modalities are preferred over exercise stress echocardiography in heart transplantation patients due to the blunted chronotropic response to physical exercise as a result of cardiac denervation [20, 22]. As pharmacological stimulation agents, dobutamine, dipyridamole, and adenosine are all safe in heart transplant patients. Heart transplantation patients exhibit an augmented chronotropic response to beta-adrenergic stimulation by dobutamine and a poor response to atropine because transplantation-related ventricular denervation results in upregulation of beta-adrenergic receptors and downregulation of muscarinic receptors [27].

35.2 Pharmacological Stress Echo for Detection of Acute Rejection

The main resting transthoracic echocardiographic variables proposed for diagnosis of acute allograft rejection include increased wall thickness and wall echogenicity, pericardial effusion, left ventricular diastolic dysfunction, and regional or global systolic dysfunction [28–31]. More recent modalities including tissue Doppler and strain imaging as well as speckle tracking are encouraging, but there is a lack of consistency between the results of different studies, and there is overlap between the findings in nonrejection and rejection groups [32–34]. In general, the results have not been reproducible, sensitive, and specific enough, and no single echocardiographic variable alone can be used for accurate and reliable detection of acute allograft rejection [28, 34].

During acute rejection, coronary flow reserve can be acutely impaired with or without transient ST-segment depression and wall motion abnormalities during stress [35]. Early microvascular dysfunction has been found to be associated with the history of rejection and underscores the importance of immune mechanisms [5, 36]. It is well

known that antibody-mediated rejection targets the endothelium of small vessels. However, the potential role of coronary flow reserve for the diagnostic evaluation of acute allograft rejection needs further investigation. Rest and stress echocardiography remain particularly insensitive in mild degrees of acute rejection [5, 28]. On the other hand, in patients with normal coronary angiography, and without significant intimal hyperplasia in vessels visualized by IVUS, wall motion abnormalities can be detected by dobutamine stress echocardiography in around 10 % of the patients [25]. However, dobutamine stress echocardiography does not allow us to discriminate whether the impairment of myocardial function is due to myocardial damage, interstitial fibrosis, or microcirculatory dysfunction. Inducible wall motion abnormalities that are not related to vasculopathy are transient and have a more benign course [37, 38].

35.3 Pharmacological Stress Echo for Detection of Chronic Rejection

CAV is the hallmark of chronic allograft rejection. Resting wall motion abnormalities can be detected in some of the patients with CAV; in other patients, pharmacological stress echocardiography is helpful to screen for CAV. Stress-induced wall motion abnormalities can be detected with pharmacological stress echocardiography using dipyridamole [39, 40] or dobutamine [37, 41–53] (Fig. 35.1).

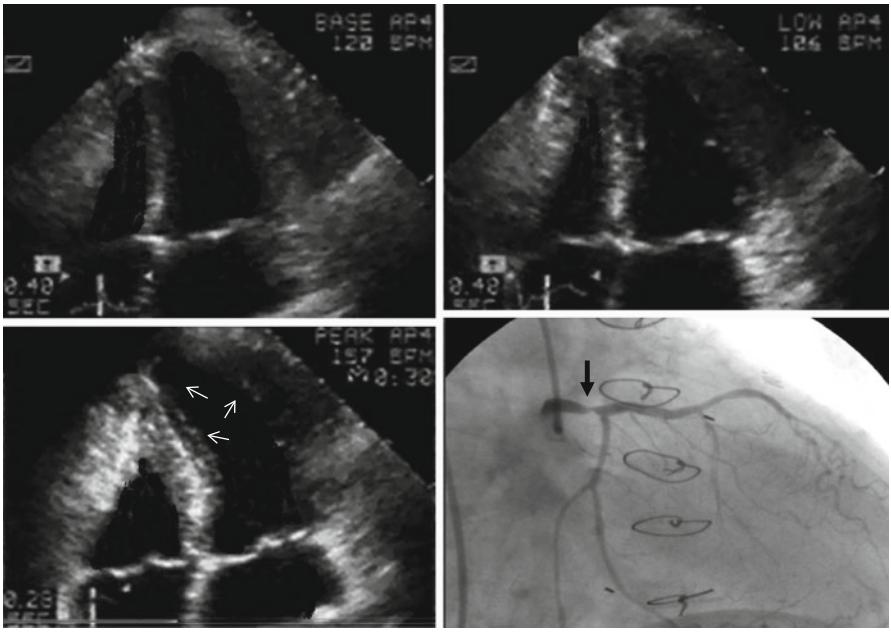

Fig. 35.1 Patients with no chest pain, 4 years after heart transplantation. Surveillance dobutamine stress echo revealed normal wall motion at rest (*left upper panel*, REST) and low dose (*right upper panel,* LOW DOSE), with severe wall motion abnormalities in the LAD and CX territories at peak dose (*left lower panel*, PEAK). Coronary angiography shows critical left main (*arrow*) coronary stenosis (*right lower panel*)

As in native coronary artery disease, both tests have a high feasibility rate and a low incidence of reported limiting side effects. The characteristic diffuse intimal proliferation with distal tapering of CAV may remain undetected by routine angiography. IVUS imaging detects significant intimal thickening in two thirds of the patients with apparently normal coronary angiograms [13, 25, 54]. One should consider that angiography is relatively insensitive in detecting CAV and that a normal angiogram in a heart transplant recipient does not exclude functionally relevant CAV [23, 38, 45, 54], which may be mirrored by functional abnormalities during stress (Figs. 35.2 and 35.3).

In a series systematically evaluating coronary angiography and intracoronary ultrasound, dobutamine stress echocardiography demonstrated wall motion abnormalities in 44–50 % of patients with a normal angiogram [25, 44]. If angiography is used as a reference method, these findings have to be interpreted as false-positive dobutamine stress tests and would therefore explain the relatively low specificity of the stress tests compared to angiography [41, 43, 44, 46]. Overall, dobutamine stress echocardiography has variable sensitivity and specificity ranging from 32 to 100 %, depending on the extent and severity of CAV and depending on the reference standard for CAV diagnosis (Table 35.2).

The assessment of coronary flow reserve (CFR) by transthoracic Doppler echocardiography as a means of determining both macrovascular and microvascular function has also been proposed as an alternative method for detecting CAV [6, 38, 55]. CFR can be impaired in early stages of the disease course before any coronary abnormality is discernible by coronary angiography. CFR measurements relate not only to epicardial vessel disease but also to the microcirculatory function, so the choice of the sample vessel does not affect the results [56]. Higher coronary flow velocities at rest together with blunted hyperemic flow responses are detected in patients with CAV [6, 7]. Coronary vasomotor capacity can be altered early because of functional or structural microvascular dysfunction as a consequence of immune-mediated microvascular damage, in the absence of flow-limiting stenosis in heart transplant patients [36, 57, 58]. Therefore, CFR appears to be highly sensitive and indicates CAV earlier than the angiographic evidence of CAV and earlier than dobutamine stress echo in most of the patients [38] (Fig. 35.4).

Thus, CFR helps to exclude CAV with confidence, and the combination of CFR with DSE can help diagnose CAV with good specificity [38]. Also, the use of contrast or quantification tools may be rewarding in increasing the accuracy of stress echocardiography for the diagnosis of CAV [6, 47, 49, 55].

A normal pharmacological stress echocardiography result after heart transplantation has a high predictive value for an uneventful clinical course [7, 37, 45, 53]. The value of the test seems to be at least comparable to that of a normal angiogram, and a normal pharmacological stress test has high negative predictive value (in most studies >90 %) that allows invasive diagnostic procedures to be safely delayed [7, 37, 40–43, 45, 50], especially if coronary flow reserve detectable by transthoracic

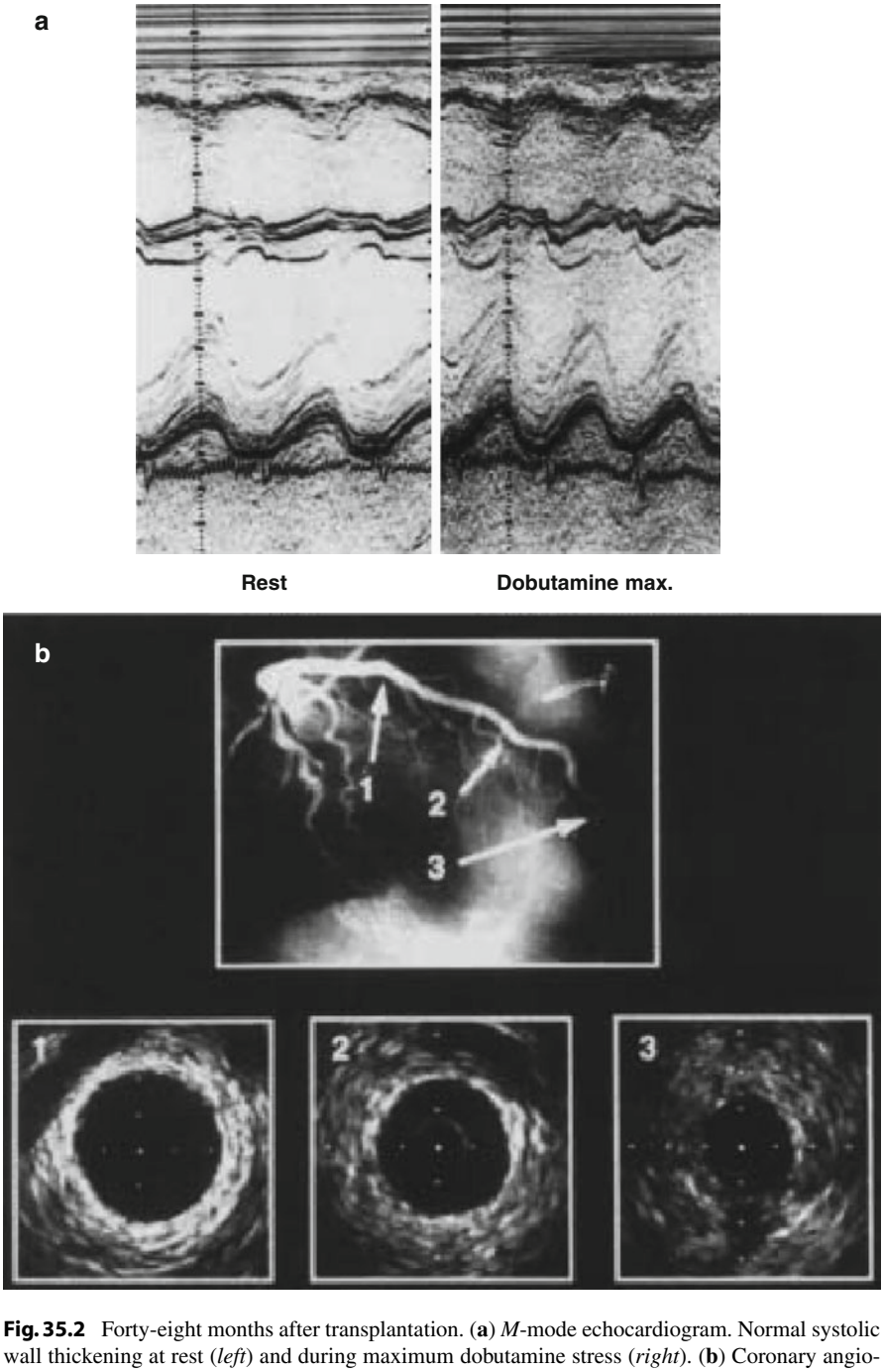

Fig. 35.2 Forty-eight months after transplantation. (**a**) *M*-mode echocardiogram. Normal systolic wall thickening at rest (*left*) and during maximum dobutamine stress (*right*). (**b**) Coronary angiogram and intravascular ultrasound (IVUS). Normal left coronary artery by angiography. Absence of significant intimal hyperplasia at three sites (*arrows*) of the left anterior descending artery by IVUS (From Ref. [44], with permission)

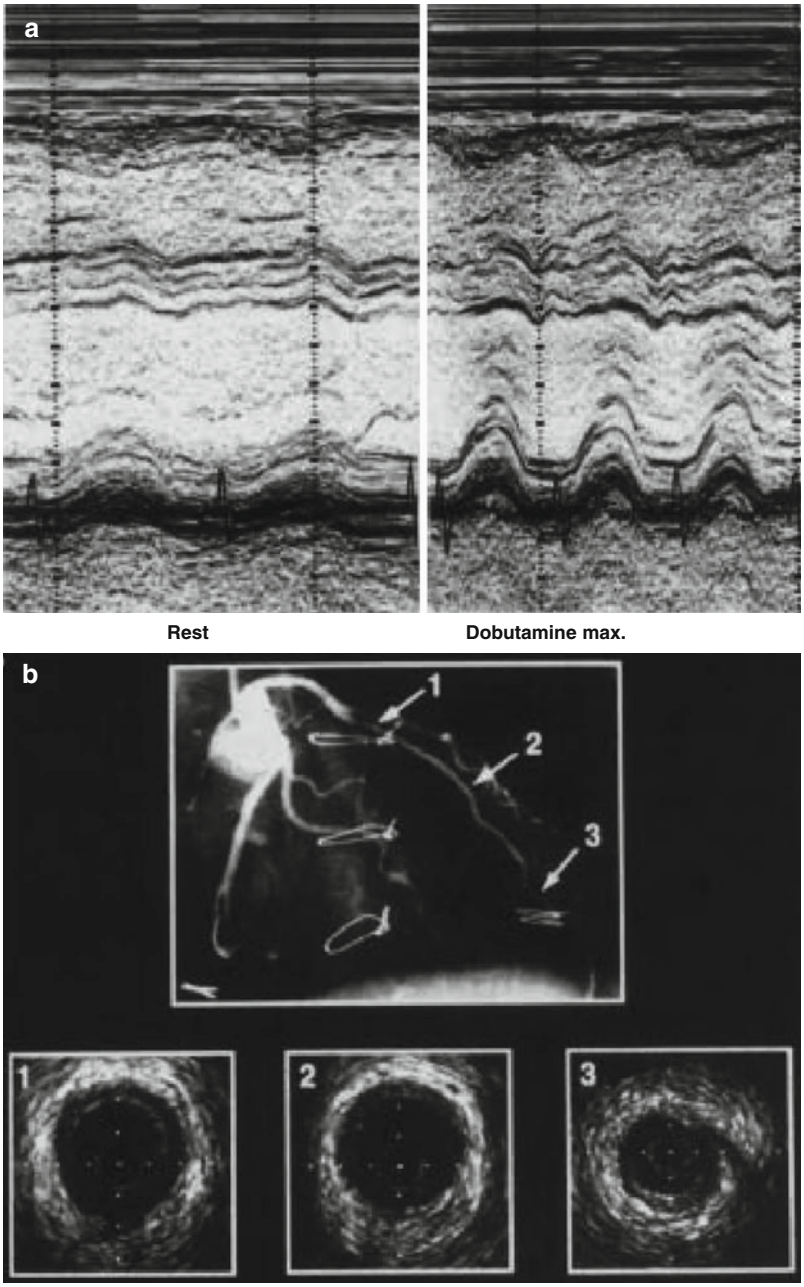

Fig. 35.3 Forty-eight months after transplantation. (**a**) *M*-mode echocardiogram. Reduced systolic wall thickening at rest (*left*). During maximum dobutamine stress (*right*), septal thickening remains unchanged, whereas posterior wall thickening increases. (**b**) Coronary angiogram and intravascular ultrasound (IVUS). Contour irregularities without relevant stenosis in the left coronary artery by angiography. Severe intimal hyperplasia at three sites (*arrows*) of the left anterior descending artery by IVUS (From [Spes *Am J Cardiol* 1996], Ref. [44], with permission)

Table 35.2 Accuracy of pharmacological stress echocardiography for the detection of CAV in different studies

Author, year, ref	Number of patients	Stress agent	Time post-HT (months)	Gold standard	Sensitivity (%)	Specificity (%)
Akosah et al. (1994) [41]	41	Dobutamine	57 ± 5	CA	95	55
Akosah et al. (1995) [43]	45	Dobutamine	58 ± 30	CA[a]	96	53
Derumeaux et al. (1995) [42]	41	Dobutamine	40 ± 20	CA	86	91
Spes et al. 1996 [44]	46	Dobutamine	46 ± 26	CA[a]	83	56
				IVUS	79	83
Derumeaux et al. (1998) [46][b]	37	Dobutamine	37 ± 20	CA[a]	65	95
			56 ± 21		92	73
Spes et al. (1999) [25]	109	Dobutamine	38 ± 37	CA[a]/IVUS	72	88
Bacal et al. (2004) [53]	39	Dobutamine	86 ± 31	CA	64	91
Rodrigues et al. (2005) [47][c]	35	Dobutamine	72 ± 32	CA	70	96
Eroğlu et al. (2008) [49]	42	Dobutamine	72 ± 48	CA[a]	75	79
Sade et al. (2014) [38][d]	23	Dobutamine	46 ± 17	CA[a]	56	64
		Dipyridamole			100	64
		Combined			78	87
Ciliberto et al. (1993) [39]	80	Dipyridamole	27 ± 18	CA[a]	32	100
Ciliberto et al. (2003) [40]	68	Dipyridamole	35 ± 23	CA	100	87
Tona et al. (2006) [6][c, d]	73	Adenosine	96 ± 54	CA	82	87
Tona et al. (2010) [55][c]	22	Adenosine	72 ± 48	IVUS	80	100

[a]Any coronary lesion including luminal irregularities
[b]The study examined the accuracy of stress echocardiography in the same patient population at two time points
[c]Contrast-enhanced studies
[d]Coronary flow reserve was assessed with dipyridamole or adenosine, *CA* coronary angiography, coronary stenosis >50 % in at least one vessel

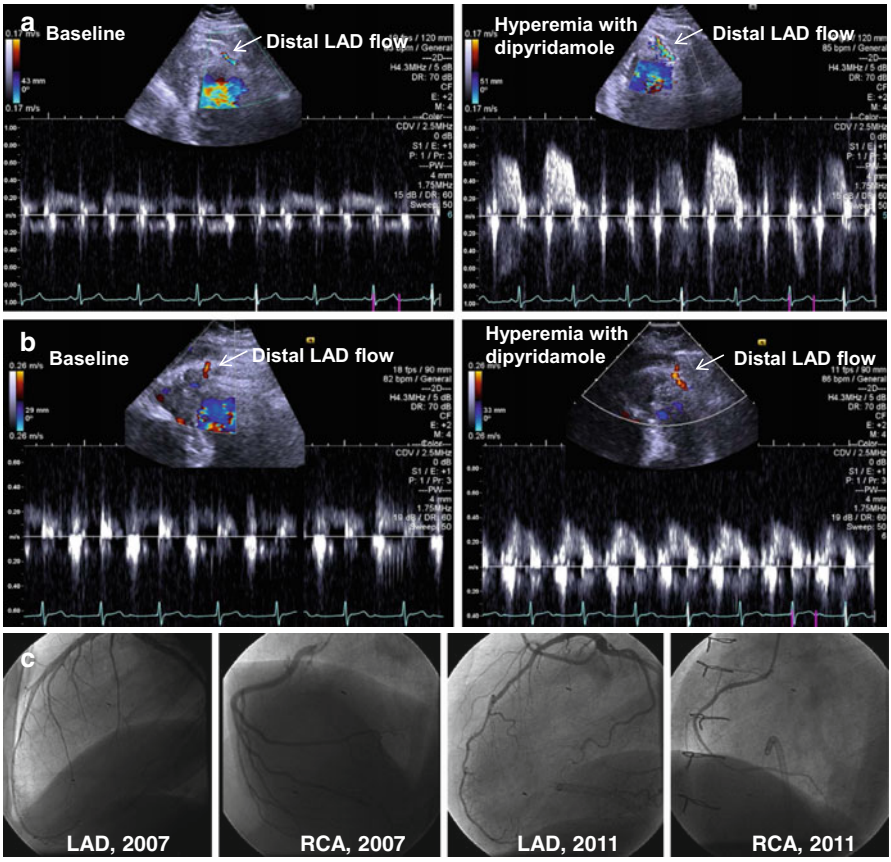

Fig. 35.4 (**a**) 1 year after transplantation, normal coronary flow reserve (CFR). Note the increase in baseline diastolic flow velocity from 30 to 90 cm/s under dipyridamole infusion yielding a CFR of 3. (**b**) A patient with blunted hyperemic response to dipyridamole. Note that the baseline diastolic flow velocity increased from 25 to 40 cm/s yielding a CFR of 1.6 after 4 years of transplantation. (**c**) Coronary angiograms of the patient in (b), showing significant distal tapering and diffuse narrowing in 2011 as compared to older angiogram. Note that CAV could be overlooked without comparison with the previous angiogram

echocardiography is also normal [38]. If the stress test is normal by wall motion and coronary flow reserve criteria, invasive diagnosis can be delayed and the next test is scheduled after 12 months (Fig. 35.5). If stress echocardiography shows wall motion abnormalities, angiography is performed, and if this test does not yield evidence of CAV, an additional IVUS study might be warranted. This algorithm helps avoid repeat cardiac catheterization in some patients and leads to a closer surveillance of patients with evidence of functionally relevant and/or progressive CAV. This aspect of noninvasive radiation-free follow-up of heart transplant patients is especially important in pediatric patients, in whom dobutamine stress echocardiography is highly feasible and effective for diagnostic and prognostic purposes [50, 51].

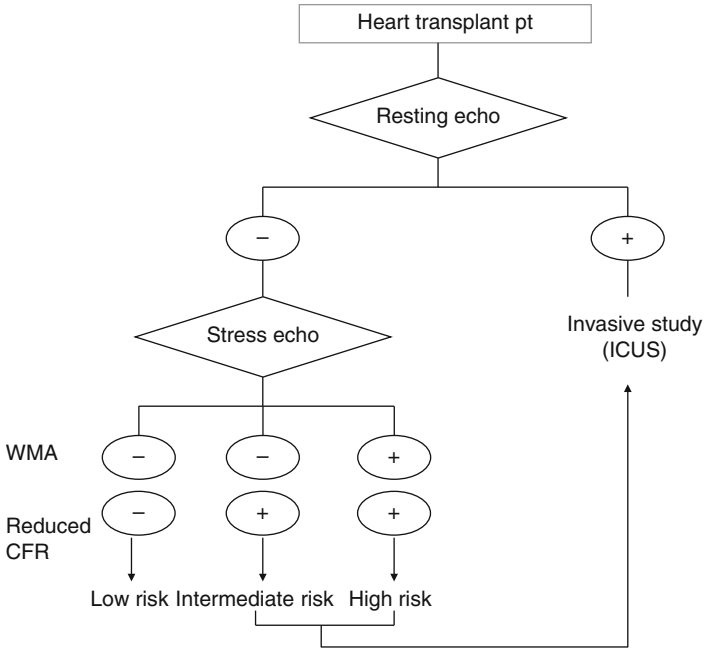

Fig. 35.5 A proposed diagnostic flowchart in the surveillance of posttransplantation patient. Yearly testing with pharmacological stress echocardiography may help reduce the need for invasive studies. The reliability of pharmacological stress echocardiography is stronger when the test response shows no wall motion abnormalities and normal coronary flow reserve on the left anterior descending artery during transthoracic vasodilation stress echocardiography. *CFR* coronary flow reserve, *ICUS* intracoronary ultrasound, *WMA* wall motion abnormalities

35.4 Pharmacological Stress Echo for Recruitment of Donor Hearts

Heart transplantation is a treatment for heart failure that is not responding to medication, and its efficacy is already proven; unfortunately, organ donation is the limiting step of this life-saving procedure. Heart donor shortage has been a societal problem [59]. Patients on the heart transplant waiting list have a 7.3 % death rate, and the average waiting time is 2–3 years. As an example, in Italy, approximately 650 patients are on the transplant list and only about 300 transplantations are performed each year. An effective way to solve the current shortage would be to accept an upward shift of the age cutoff limit (from the current 45 to 70 years) but age-related high prevalence of asymptomatic coronary artery disease and occult cardiomyopathy severely limit the feasibility of this approach. An alternative approach is based on pharmacological stress echocardiography performed at bedside in marginal donors (age >55 years) [60]. When resting and stress echocardiography results are negative, a prognostically meaningful underlying coronary artery disease or cardiomyopathy can be ruled out and the heart can be rescued and transplanted

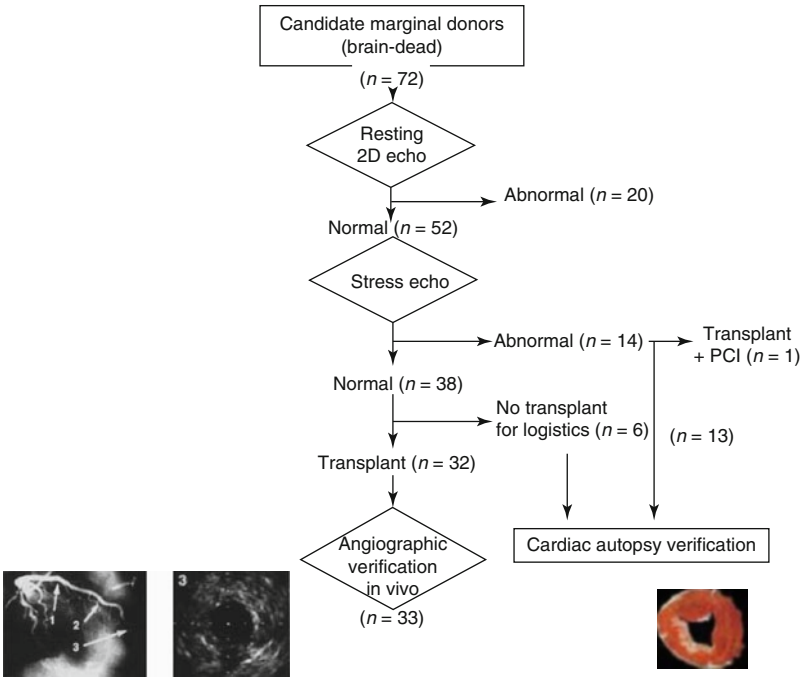

Fig. 35.6 The initial experience with pharmacological stress echocardiography in recruiting hearts from marginal donors (>55 years). A negative stress echocardiography result deems hearts otherwise lost to donation, eligible for donorship. *IVUS* intravascular ultrasound (Updated and adapted from Refs. [62, 63])

(Fig. 35.6). Another potential advantage of stress echocardiography is that it can be helpful to evaluate contractile reserve which indicates reversible LV dysfunction due to calcium excess or other effects of neurohumoral activation in donors who would otherwise be discarded due to resting wall motion abnormalities [61].

Transesophageal echocardiography may be needed when image quality is poor, particularly in ventilated patients. Contrast may also be needed when the LV segments are poorly visualized; however, the potential pulmonary toxicity of contrast agents may preclude lung donation. Dipyridamole is the preferred stress agent for the selection of donor hearts since it is infused over a shorter time period than dobutamine which makes it more convenient at bedside. Furthermore, many potential donors may already be under inotropic support, making the addition of dobutamine less effective and potentially harmful. Although certainly more data are needed with the use of stress echo to select marginal donors, the appeal of this stress echocardiography-driven way to select hearts "too good to die" is exciting for its potential to drastically solve the current mismatch between donor need and supply, with a very favorable cost-benefit profile. The cost of a donor heart is estimated to be around €200,000 on the "transplant black market." We can recruit otherwise ineligible hearts at the cost of one stress echocardiography (around 500 € per stress echo at the average cost in Europe), with obvious downstream economic benefits [62–64].

35.5 Pitfalls

As the transplanted heart is surgically denervated and remains without functionally relevant reinnervation in most patients, angina pectoris does not usually occur. Several noninvasive tests have proven to be of limited value for the detection of CAV [20–23]. This may be explained by some of the specific features of CAV and by the specific alterations of cardiac physiology in heart transplant recipients. For example, exercise electrocardiography is a priori restricted to a minority of transplant recipients due to the high prevalence of (most commonly right) bundle branch block and altered repolarization in this population. In addition, the mode of provocation of ischemia is important. Physical exercise may not be adequate, because heart transplant recipients frequently have a reduced exercise capacity due to muscular weakness following long-term deconditioning and corticosteroid immunosuppression. More important, the chronotropic response to physical exercise is limited due to cardiac denervation; the reduced increase in heart rate may therefore not be adequate to reach the ischemic threshold in all heart transplantation patients. The limitations of a physical exercise test in transplantation patients have been shown in combination with various diagnostic techniques such as exercise electrocardiogram, radionuclide angiography, or exercise echocardiography [20–24]. Coronary angiography only presents a luminogram and may not be able to detect diffuse concentric thickening of the vessel wall. Intravascular ultrasound (IVUS) is the method of choice for detecting alterations in the vessel wall and has emerged as the most sensitive invasive method for diagnosing CAV [13, 65]. Although most investigators measure thickness and extension of intimal hyperplasia by IVUS, no commonly accepted cutoff points or standardized IVUS definitions for CAV exist (minimal number of coronary segments and vessels necessary for valid diagnosis, grading by worst affected sites or mean values). Furthermore, IVUS has limitations in determining CAV with distal vessel involvement or at the microvascular level or functional CAV.

One should be cautious when comparing sensitivities and specificities of stress echocardiography between the studies. The accuracy of stress echocardiography either by wall motion analysis or by coronary flow assessment varies considerably depending on the gold standard used and depending on the cutoff value adopted for CFR. The sensitivity and negative predictive values decrease when IVUS is the gold standard instead of coronary angiography. Also, the cutoff value of CFR varies from 2 to 2.9 in different studies [6, 38]. Posttransplant septal motion abnormalities are frequent in the first posttransplant year and may be misleading. These are expected to normalize during stress; however, any septal wall motion abnormality after the first year should raise the suspicion of CAV.

35.6 Clinical Guidelines

The International Society of Heart and Lung Transplantation Guidelines for the care of heart transplant recipients recognize that stress echocardiography "may be useful for the detection of cardiac allograft vasculopathy in heart transplant recipients

Table 35.3 Clinical applications of stress echocardiography in heart transplantation

	A	M	R	COR	LOE	Reference
Heart transplant recipients						
Detection of cardiac allograft vasculopathy	√			IIa	C	ISHLT [65]
Heart donors						
Detection of occult CAD in marginal, aged donors		√		EC		CNT [66]

A appropriate, *M* maybe appropriate, *R* rarely appropriate, *COR* class of recommendation, *LOE* level of evidence, *EC* expert consensus, *ISHLT* International Society for Heart and Lung Transplantation, *CNT* Italian Centro Nazionale Trapianti

unable to undergo invasive evaluations" [65]. Stress echocardiography has been included in national recommendations of the Italian Transplant Center to encourage the selection of marginal (age >55 years) donors to limit the current shortage of hearts for cardiac transplantation [66] (Table 35.3). The recent recommendations of the European Association of Cardiovascular Imaging and Brazilian Society of Cardiology for the use of cardiac imaging in patients after heart transplantation suggest that pharmacological stress echocardiography might be a suitable alternative to routine coronary angiography to assess cardiac allograft vasculopathy at centers with adequate experience with the methodology, and coronary flow reserve and/ or contrast infusion might be combined with stress echo to assess myocardial perfusion and improve the accuracy of the test [67] – which can otherwise remain unsatisfactory if based only on wall motion abnormalities [68].

Table of Contents Video Companion

See illustrative case numbers 36, 37, and 38 by Prof Sade, MD, Ankara, Turkey, and case numbers 39 and 40 by Tonino Bombardini, MD, PhD, Pisa, Italy.

See also, in the section Nuovo Cinema Paradiso remastered, the short movie: "A novel silver heart from National Research Council," by Tonino Bombardini, MD, PhD, Pisa, Italy.

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Stress Echocardiography in Valvular Heart Disease

36

Patrizio Lancellotti, Philippe Pibarot, and Eugenio Picano

Major advances in diagnosis and risk stratification, combined with enormous progress in surgical valve replacement and repair, have led to improved outcomes of patients with valvular heart disease over the past 30 years. The most important indication for surgical intervention in patients with hemodynamically significant aortic or mitral valve disease is the development of symptoms, as emphasized in recent guidelines [1–3]. As symptoms may develop slowly and indolently in these chronic conditions, many patients are unaware of subtle changes in effort tolerance, even when questioned directly by their physicians. Hence, recent guidelines of both the American College of Cardiology/American Heart Association (ACC/AHA) and the European Society of Cardiology (ESC) [2, 3] have placed renewed emphasis on the role of exercise testing to provide objective evidence of exercise capacity and symptom status. In addition, while Doppler echocardiography is the method of choice for assessing severity of valvular disease, there is a growing utilization of stress two-dimensional and Doppler echocardiography to assess dynamic changes in hemodynamics in concert with the clinical findings of exercise testing.

Stress echocardiography has become an established method for evaluating patients with coronary artery disease [4–6]. The role of stress echocardiography has been recently expanded to the assessment of the hemodynamic consequences of valvular lesions during stress [7–9]. In a number of clinical conditions, particularly in patients with low-flow, low-gradient aortic valve stenosis (AS), the use of stress echocardiography in the decision-making process has significantly modified the clinical outcome. Evidence accumulated over the last decade has led to the incorporation of stress echocardiography in the guidelines of the ACC/AHA [2], the ESC [3], the American Society of Echocardiography [10], and the European Association of Cardiovascular Imaging [11].

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36.1 Aortic Stenosis

36.1.1 Aortic Valve Stenosis with Low Flow, Low Gradient, and Left Ventricular Dysfunction

Patients with severe AS and left ventricular (LV) systolic dysfunction (ejection fraction <40 %) often present with a relatively low flow and pressure gradient, i.e., mean gradient less than 40 mmHg (Fig. 36.1). This entity represents a diagnostic challenge because it is difficult to distinguish between patients having true anatomically severe AS from those having pseudo-severe AS. In true severe AS, the primary culprit is the valve disease, and the LV dysfunction is a secondary or concomitant phenomenon. The small and relatively fixed aortic valve area (AVA) contributes to raising afterload, decreasing ejection fraction, and reducing stroke volume. In pseudo-severe AS, the predominant factor is myocardial disease, and the severity of AS is overestimated on the basis of AVA because there is incomplete opening of the valve due to reduction in the opening force generated by the weakened ventricle. In both situations, the low-flow state and low-pressure gradient contribute to a calculated AVA that meets criteria for severe AS at rest ($\leq$1.0 cm^2) (Fig. 36.1). Hence, the resting echocardiogram does not distinguish between these two situations. Yet this distinction is essential since patients with true severe AS and poor LV function will

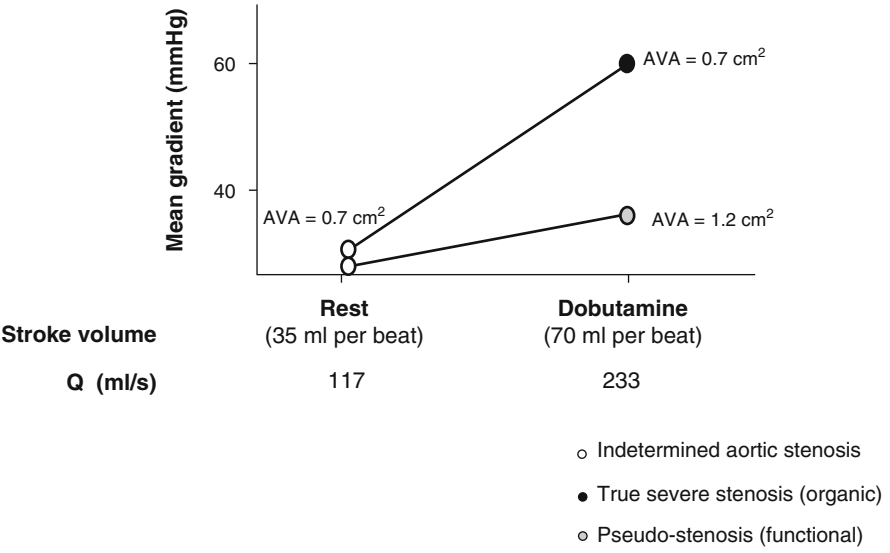


Fig. 36.1 Hemodynamic principles supporting use of dobutamine stress echocardiography in low-flow, low-gradient aortic stenosis. At rest, the mean gradient is low regardless of aortic valve area (*AVA*) because the transvalvular flow rate is low (*white dot*). The stroke volume (*SV*) on the *x*-axis is low at rest (35 ml, *white dot*) and may normalize following dobutamine (70 ml). For a given left ventricular ejection time of 0.3, the mean transvalvular flow rate (*Q*) will increase from 117 to 233 ml s^{-1}. With augmentation of flow with dobutamine, there is a marked increase in gradient (14–57 mmHg in this example) in the case of a true severe stenosis (AVA = 0.7 cm^2), whereas there is only a modest increase in gradient (7–19 mmHg) in the case of moderate stenosis (AVA = 1.2 cm^2)

generally benefit significantly from aortic valve replacement (AVR), whereas the patients with pseudo-severe AS will not.

In patients with low-flow, low-gradient AS and LV dysfunction, it may be useful to determine the transvalvular pressure gradient and to calculate AVA during a baseline resting state and again during low-dose dobutamine stress, to determine whether the stenosis is severe or only moderate [12–20] (Figs. 36.1 and 36.2). Side effects

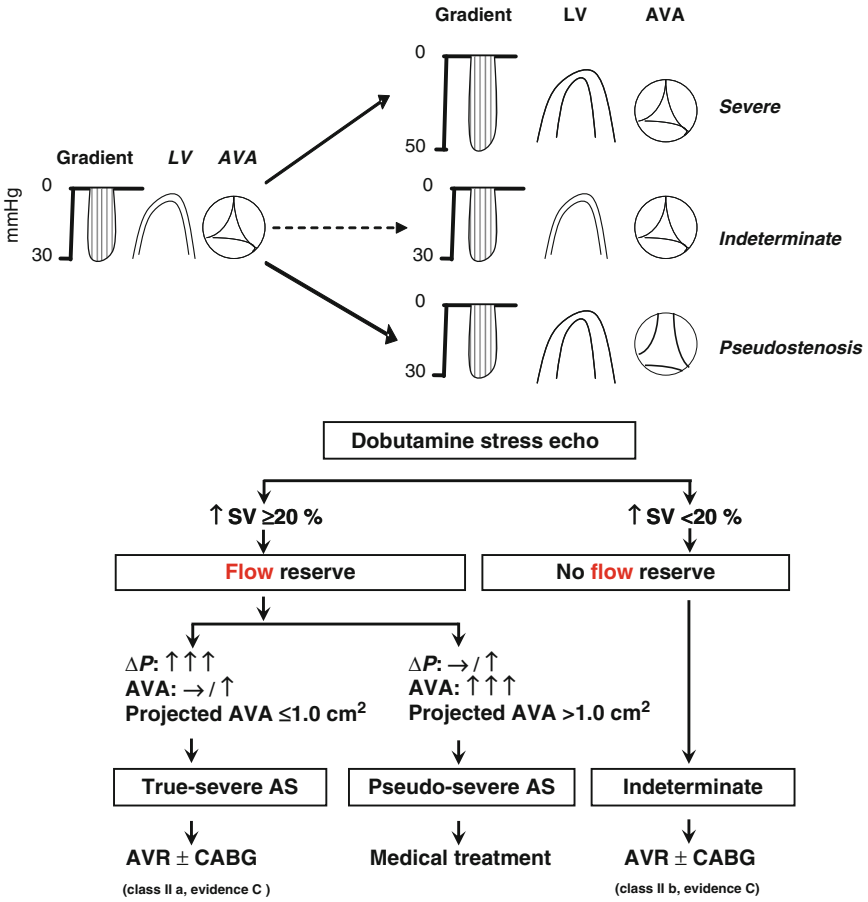


Fig. 36.2 (**a**) Hemodynamic principles supporting dobutamine stress echocardiography in low-gradient aortic stenosis (AS) with left ventricular dysfunction. The resting transaortic gradient (<40 mmHg), left ventricular (*LV*) function (<40 %), and calculated aortic valve area (*AVA*, <1 cm^2) are depicted on the *left*. On the *right*, the three possible responses to dobutamine are shown: in severe AS, the increase in stroke volume (>20 %) leads to an increase in gradient with no or only a minimal increase in AVA, but in pseudo-stenosis, there is only a mild increase in gradient associated with an increase in AVA. The stenosis severity remains "indeterminate" when there is no inotropic response of the left ventricle and thus no significant increase in stroke volume and transvalvular flow rate. (**b**) Algorithm for the interpretation of the results of dobutamine stress echocardiography in patients with low-flow aortic stenosis. *AVA* Aortic valve area, *ΔP* Transvalvular pressure gradient, *SV* Stroke volume, *AVR* Aortic valve replacement, *CABG* Coronary artery bypass graft surgery, *sideward arrow* No change, *upward arrow* Mild increase, *multiple upward arrows* Marked increase

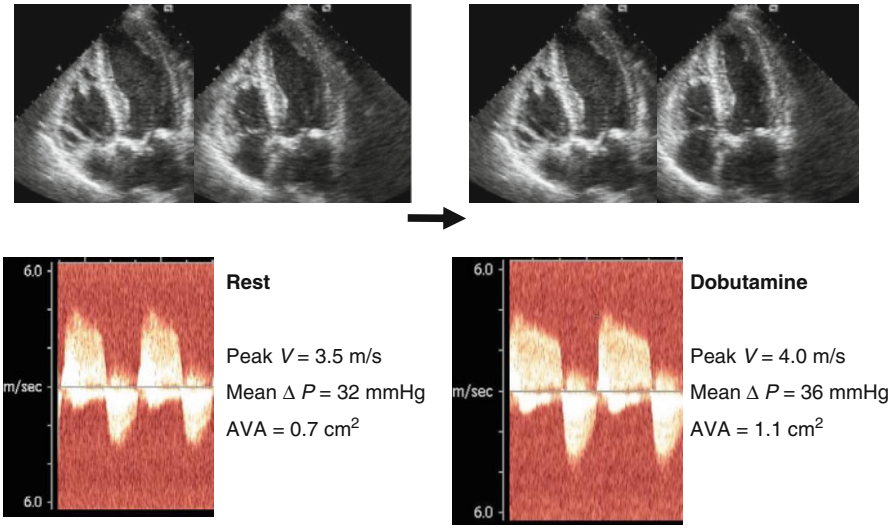


Fig. 36.3 Pseudo-severe aortic stenosis unmasked by dobutamine stress echocardiography in a patient with reduced left ventricular function and low gradient at rest. *Upper panels*: end-diastolic and end-systolic frames at rest (*left*) and after dobutamine (*right*), showing an increase in regional thickening. *Lower panels*: slight increase in pressure gradient (ΔP) and significant increase in aortic valve area (*AVA*)

are not infrequent with full-dose dobutamine in unselected patients with normal or moderately reduced LV ejection fraction [11–21] and can occur in one out of five patients with low-flow, low-gradient AS [22]. The main objective of dobutamine stress echocardiography in the context of low-flow AS is to increase transvalvular flow rate while not inducing myocardial ischemia. Hence, a low-dose protocol (i.e., up to 20 μg kg^{-1} min^{-1}) should be used for these patients. Moreover, it is preferable to use longer dobutamine stages (5–8 min instead of the 3–5 min generally used for the detection of ischemic heart disease) to ensure that the patient is in a steady-state condition during Doppler echocardiography data acquisition and before proceeding to the next stage. The increase in heart rate should also be taken into consideration given that it may predispose the patient to myocardial ischemia and at one point may override the inotropic effect, thereby limiting the increase in transvalvular flow.

The dobutamine stress approach is based on the notion that patients who have pseudo-severe AS will exhibit an increase in the AVA and little change in transvalvular gradient in response to the increase in transvalvular flow rate [13] (Figs. 36.2 and 36.3). In contrast, patients with true severe AS will have no or minimal increase in AVA and a marked increase in gradient when flow is increased because the valve is rigid (Figs. 36.2 and 36.4). Several criteria have been proposed in the literature to differentiate pseudo- from true severe AS including a peak stress mean gradient less than 30 or less than 40 mmHg depending on the study, a peak stress AVA greater than 1.0 or greater than 1.2 cm^2, and an absolute increase in effective orifice area

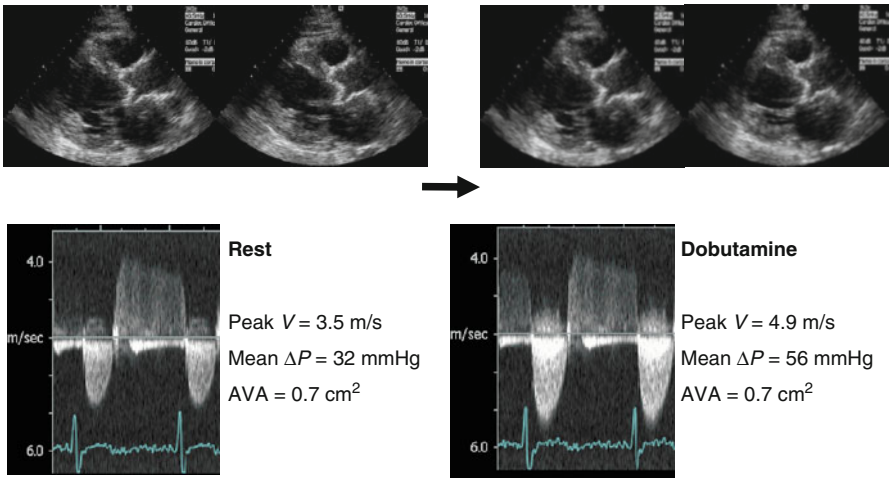
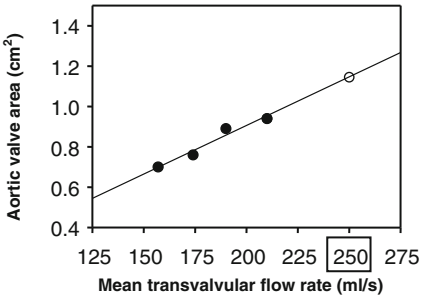


Fig. 36.4 True severe aortic stenosis unmasked by dobutamine stress echocardiography in a patient with reduced left ventricular function and low gradient at rest. *Upper panels*: end-diastolic and end-systolic frames at rest (*left*) and after dobutamine (*right*), showing an increase in regional thickening. *Lower panels*: marked increase in pressure gradient (ΔP) and no increase in aortic valve area (*AVA*)

(EOA) greater than 0.3 cm^2 during dobutamine stress [14–20]. Although the dichotomization of patients into two categories (true or pseudo-severe AS) is convenient, it is an oversimplification, and the classification of the individual patient may not always be as easy as it may appear. The changes in gradient and AVA during dobutamine stress depend largely on the magnitude of the flow augmentation achieved, which may vary considerably from one patient to another. The AVA and gradient are therefore measured at flow conditions that differ dramatically from one patient to another, and the utilization of these indices which are not normalized with respect to the flow increase may lead to misclassification of stenosis severity in some patients. To overcome this limitation, the investigators of the Truly or Pseudo-Severe Aortic Stenosis (TOPAS) multicenter study [23] have proposed a new echocardiographic parameter: the projected AVA at a standardized normal flow rate (Fig. 36.5). A projected AVA of less than 1.0 cm^2 is considered as an indicator of true severe stenosis [23]. Patients who fail to manifest an increase in stroke volume with dobutamine of 20 % or greater have a lack of contractile reserve and have been shown to have a poor prognosis with either medical or surgical management [20]. Moreover, in this subset of patients, it is difficult to determine the true severity of the stenosis. Patients identified as having true severe AS and contractile reserve on dobutamine stress have a much better outcome with AVR than with medical therapy [18–20]. A number of patients without contractile reserve can also benefit from AVR [20], but decisions in these high-risk patients must be individualized, in the absence of clear guidelines. To this effect, plasma brain natriuretic peptide



Projected AVA = Baseline AVA + VC × (250 – Baseline flow rate)

Projected AVA = 0.7 + 0.0048 × (250 – 157) = 1.15 cm²

Fig. 36.5 Concept of the projected aortic valve area (*AVA*). Values of AVA obtained at different stages of dobutamine infusion are plotted as a function of flow rate (stroke volume divided by ejection time). The slope of the regression line is the valve compliance (*VC*). The VC can also be obtained using a simplified method by dividing the absolute increase in AVA measured during dobutamine stress by the absolute increase in flow rate. The projected AVA (*open circle*) at a normal flow rate (250 ml s^{-1}) is calculated using the regression equation. In this example, the peak AVA obtained during dobutamine is 0.94 cm^2, and the absolute increase in AVA is 0.24 cm^2, which would suggest true severe stenosis. However, calculation of the projected AVA using the baseline values of AVA (0.7 cm^2) and flow rate (157 ml s^{-1}) and the valve compliance (0.48 cm^2 100 ml^{-1} s^{-1}) yields a value of 1.15 cm^2, which is consistent with moderate stenosis

(<550 pg ml^{-1}) may be useful to identify the patients with lack of contractile reserve who may benefit from AVR [24]. Also, the assessment of aortic valve calcification by multislice computed tomography may be helpful to corroborate the stenosis severity in these patients [25].

In patients with low-flow, low-gradient AS, the indication for dobutamine stress echocardiography is rated as class IIa, with level of evidence B [2], with the caveat that dobutamine stress testing in patients with AS should be performed only in centers with experience in pharmacological stress testing, and with a cardiologist in attendance.

36.1.2 Aortic Valve Stenosis with Low Flow, Low Gradient, and Preserved Left Ventricular Function

Low-flow (<35 ml/m^2), low-gradient (<40 mmHg) ("paradoxical"), and severe aortic stenosis (AVA <1 cm^2) can also be observed in patients with preserved LV ejection fraction [26, 27]. This pattern shares many pathophysiological and clinical similarities with heart failure and preserved LV ejection fraction. It is characterized by: (1) pronounced/exaggerated myocardial concentric remodeling, (2) small LV cavity size, (3) reductions in LV compliance and filling, (4) increased global LV afterload, (5) decreased LV longitudinal function, and (6) myocardial fibrosis. These patients are likely to benefit from AVR with improved outcome as compared

to medical treatment [28]. In practice, the management of this challenging entity starts with the confirmation of AS severity. Dobutamine stress echocardiography can be of interest in this setting but should be used cautiously. In case of severe LV concentric hypertrophy, a dynamic intraventricular obstruction can occur. The protocol and goals of dobutamine stress test are similar to the situation of depressed LV ejection fraction. The increase in transvalvular flow rate due to dobutamine infusion is translated into a rise in transvalvular pressure gradient (mean ≥40 mmHg) and a slight change in AVA (<1 cm^2) [29]. However, the risk-benefit ratio of stress echocardiography in this context needs to be better established in larger series of patients before it can be advocated for routine clinical utilization.

36.1.3 Asymptomatic Severe Aortic Stenosis with High Gradient

Management of asymptomatic patients with severe AS, defined as peak velocity greater than 4 m/s, mean pressure gradient greater than 40 mmHg, and/or AVA less than 1 cm^2 [2, 3], remains a source of debate. The wide interindividual variation in the rate of progression and in the outcome of the disease has recently prompted some authors to recommend early elective surgery in asymptomatic patients with severe AS. The rationale for using this approach is that if one applies a strategy of waiting for symptoms before recommending surgery, the patient may be operated too late in the course of the disease at a stage in which myocardial damage is, at least in part, irreversible.

In this regard, it is also important to emphasize that some patients and especially elderly patients may ignore or not report their symptoms, while others may reduce their level of physical activity to avoid or minimize symptoms. The principal role of exercise testing is to unmask symptoms in a significant proportion of patients with AS who claim to be asymptomatic, as these symptoms can predict outcome [30–33]. Reduced exercise tolerance, with development of dyspnea or ST segment depression, is associated with a worse outcome [31–33]. In this respect, exercise testing is an important tool, and several studies have shown its prognostic value. Moreover, an increase in the mean aortic pressure gradient of more than 20 mmHg, reflecting limited valve compliance and severe stenosis, during exercise in asymptomatic patients is another predictor of symptom onset in the short-term, suggesting that this may also be used as a criterion to recommend early elective AVR (ESC class IIb indication) (Fig. 36.6) [34, 35]. When the aortic valve is no longer compliant or in case of profound myocardial damage, a mismatch between afterload and contractility may occur during exercise, which is characterized by a limited contractile reserve (small/no change in ejection fraction or in global longitudinal function) [36]. These patients are at increased risk of cardiovascular events. Similarly, those who develop pulmonary hypertension (systolic pulmonary artery pressure >60 mmHg, measured from the tricuspid regurgitant velocity) during test displayed decreased survival rates [37]. However, more confirmatory data are needed to support the routine use of exercise echocardiography in the management of asymptomatic patients with severe AS.

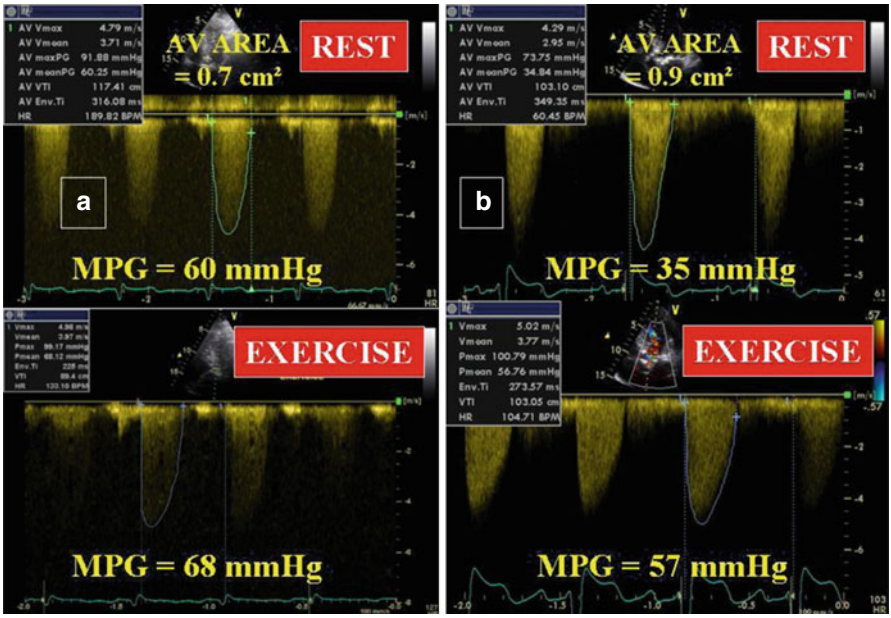


Fig. 36.6 Examples of exercise-induced changes in mean transaortic pressure gradient (*MPG*) in two asymptomatic patients with severe aortic stenosis. (**a**) Small increase in MPG with exercise. (**b**) Significant exercise-induced increase in MPG

36.2 Aortic Regurgitation

As is the case with AS and chronic mitral regurgitation (MR), development of irreversible LV dysfunction is a major concern in asymptomatic patients with severe aortic regurgitation (AR). In those with normal resting LV systolic function, an increase in LV ejection fraction during either exercise or pharmacologic stress prior to surgery indicates the presence of contractile reserve, and this may predict improvement in LV function after AVR [38]. The assessment of contractile reserve can be extended for the evaluation of patients with AR who have developed LV dysfunction. In these latter patients, exercise tolerance is an important predictor of reversal of LV dysfunction and survival after AVR [39, 40].

The development of symptoms during exercise testing is useful in predicting outcome in patients with severe AR who are apparently asymptomatic at rest. The additional value of stress imaging is unclear. The observed magnitude of change in ejection fraction or stroke volume from rest to exercise is related not only to myocardial contractile function but also to severity of volume-overload and exercise-induced changes in preload and peripheral resistances [2]. The validity of stress echocardiography in predicting outcome of patients with asymptomatic AR is limited mainly by the small number of available studies [41, 42] but is supported by a number of studies using exercise radionuclide angiography [43–47]. Some data

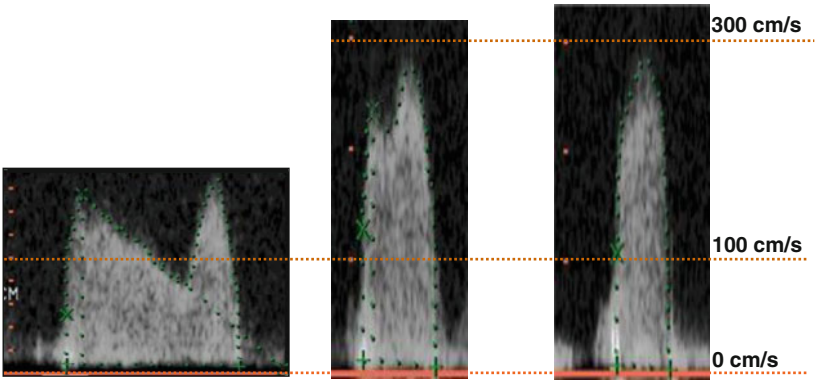
supporting the prognostic value of this functional stratification exist in the literature, but they are too few to recommend this specific application for routine clinical use.

To this effect, the ACC/AHA guidelines do not recommend exercise or dobutamine stress echocardiography for routine assessment of LV function in patients with AR [2]. More data are needed to corroborate this application, since the incremental value of stress imaging to LV dimensions and ejection fraction at rest remains unclear [10].

36.3 Mitral Stenosis

A baseline resting transthoracic echocardiography examination is usually sufficient to guide management in asymptomatic patients with mild-to-moderate mitral stenosis (MS) and in symptomatic patients with moderate-to-severe MS who are candidates for either percutaneous balloon valvuloplasty or surgical mitral valve repair or replacement. In some patients, more detailed assessment of valve function and its hemodynamic consequences is needed, particularly when symptoms and Doppler findings are discordant. In asymptomatic patients with severe MS (ESC mean gradient >10 mmHg and mitral valve area <1.0 cm^2, ACC/AHA <1.5 cm^2) or symptomatic patients with moderate MS (ESC mean gradient of 5–10 mmHg and mitral valve area of 1.0–1.5 cm^2), the measurement of pulmonary artery pressures and mean transmitral pressure gradient during exercise stress echocardiography may help distinguish those who could benefit from valvuloplasty or valve replacement from those who should be maintained on medical therapy [2, 48–50]. As is the case with the aortic valve, the transmitral valve pressure gradient is related to the valve orifice area. However, it should be emphasized that the transmitral gradient is much more sensitive to the chronotropic conditions than that of the transaortic gradient and that these conditions may vary extensively from one patient to another. Moreover, for a given valve orifice area, patients with reduced atrioventricular compliance exhibit a more pronounced increase in pulmonary arterial pressure during exercise than those with normal compliance [49–51]. Hence, the resting values of transmitral gradient or pulmonary arterial pressure do not necessarily reflect the actual severity of the disease. Exercise echocardiography may therefore be highly useful for confirming the severity of MS and assessing its consequences on the hemodynamic and symptomatic status of the patient under exercise conditions. It is indicated prior to major noncardiac surgery or pregnancy planning in <1.5 cm^2 MS [2, 3]. This test is clearly indicated when there is discordance between the severity of MS as assessed by resting echocardiography and the patient's symptomatic status. Dobutamine stress echocardiography has been less used in MS and is favored when exercise test is not applicable.

Gradient thresholds for severe MS have been established as >15 mmHg on exertion or >18 mmHg during dobutamine infusion. Also, pulmonary artery systolic pressure >60 mmHg on exertion suggests severe MS, especially when it occurs at low-level exercise (Figs. 36.7 and 36.8) [2, 3, 52]. Above these values, valvuloplasty or valve replacement is recommended, even for patients with apparently



	Rest	30-W exercise	Peak exercise
HR (b/min):	55	116	159
DFT (ms):	607	228	200
SV (ml):	66	59	57
Q_{mean} (ml/s):	109	259	284
ΔP (mmHg):	5	23	27
PAPs (mmHg)	40	62	69

Fig. 36.7 Exercise stress echocardiography in a symptomatic patient with mitral stenosis (mitral valve area, 1.2 cm^2) and relatively low resting mean transmitral pressure gradient (ΔP). With exercise, there is a marked increase in the transvalvular gradient and systolic pulmonary arterial pressure (*PAPs*). In this patient, the exercise-induced increase in mean transvalvular flow rate (Q_{mean}) was caused by the dramatic shortening in diastolic filling time (*DFT*). *HR* Heart rate, *SV* Stroke volume

moderate MS at rest [2, 10, 11]. The use of this stress echocardiography application in MS is rated as class I with level of evidence C for patients with discordant symptoms and stenosis severity [2]. As with other valve conditions, a major role of stress testing in patients with MS is to evaluate exercise capacity and exercise-induced symptoms.

36.4 Mitral Regurgitation

36.4.1 Primary (Organic) Mitral Regurgitation

The severity of primary MR can be reliably assessed by resting color flow Doppler echocardiography with the use of semiquantitative or quantitative methods [2, 3, 53]. Such information is useful to predict the development of LV dysfunction and of symptoms [54]. There is presently an important ongoing controversy on whether asymptomatic patients with severe MR should undergo early elective mitral valve repair [54–56]. In selected patients in whom there is a discrepancy between symptoms and severity of MR and especially in asymptomatic patients with severe MR, exercise stress echocardiography may help to identify patients with subclinical

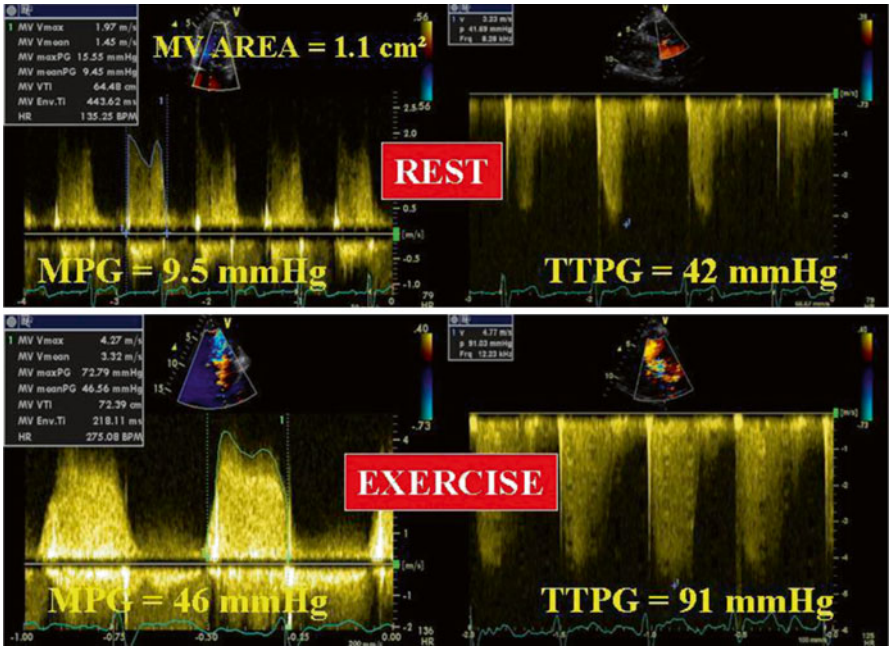


Fig. 36.8 Example of an asymptomatic patient with severe mitral valve stenosis but with moderately elevated mean transmitral pressure gradient (*MPG*) at rest. During exercise, the MPG increases markedly as does the systolic transtricuspid pressure gradient (*TTPG*) indicative of pulmonary hypertension

latent LV dysfunction and poor clinical outcome. The worsening of MR severity (by >1 grade), a marked increase in systolic pulmonary arterial pressure (>60 mmHg), the absence of contractile reserve (less than 4 % increase in ejection fraction or of 2 % in global longitudinal strain), an impaired exercise capacity, a limited right ventricular contractile recruitment (quantified by tricuspid annular plane systolic excursion <18 mm), and the occurrence of symptoms during exercise echocardiography can be useful findings to identify the subset of high-risk patients who may benefit from early surgery [57–59]. Exercise capacity itself predicts worse outcome in asymptomatic patients with significant myxomatous MR, and high resting right ventricular systolic pressure and lower resting LV ejection fraction predict worse outcome better than exercise values [60]. Recommendations for early surgery in asymptomatic patients should only be made in those who are candidates for mitral valve repair and in experienced centers in which there is a high likelihood (>90 %) of successful mitral repair without residual MR [2]. In the ESC guidelines, mitral valve repair is indicated in patients with exercise symptoms and may be considered in case of exercise pulmonary hypertension (IIb).

Exercise echocardiography has also been used to unmask the development of severe MR with exercise in patients with rheumatic mitral valve disease and only mild or moderate MR at rest [61]. The application of stress echocardiography in

asymptomatic patients with severe MR is rated as a class IIa recommendation with level of evidence C [2].

36.4.2 Secondary (Functional) Mitral Regurgitation

Exercise stress echocardiography is valuable in identifying hemodynamically significant MR in patients with LV systolic dysfunction, especially when ischemic heart disease is the underlying etiology. Secondary MR is primarily a disease of the LV myocardium and develops with a structurally normal mitral valve. The magnitude of secondary MR varies dynamically in accordance with changes in loading conditions, annular size, and balance of tethering versus closing forces applied on the mitral valve leaflets. Hence, the severity of MR assessed by resting echocardiography does not necessarily reflect the severity under exercise conditions. In patients with secondary MR, quantitative assessment of exercise-induced changes in the degree of MR is useful to unmask patients at high risk of poor outcome. A $\geq$13 mm^2 increase in the effective regurgitant orifice area or a >60 mmHg increase in systolic pulmonary arterial pressure (Fig. 36.9) at peak exercise stress is predictive of increased morbidity and mortality [62]. Of note, more than 30 % of patients with secondary MR have a significant dynamic increase in MR during exercise (increase by >1 grade). The effective regurgitant orifice at rest does not predict the effective regurgitant orifice at exercise. Hence, exercise Doppler echocardiography provides important incremental information over resting echocardiography in patients with secondary MR.

Lancellotti et al. [63–65] have proposed that exercise stress echocardiography in patients with secondary MR can provide useful information in the following situations: (1) patients in whom risk stratification is contemplated, (2) patients with exertional dyspnea out of proportion to the severity of resting LV dysfunction or MR, (3) patients in whom acute pulmonary edema occurs without an obvious cause, and (4) patients with moderate MR before surgical revascularization. The ESC guidelines consider combined surgery (CABG + mitral valve surgery) as a class IIa in patients with shortness of breath and exercise pulmonary hypertension in the setting of dynamic worsening of secondary MR [3].

36.5 Prosthetic Heart Valves

Echocardiography is the method of choice for evaluating prosthetic valve function. This evaluation follows the same principles used for the evaluation of native valves with some important caveats [66, 67]. First, imaging of the valve occluder and assessment of transprosthetic flow are limited by reverberations and shadowing caused by the valve components. Second, the fluid dynamics of mechanical prosthetic valves may differ substantially from that of a native valve. The flow is eccentric in monoleaflet valves and is composed of three separate jets in bileaflet valves,

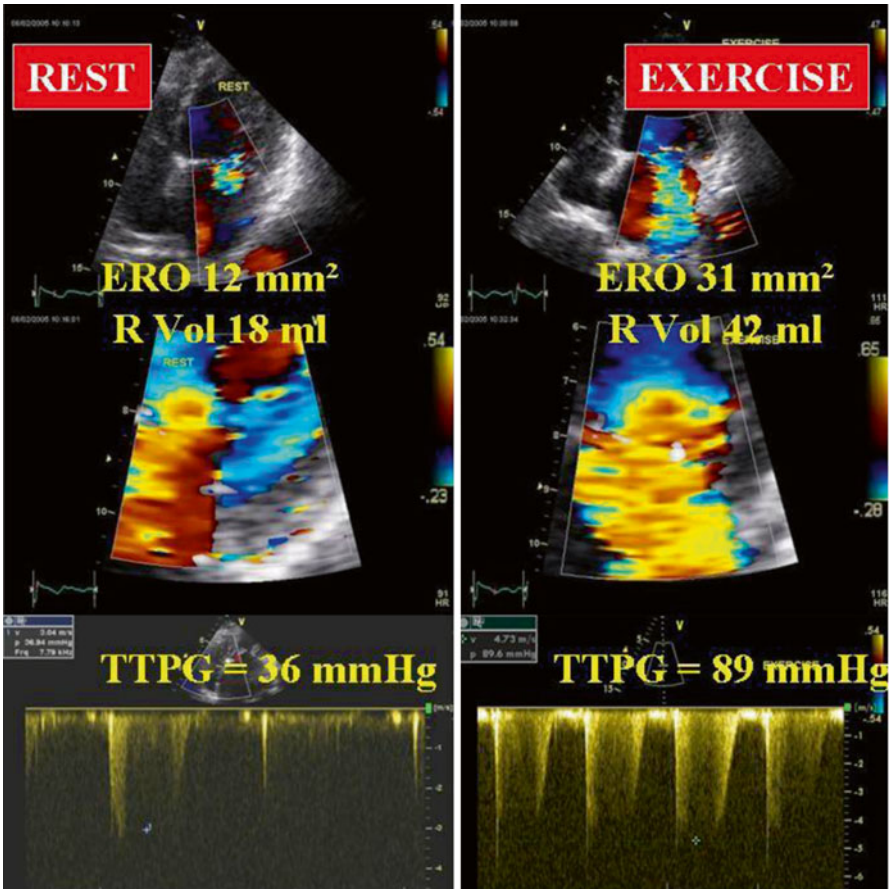


Fig. 36.9 Apical 4-chamber view showing color flow Doppler and proximal flow convergence region at rest and during exercise in a patient with a large exercise-induced increase in mitral regurgitation and estimated pulmonary artery systolic pressure. *ERO* effective regurgitant orifice, *RVol* regurgitant volume, *TTPG* systolic transtricuspid pressure gradient

with the flow velocity potentially higher in the central orifice jet than in the two lateral orifice jets.

Because most prosthetic valves are inherently stenotic, the EOA of a prosthetic valve is often too small in relation to body size, a phenomenon known as prosthesis–patient mismatch (PPM). In the aortic position, PPM is considered moderate when the indexed EOA is less than or equal to 0.85 cm^2/m^2 and severe when it is less than or equal to 0.65 cm^2/m^2 [67]. In the mitral position, the cutoff values are 1.2 and 0.9 cm^2/m^2, respectively. PPM has been linked to impaired exercise capacity, suboptimal symptomatic improvement, incomplete regression of LV hypertrophy and pulmonary hypertension, and increased cardiac events and mortality following valve replacement [68–72].

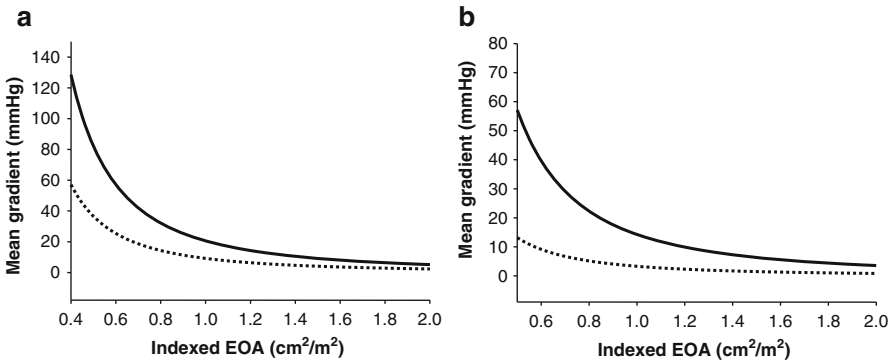


Fig. 36.10 Mean transprosthetic pressure gradient at rest (*dotted lines*) and during sustained physical exercise (*continuous lines*) as a function of the indexed effective orifice area (*EOA*) for aortic (**a**) and mitral (**b**) prostheses. Compared to patients, no. 2 and 4 who have large prosthetic EOAs, patients 1 and 3 with small EOAs exhibit a major increase in gradient with exercise, thus suggesting the presence of severe prosthetic stenosis or prosthesis–patient mismatch in these latter patients

As opposed to normally functioning and well-matched prostheses or to bileaflet mechanical valves with localized high gradient, the presence of valve stenosis or significant PPM is generally associated with a marked increase in gradients and pulmonary arterial pressure, the occurrence of symptoms, and an impaired exercise capacity on stress exercise echocardiography [67, 73–85]. An absolute increase in mean gradient ≥20 mmHg in the aortic position and ≥12 mmHg in the mitral position suggest severe prosthesis dysfunction or PPM (Fig. 36.10). High resting and stress gradients occur more often with biological rather than mechanical prostheses, stented rather than stentless bioprostheses, smaller (≤21 for aortic and ≤25 for mitral) rather than larger prostheses, and mismatched rather than nonmismatched prostheses. A peak stress systolic pulmonary arterial pressure ≥60 mmHg is consistent with the presence of a hemodynamically significant mitral prosthesis stenosis or regurgitation or mitral PPM.

As is the case in native aortic valves that have developed low-flow, low-gradient AS, dobutamine stress echocardiography may also be useful in differentiating true prosthesis stenosis from pseudo-stenosis or PPM in patients with prosthetic valves and low cardiac output. In the case of pseudo-stenosis with low output, the resting transprosthetic flow rate and thus the force applied on the leaflets are too low to completely open the prosthetic valve. During infusion of dobutamine, however, these patients manifest a substantial increase in the prosthesis EOA with the increasing flow rate, with no or minimal elevation in the prosthetic gradient. In contrast, true severe prosthetic stenosis or PPM is associated with no significant increase in EOA and a marked increase in gradient with dobutamine, often with additional diagnostic changes (such as LV dysfunction or marked elevation in pulmonary arterial pressure) and symptoms.

It should be emphasized that exercise or dobutamine stress echocardiography does not distinguish between acquired prosthesis stenosis and PPM, as in both

cases, the EOA remains small and the gradient increases markedly with stress. In this situation, one should compare the EOA values obtained during stress echocardiography with the normal reference values of EOA for the model and size of the specific prosthesis that has been implanted in the patient [67]. If the measured EOA is substantially lower than the normal reference EOA, one should suspect prosthesis dysfunction. If, on the other hand, the measured EOA is within the normal reference range and the indexed EOA is low, one should consider the presence of PPM.

In patients undergoing surgical correction of secondary MR, a restrictive annuloplasty combined with coronary artery bypass grafting is the most common approach. However, this procedure is associated with a relatively high rate of recurrence of MR, and restrictive annuloplasty may result in functional MS in some patients [86]. In patients with postoperative symptoms, residual MR, persistent pulmonary hypertension, or functional MS, exercise testing may be useful to assess symptoms and exercise capacity. Although the assessment of exercise hemodynamics with stress echocardiography can provide additional information regarding the significance of MS and/or of dynamic MR, more data are needed to confirm its clinical value.

36.6 Coronary Artery Disease and Coronary Flow Reserve

36.6.1 Diagnosis of Coronary Artery Disease in Patients with Valvular Heart Disease

Although stress echocardiography is a widely accepted, accurate, and safe noninvasive technique to diagnose the presence and severity of coronary artery disease in patients without valvular heart disease, relatively few data are available on its accuracy and safety in patients with hemodynamically significant valve disease. In general, one can expect that the sensitivity of stress echocardiography will be similar in patients with and without valvular heart disease but the specificity will be lower [87, 88]. Coronary flow reserve can be severely reduced in patients with AS or AR even when the epicardial coronary arteries are normal [89–91]. For this same reason, the specificity of perfusion imaging is also suboptimal in patients with LV hypertrophy secondary to valvular heart disease [87]. For practical purposes, conventional coronary angiography remains the established investigation for ruling out significant coronary artery disease in the preoperative evaluation of patients awaiting valve surgery, although cardiac computed tomography may also have a role in patients without coronary calcification. With both techniques, fractional flow reserve can be evaluated. When reduced, significant coronary artery disease is present [92].

36.6.2 Coronary Flow Reserve in Valvular Heart Disease

In patients with severe AS and normal coronary arteries, the reduced coronary flow reserve is more closely related to the severity of the stenosis than to the degree of LV hypertrophy [93]. The impairment of coronary flow reserve classically observed

in AS may be caused by several factors including extravascular compression of the coronary microvasculature due to elevated LV diastolic pressures, a shortening of diastolic perfusion time, and an increase in myocardial metabolic demand resulting from the LV pressure overload [94]. Of note, the reduction in coronary flow reserve is linked to BNP release. Patients with AS, nonobstructed coronary arteries, and reduced coronary flow reserve display lower survival rate that those with preserved flow reserve [95]. Following AVR or transcatheter aortic valve implantation, normalization of coronary flow reserve is directly related to the augmentation in valve EOA [91, 96].

Stentless bioprostheses are associated with greater improvement in coronary flow reserve compared to that of stented bioprostheses or mechanical valves [93], presumably because stentless bioprostheses generally provide a larger EOA for a given annulus size. In the future, the assessment of coronary flow reserve is likely to play an increasingly important role in the assessment of patients with valvular heart disease, especially aortic valve disease, before and after AVR.

Positron emission tomography has an established role in quantifying coronary flow reserve, and cardiac magnetic resonance imaging is evolving as another noninvasive method for this assessment [97], with the potential to quantify the transmural gradient of flow reserve across the myocardial wall [98]. Reduced myocardial perfusion reserve on cardiac resonance imaging is associated with aerobic exercise capacity in severe AS [99]. Both imaging techniques have been applied to study changes in coronary flow reserve in patients with AS after AVR [91, 93]. Transthoracic echocardiography also has the potential to study coronary flow reserve of the mid-distal left anterior descending coronary artery [100], and this technique has been applied to patients with AS [101] (Fig. 36.11). Echocardiography has the obvious advantage of wide availability and relatively low cost, and with further experience, this technique could be added to the standard routine applications of echocardiography in evaluating valve disease [102, 103].

36.7 Pitfalls

Many indications in stress echo applications in valvular heart disease are based on a level C weight of evidence, and the proposed cutoff values remain consensus driven rather than supported by outcome-based evidence [8]. The Doppler assessment of PASP – which is central in the evaluation of several conditions – has imperfect agreement with the gold standard of right heart catheterization, remains unfeasible in 15 % of patients with inadequate tricuspid regurgitation jet, and is unreliable in massive tricuspid regurgitation. During stress, we still lack accepted cutoff values between normal and abnormal responses. Pulmonary artery systolic pressure values are linearly dependent on cardiac output, and multipoint pulmonary artery pressure–flow relationship should also be integrated with the evaluation of pulmonary vascular resistances. Post-exercise measurements are unreliable because

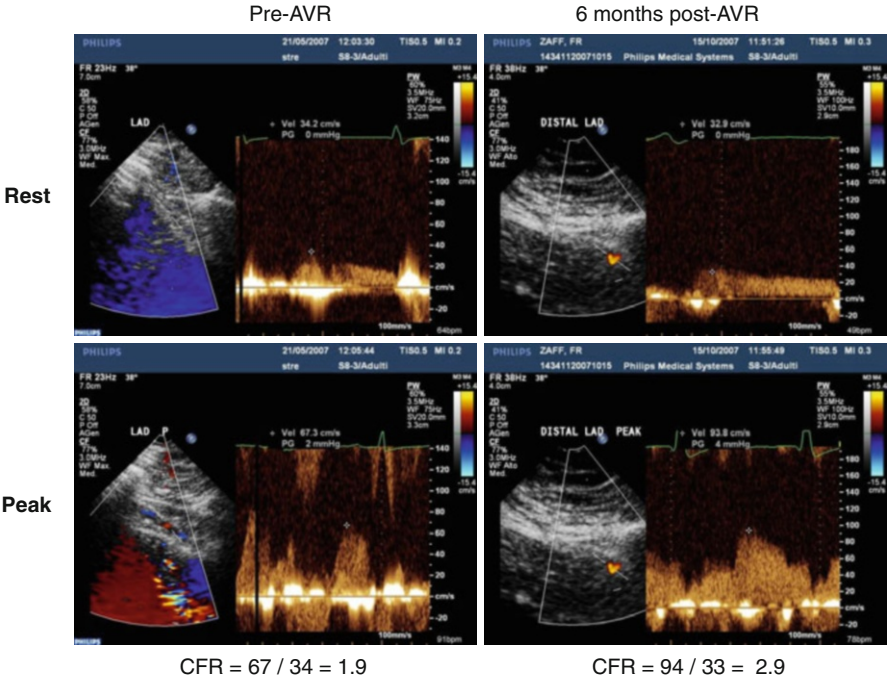


Fig. 36.11 Coronary flow reserve (*CFR*) assessed at rest and during adenosine administration by transthoracic stress echocardiography in a patient with severe aortic stenosis and angiographically normal coronary arteries before (*left panel*) and 6 months after (*right panel*) aortic valve replacement (*AVR*). In the postoperative assessment, left ventricular hypertrophy is not yet regressed, but CFR has substantially improved (Courtesy of Dr. Fausto Rigo, Venice, Italy)

of rapid return to baseline of pulmonary hemodynamics [8]. Prospective large-scale and randomized outcome studies are needed to support more evidence-based, stress echo-driven treatment strategies.

36.8 Clinical Guidelines

Recent guidelines have accepted the use of stress echocardiography to help risk stratify patients to aid the diagnosis and, in selected cases, guide decisions for valve intervention (ESC 2012). The most frequent indications are for the assessment of mitral regurgitation (52 %), aortic stenosis (34 %), mitral stenosis (8 %), and aortic regurgitation (6 %). The indications are inappropriate in 15 % of referrals [103]. A positive result was found in 1 out of 3 patients. The main indications of stress echo in VHD are summarized in Table 36.1, the criteria of positivity are listed in Table 36.2 and the implementation of the results into the management are depicted in Table 36.3.

Table 36.1 The main applications of stress echo in valvular heart disease

	A	M	R	COR	LOE	
Asymptomatic VHD						
Severe MR	√			IIa	C	ACCF/AHA 2011
Severe MS	√			I	C	ACCF/AHA 2011
Severe AR	√			EC		ACCF/AHA 2011
Severe AS, normal EF		√		C	IIb	ACCF/AHA 2011
Moderate AS, AR, MR, MS		√		EC		ACCF/AHA 2011
Mild MS, MR, AS, AR			√	EC		ACCF/AHA 2011
Symptomatic VHD						
Moderate MS	√			I	C	ACCF/AHA 2011
Low-flow, low-gradient AS	√			IIa	B	ACCF/AHA 2014
Moderate MR	√				EC	ACCF/AHA 2011
Mild MS, MR		√			EC	ACCF/AHA 2011
Severe AS, MS, MR			√		EC	ACCF/AHA 2011

Adapted from Ref. [103]
A appropriate, *M* may be appropriate, *R* rarely appropriate, *COR* class of recommendation, *EC* expert consensus, *LOE* level of evidence

Table 36.2 Criteria for positive stress echocardiogram applications in assessment of valvular heart disease

Valve assessment	Criteria for positive test results
Assessment of mitral regurgitation in patients with symptoms but mild or moderate mitral regurgitation at rest	Increase in severity of mild or moderate mitral regurgitation to severe. Effective orifice area ≥0.4 cm^2 (organic) or ≥0.2 cm^2 (functional)
Assessment of asymptomatic severe mitral regurgitation	Increase in pulmonary artery systolic pressure >60 mmHg. Lack of increase in LVEF ≥4 % or global longitudinal strain ≥2 %
Assessment of mitral stenosis in patients with symptoms but mild or moderate mitral stenosis at rest	Increase in the mean transmitral gradient ≥15 mmHg or estimated pulmonary artery systolic pressure ≥60 mmHg
Assessment of asymptomatic severe mitral stenosis	As above and symptoms
Assessment of asymptomatic severe aortic stenosis (AVA <1 cm^2)	Increase in mean transaortic gradient ≥20 mmHg
Assessment of asymptomatic severe aortic regurgitation	Lack of increase in LVEF ≥5 % or exercise-induced reduction in LVEF
Asymptomatic severe MR	Increase in PASP ≥60 mmHg
Asymptomatic severe MS	Increase in PASP ≥60 mmHg
Asymptomatic severe AS	Increase in transvalvular gradient ≥20 mmHg
Asymptomatic severe AR	Lack of increase (or decrease) in LVEF ≥5 %

Equivocal aortic prosthetic valve PPM/stenosis increase transvalvular gradient ≥20 mmHg
Equivocal mitral prosthetic valve PPM/stenosis increase transvalvular gradient ≥12 mmHg

Table 36.3 Clinical implementation of results per stress echocardiography indication

Indication	Stress echo result	Management (Ref.)
Symptomatic patient		
Non-severe MR	Non-severe MR	Conservative management
	Severe MR	Surgical indication [2]
Pulmonary edema	Inducible ischemia +/− MR	Revascularization +/− MV repair
Mild MR before CABG	No dynamic MR	CABG only
	Dynamic MR + PASP rise	CABG + MV repair [3]
Non-severe MS	Non-severe MS	Conservative management
	Severe MS	Intervention: class I indication [2, 3]
Non-severe AR	Normal response	Conservative management
	Abnormal response	Case discussion by the Heart Valve Team
Non-severe AS	Non-severe AS	Investigate symptoms as noncardiac
	Severe AS	Intervention: class I indication [2, 3]
Paradoxical low-flow AS	Non-severe AS	Conservative management
	Severe AS	Intervention: class IIa indication [2, 3]
Equivocal PPM/ stenosis	Non-severe PPM/stenosis	Conservative management
	Severe PPM/stenosis	Case discussion by the Heart Valve Team considering intervention
Asymptomatic patient		
Severe MR	Symptoms	Surgery: class I indication [2, 3]
	No symptoms + normal VSE	Review at 6 months
	No symptoms + PASP >60 mmHg	Repair if durable low risk: class IIb indication [3]
	No symptoms + no LV CR	Case discussion by the Heart Valve Team considering intervention
Significant MS	Symptoms	Intervention: class I indication [2, 3]
	No symptoms	Conservative management*
Severe AR	Symptoms	Surgery: class I indication [2]
	No symptoms	Review at 6 months
	No symptoms + no LV CR	Close surveillance
Severe AS	Symptoms	Intervention: class I indication [2, 3]
	No symptoms + normal VSE	Review at 6 months
	No symptoms + blood pressure drop	Intervention: class IIa indication [2, 3]
	No symptoms + mean gradient rise >20 mmHg	Intervention: class IIb indication [3]
Low LV ejection fraction		
Low-flow AS	Non-severe AS	Conservative management
	Severe AS + flow reserve	Intervention: class IIa indication [2, 3]
	Severe AS + no flow reserve	Intervention: class IIb indication [3]/ class IIa indication [2]

*Hemodynamically significant MS may require intervention prior to non-cardiac surgery or pregnancy planning

BP Blood pressure, *CR* contractile reserve of left ventricle, *HVT* discussion with Heart Valve Team considering intervention

Conclusion

Exercise testing has an established role in the evaluation of patients with valvular heart disease that can aid significantly in clinical decision-making. Stress echocardiography has emerged as an important component of stress testing, in which the noninvasive assessment of dynamic changes in valve function, ventricular function, and hemodynamics can be coupled with assessment of exercise capacity and symptomatic responses. Surprisingly, this role is now better established in both American [2] and European [3] general cardiology guidelines, despite some discrepancy in the indications and implementation of the results into the management. Stress echocardiography has the advantages of wide availability, low cost, and versatility for the assessment of disease severity [2, 3, 10, 11]. In addition to its established applications in valvular heart disease, transthoracic Doppler echocardiography also has the potential to assess coronary flow reserve. The versatile applications of stress echocardiography can be tailored to the individual patient with aortic or mitral valve disease, both before and after valve replacement or repair. Hence, exercise-induced changes in valve hemodynamics, ventricular function, and pulmonary artery pressure, together with exercise capacity and symptomatic responses to exercise, provide the clinician with diagnostic and prognostic information that can contribute importantly to subsequent clinical decisions [104].

Table of Contents Video Companion

See illustrative cases number 32, 33, 34, and 35 (aortic stenosis with low-flow, low-gradient, and reduced ejection fraction) by Maria Joao Andrade, MD, Carnaxide, Lisbon, Portugal

See also, in the section Nuovo Cinema Paradiso remastered, the short movie: The Rocky Horror Stress echo picture show (with a complicated stress echo case in a patient with aortic stenosis).

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Pediatric Stress Echocardiography

37

Michael Henein and Eugenio Picano

The rationale for applying stress echocardiography in children is not different from application of the technique in adults [1]. Sick children may need cardiac stress imaging, and stress echocardiography is becoming more common in the pediatric population [2]. Obviously, to perform these procedures in the most adequate way, proper training of personnel and staffing of the pediatric stress laboratory are required to ensure the safety of patients and that the desired testing information is obtained. For these reasons, and as recommended by a recent 2006 statement of the American Heart Association (AHA), pediatric testing should remain an integral part of pediatric cardiology training [3]. The versatility of stress echocardiography is ideally suited to tailor the most appropriate test to the individual patient, with specific signs used to address the particular diagnostic question in the individual patient (Table 37.1).

37.1 Pediatric Coronary Artery Disease

There are several patient populations for whom stress echocardiography can be used to detect ischemia-producing coronary artery stenosis in children. Kawasaki disease (KD) is an acute self-limited vasculitis of childhood that is characterized by fever, bilateral non-exudative conjunctivitis, erythema of the lips and oral mucosa, changes in the extremities, rash, and cervical lymphadenopathy. Advances in clinical therapies (with intravenous immunoglobulin and aspirin) have reduced, but not eliminated, the incidence of coronary artery abnormalities in affected children. Today, KD is the most common cause of acquired cardiovascular disease in children in the USA. Coronary artery aneurysms or ectasia develops in 20 % of untreated children and may lead to ischemic heart disease or sudden death [4]. According to 2004 AHA guidelines on KD, cardiac stress testing for reversible ischemia is indicated to assess the existence and functional consequences of coronary artery abnormalities in children with KD and coronary aneurysms (evidence level A). Irrespective of the chosen stress modality, diagnostic accuracy for identifying angiographic-proven

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Table 37.1 Application of pediatric stress echocardiography

	Target	Method	Stress	Disease
CAD detection	Regional wall motion abnormalities	2D	Ex (dob, dip)	Kawasaki, transplant CAD, arterial switch
Valve stenosis	Transvalvular gradients	CW Doppler	Ex (dob)	Native aortic stenosis, native pulmonary stenosis, prosthetic valves
Pulmonary hemodynamics	PASP	CW Doppler (TR jet)	Ex (dob)	Right ventricular overload
Contractile reserve	Normal baseline function, depressed baseline function	2D	Ex (dob)	Thalassemia
Coronary flow reserve	Coronary macro- and microcirculation	Pulsed Doppler CFR	Dip, ado, cold	Kawasaki, switch, right and left ventricular overload

CAD coronary artery disease, *Ex* exercise, *dob* dobutamine, *dip* dipyridamole, *CW* continuous wave, *PASP* pulmonary artery systolic pressure, *TR* tricuspid regurgitation, *CFR* coronary flow reserve

coronary artery disease is high and comparable, with exercise or pharmacological stress-induced wall motion abnormalities representing a highly specific marker of coronary artery involvement, with excellent overall diagnostic accuracy [5–8], comparable to stress scintigraphy. The guidelines conclude that "the choice of stress modality should be guided by institutional expertise with particular techniques, as well as by the age of the child (e.g., pharmacological stress should be used in young children in whom traditional exercise protocols are not feasible)" [4]. The acute diagnostic benefit is similar between these techniques, but the long-term risk is disproportionately high with ionizing techniques (see after: Sect. 37.7). Therefore, the use of methods such as myocardial scintigraphy [9], computed tomography [10], and systematic coronary angiography [11], although informative, should be drastically minimized in the young patients.

A national survey in Japan on the pediatric cardiologist's clinical approach for patients with KD showed that for high-risk patients, as early as in 2002, more responders favored stress echocardiography when compared with nuclear imaging. For high-risk levels, 60 % of pediatric cardiologists perform coronary angiography not on a regular basis but only when coronary symptoms are present or when stress imaging suggests myocardial ischemia [12].

Clearly, more data are needed in this field, but stress echocardiography based on visual assessment of regional wall motion abnormalities will play a key role in surveillance and management of patients with coronary artery residua. To date, alternative echocardiographic approaches based on other, more quantitative markers of ischemia are available. These include longitudinal function assessment with mitral annulus plane systolic excursion [13], cyclic backscatter variation with tissue characterization techniques [14], and perfusion changes with myocardial contrast echocardiography [15]. Each of these markers has an interesting rationale. Long-axis

function can detect minor forms of ischemia, unable to affect radial function and regional systolic thickening, since longitudinal fibers run in the subendocardial layer; thus abnormalities accurately reflect subendocardial ischemic dysfunction. Longitudinal function can be impaired when radial motion is normal or even supernormal [13]. Cyclic backscatter variation is proportional to intramural contractility and higher in the subendocardium than in the subepicardium, mirroring the well-known intramural contractility gradient. Therefore, minor forms of subendocardial hypoperfusion may impair subendocardial function and blunt cyclic backscatter variation without a detectable impairment in regional systolic thickening [14]. Finally, myocardial contrast echocardiography evaluates myocardial perfusion heterogeneity, which is more sensitive (albeit less specific) than regional wall motion abnormalities as a marker of myocardial ischemia [15]. None of these markers based on new technologies or contrast stress echocardiography should be exclusively considered for clinically driven applications due to inadequate validation to date. In adolescent KD survivors, dobutamine stress echo provided long-term prognostic information, which was powerfully stratified on the basis of peak wall motion score index in the initial stress echo. Stress-induced wall motion abnormalities were observed in the presence of fixed coronary artery stenoses but also in patients with non-stenotic coronary artery lesions such as giant aneurysm, in which blood flow is sluggish and risk for thrombosis is high, suggesting the influence of dynamic coronary stenosis superimposed on any degree of anatomic fixed stenosis or microvascular changes due to systemic vasculitis and reducing coronary flow reserve [16]. Therefore, the anatomic information provided by coronary arteriography and the functional information on inducible ischemia provided by stress echo may diverge. For the prediction of outcome, the response during stress echo is even better than coronary anatomy, since it evaluates the functional significance of coronary artery lesions that are responsible for latent vulnerability of myocardial ischemia and especially in predicting future cardiac events over time in patients with KD and coronary artery lesions [17].

At present, it appears reasonable to propose a very simple diagnostic algorithm in these patients, who must be screened with resting transthoracic echocardiography to detect coronary artery morphological anomalies, which are the cornerstone of diagnosis and risk stratification (from class I, low risk, to V, high risk). A positive stress echocardiogram is frequently found in the high-risk class; therefore, it appears appropriate to use it in class IV and V patients [18], especially in view of an ischemia-driven revascularization, yielding greater prognostic benefit than an anatomy-driven revascularization (Fig. 37.1).

37.2 Transplant Coronary Artery Disease

The leading cause of death after the first year of cardiac transplant is transplant coronary artery disease, occurring in up to 43 % of patients at 3 years following transplant [19]. This form of coronary disease, also known as graft coronary disease, differs from classical atherosclerosis in both histologic and angiographic

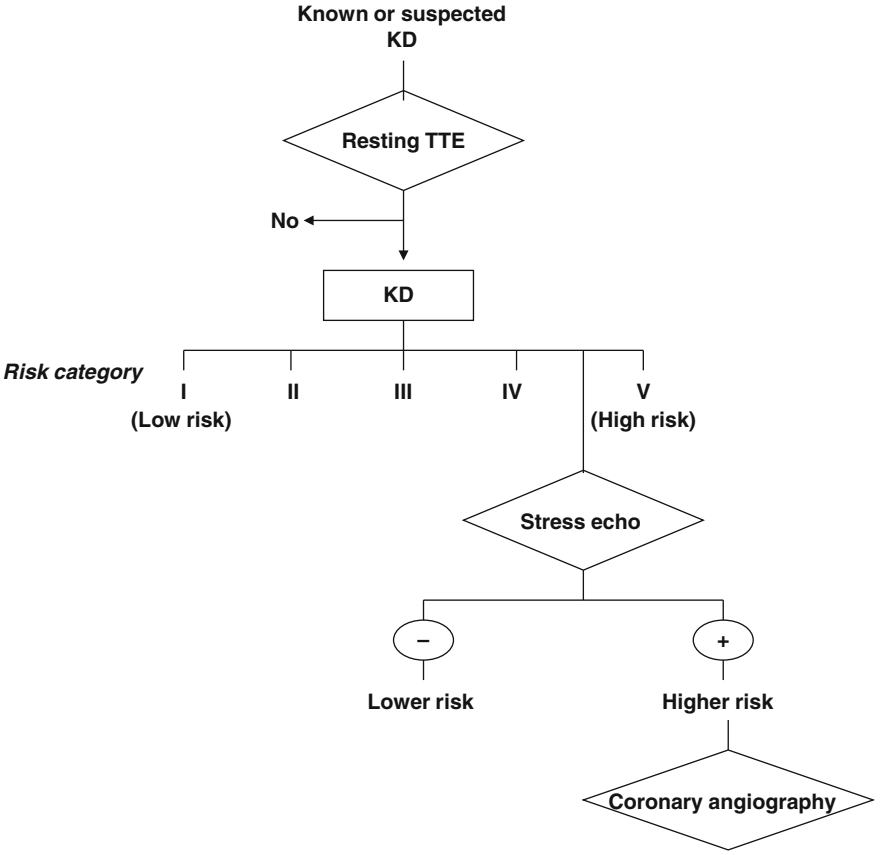

Fig. 37.1 A proposed algorithm in a young patient with known or suspected Kawasaki disease (*KD*). Resting transthoracic echocardiography is essential for the diagnosis and for risk assessment. In patients with high-risk class (AHA grade *IV* and *V*), stress echocardiography is warranted. Patients with a positive response belong to a higher-risk group warranting further investigation with coronary angiography with the perspective of an ischemia-driven revascularization (Adapted from JCS Joint Working Group [18])

features, and it progresses much more rapidly. Because the disease is diffuse and usually involves small vessels, it makes coronary arteriography an unreliable diagnostic technique—a matter that turned physicians to other modalities, such as stress echocardiography. A total of *seven* stress echo (with dobutamine or exercise) studies, including over 250 patients [20–26], showed excellent diagnostic value [20–22] and prognostic capability [23, 24], since patients with positive test results had a sixfold higher risk of subsequent cardiac events. Thus, stress echo has become routinely recommended for the detection of cardiac allograft vasculopathy in children with heart transplant [27].

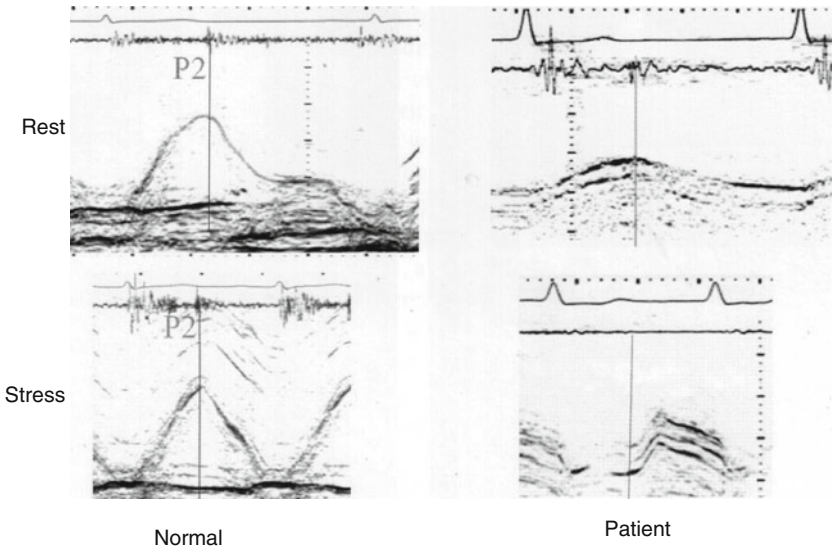

Fig. 37.2 Right ventricular free wall *M*-mode at rest (*top*) and stress (*bottom*) from a normal control and a patient after Mustard repair showing stress-induced incoordination of the patient (*right*), suggesting underlying ischemia (Modified from Li et al. [29])

37.3 Transposition of Great Arteries After Surgical Repair

The long-term problems that are associated with repaired transposition of the great arteries depend on the type of repair. The oldest patients have intra-atrial repair, either Mustard or Senning type, in which venous return is directed to the contralateral left ventricle by means of an atrial baffle. As a consequence, the right ventricle supports the systemic circulation. Relatively young patients with transposition undergo an arterial switch operation, to allow the left ventricle to function as the systemic pump [28].

In patients with Mustard or Senning repair, right ventricular dysfunction and pulmonary hypertension are a possible complication. Patients with exertional symptoms, angina-like chest discomfort, or breathlessness could be physiologically assessed by stress echocardiography. A close relationship between right ventricular function and exercise tolerance assessed by cardiopulmonary exercise testing has been found in these patients. Furthermore, right ventricular function becomes very abnormal at fast heart rate, demonstrating disturbances similar to those seen in patients with coronary artery disease, suggesting a possible underlying ischemic dysfunction [29]. These findings are consistent with those found in dilated cardiomyopathy (Fig. 37.2) in whom right ventricular dysfunction has been shown to predict exercise capacity as well as prognosis.

The arterial switch operation, which includes coronary artery transfer, is the surgical procedure of choice for transposition of the great arteries. Mortality and clinical long-term outcome depend largely on adequate perfusion through the transferred coronary arteries. Late deaths can be related to coronary occlusion, and intravascular ultrasound assessment, late after arterial switch operation revealed proximal eccentric intimal thickening in most coronary arteries, suggesting the development of early atherosclerosis in reimplanted coronary arteries [30]. These patients tend to have a consistently reduced coronary flow reserve [31]. Only anecdotal reports present in the literature on a total of 34 patients from two studies—one with dobutamine [32] and the other with transesophageal atrial pacing [33]—suggest that a stress-induced regional wall motion abnormality or reduced left ventricular long-axis function portends a negative prognosis.

37.4 Valve and Intraventricular Gradients

Several studies have been performed in native stenotic aortic, pulmonary, and prosthetic valves during high-flow states to unmask an abnormally high increase in gradients. The transvalvular gradient increases with increasing flow rates; the higher the transvalvular flow, the higher the pressure gradient. A moderately and a severely diseased native valve, and a normal or abnormally functioning prosthesis, may display similar gradients at rest, but the marked rise in mean gradients during stress in the latter is to be distinguished from the fairly flat gradient response of the moderately diseased native or normally functioning prosthetic valves. The rationale of this application is very strong, but systematic data, especially in children, are still conspicuously lacking to date [34]. A similar application evaluates the development of intracardiac gradients in young athletes or patients with hypertrophic cardiomyopathies, in whom dobutamine or exercise can unmask an intraventricular obstruction unapparent at rest and which may have prognostic and therapeutic implications [3].

The measurement of gradients is especially important in left-sided heart obstructive lesions: aortic valve disease, subvalvular and supravalvular aortic stenosis, and coarctation of the aorta. According to 2008 ACCF/AHA guidelines for adults with congenital heart disease, patients with subaortic stenosis, resting peak gradients less than 50 mmHg, and symptoms of breathlessness and fatigability should be investigated with exercise Doppler to determine whether the gradient increases with exertion. In aortic coarctation, stress echocardiography Doppler is valuable and is targeted at obtaining the rest and exercise suprasternal notch continuous-wave Doppler coarctation gradient, including the diastolic profile. In the follow-up post-correction, mean gradient >20 mmHg with diastolic runoff is indicative of recoarctation [3] (Fig. 37.3).

37.5 Contractile Reserve

Patients with normal ejection fraction at rest can indeed have subtle alteration in left ventricular function. This initial impairment can be detected as a reduction in long-axis function detected by mitral annular plane systolic excursion or tissue Doppler

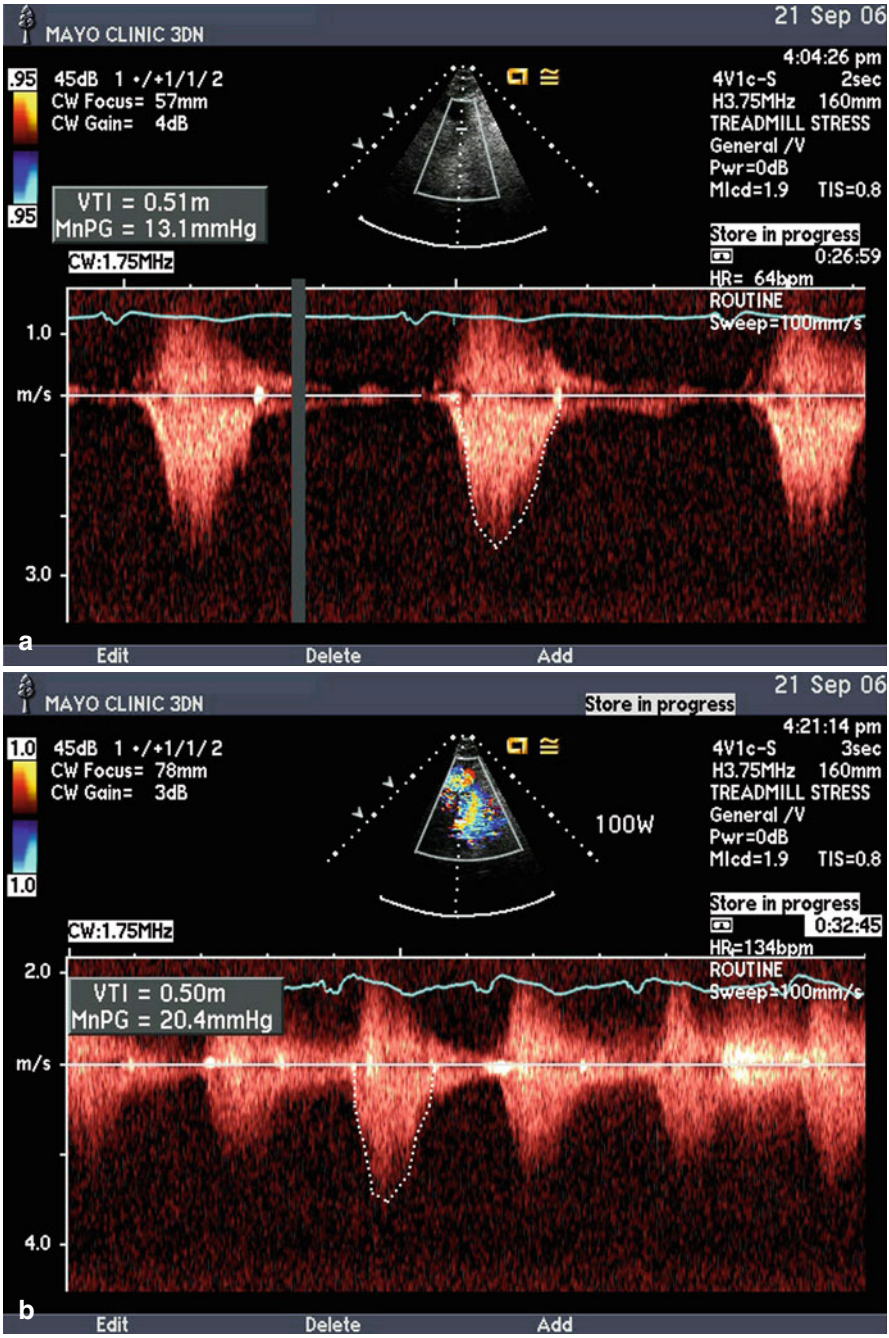

Fig. 37.3 Transcoarctation gradients from suprasternal window before (panel **a**) and at peak (panel **b**) exercise. There is an increase in mean gradient (from 13 mmHg at rest to >20 mmHg at peak exercise) with diastolic runoff at peak exercise, indicating coarctation (By courtesy of Patricia Pellikka, MD, Mayo Clinic, Rochester, USA)

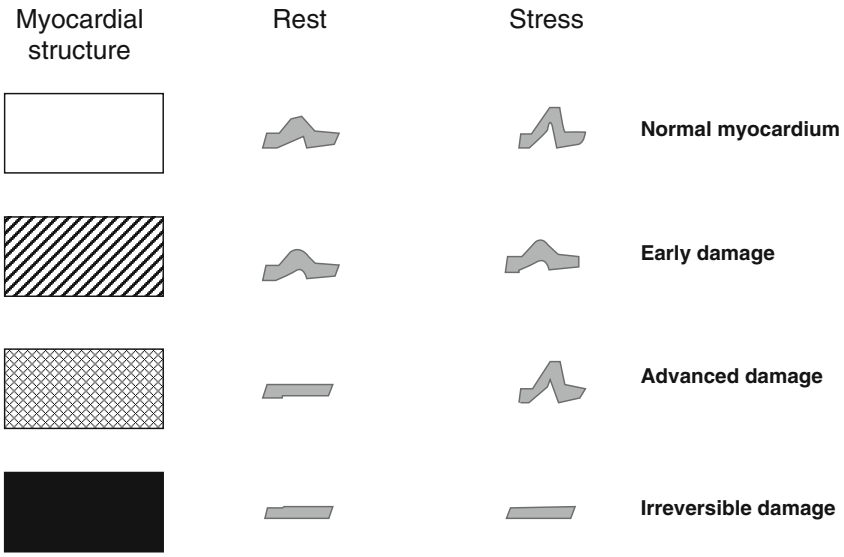

Fig. 37.4 Different stages of severity of myocardial damage in cardiomyopathy, due to, for instance, thalassemia or cardiotoxic chemotherapy

imaging, both in experimental models [35] and in patients [36]. Alternatively, an initial myocardial damage can be detected as a blunted contractile response to an inotropic stress, such as dobutamine or exercise. This pattern has been described in anthracycline-treated long-term survivors of childhood cancer [37–40] or in thalassemic patients at an early stage of disease [41]. At a more advanced stage, left ventricular function can be depressed, and the inotropic challenge can restore a normal function in patients who might have a better cardiac outcome if cardiotoxic chemotherapy is discontinued [4] (Fig. 37.4).

The assessment of contractile reserve of the right ventricle is of great importance [29]. In patients with Mustard repair for transposition of the great arteries or repaired tetralogy of Fallot [42], impaired exercise tolerance can be predicted by right ventricular long-axis function at baseline and during stress. Longitudinal function can be assessed by simple long-axis amplitude of motion (from TAPSE for the right and MAPSE for the left ventricle) or from peak systolic velocity of basal left ventricular segments by tissue Doppler imaging [29, 42].

37.6 Coronary Flow Reserve

Coronary flow reserve can be reduced in children with congenital heart disease as a consequence of epicardial coronary artery anomalies due to primary coronary microcirculatory damage or ventricular hypertrophy [43]. Pulsed Doppler transthoracic echocardiography is ideally suited for assessing coronary flow reserve in these patients, both in the mid-distal left anterior descending coronary artery (with >90 % feasibility) and in the right coronary posterior descending arteries (with >70 %

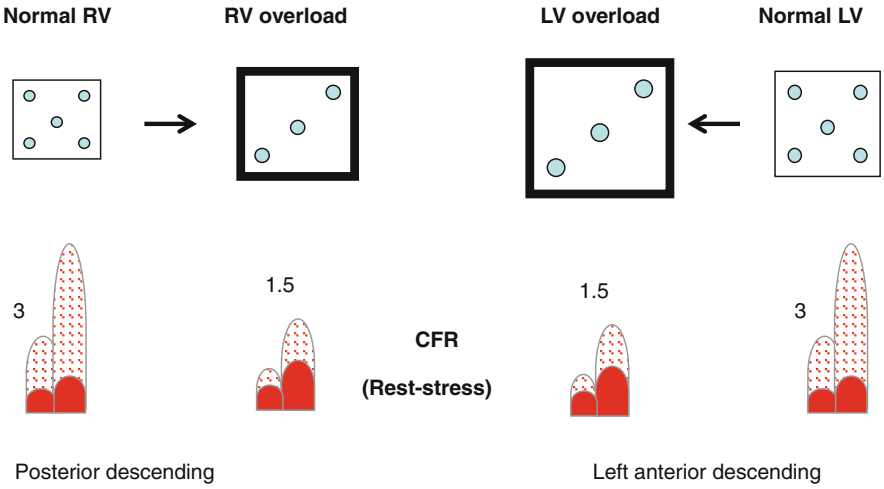

Fig. 37.5 Schematic representation of the coronary flow reserve (*CFR*) pattern, as can be visualized by transthoracic vasodilator stress echocardiography, in patients with left ventricular (*right panel*) or right ventricular (*left panel*) overload

feasibility). High-frequency transducers with second harmonic technology greatly enhance the success rate of the technique in expert hands, often not requiring contrast injection. The employed stressor is usually adenosine or dipyridamole, but the cold pressor test has also been fruitfully proposed in children. The normal increase in coronary flow reserve is about 250 % following adenosine (or dipyridamole, which accumulates endogenous adenosine) and about 200 % after cold, which mainly acts through a hemodynamically mediated increase in heart rate and blood pressure [44]. Coronary flow reserve could be impaired—even in the absence of anatomic epicardial coronary artery disease—in children 5–8 years after the switch operation, which is mirrored by reduced vasodilation following nitrates, an endothelium-independent vasodilator stimulus [31]. In KD, the impairment in coronary flow reserve is largely independent of epicardial coronary artery lesions and aneurysms, again suggesting primary coronary microcirculation impairment [45]. The reduction of coronary flow reserve can be either diffuse or branch specific [44–48]. The impairment of coronary flow reserve is an integrated index of epicardial vessel status, myocardial hypertrophy, and coronary microcirculation structural and functional conditions [49, 50] (Fig. 37.5). In adults, the reduction in coronary flow reserve has a clinically relevant prognostic value, over and above regional wall motion (see Chap. 9). Whether this is true also for children remains to be established.

37.7 Radiation Exposure in Children: Implications for Imaging Strategy

For any given radiological effective dose, the risk for some organs, including the brain, is 3–4 times higher in children than in adults [51] (Fig. 37.6). Children are at substantially higher risk than adults because they have more rapidly dividing cells

and a greater life expectancy, allowing the clinical manifestation of radiogenic cancer with long latency periods of decades. Thus, an infant or child patient has a longer lifetime risk for developing radiation-induced cancers than adult patients. At the age of 15–20 years, grown-up congenital heart disease patients have already cumulated an effective dose exposure corresponding to 20–40 mSv, with an estimated lifetime attributable extra risk of cancer of 1 in 10–1 in 100 [52]. The average child in the USA will have seven medical imaging tests involving radiation by the time he or she reaches the age of 18. About 1 in 4 children had 2 or more imaging tests involving radiation during the 3-year period and about 1 in 7 children had at least 3 tests [53]. The chest is the most frequently evaluated region of the body in children [54]. Scans are CT in 8 % of children and are often done without adjusting exposure parameters to weight, resulting in up to 50 % of the dose being unnecessary [54].

Among pediatric cardiology patients with congenital heart disease, fluoroscopically guided diagnosis and interventions account for 3.5 % of all radiological examinations performed and 84 % of their total collective dose [55]. In the USA, this issue of radiological responsibility was addressed with the Image Gently, Step Lightly Campaign, especially focused on the risks of unnecessary and excessive medical radiation exposure from interventional radiology administered to pediatric patients [56]. In perspective, CMR-guided catheterization has the potential to replace the current X-ray-based diagnostic and interventional procedures for

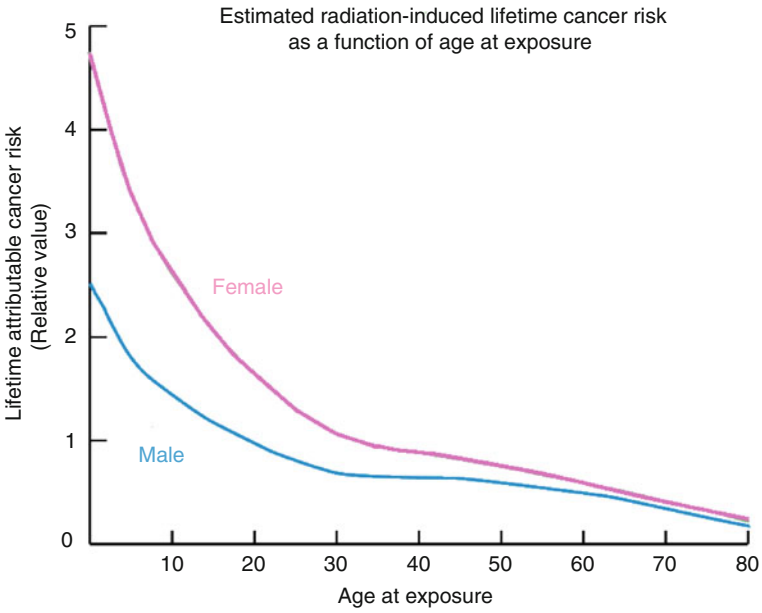

Fig. 37.6 Attributable lifetime risk for a single small dose of radiation according to age at time of exposure. The oncologic, stochastic risk is about 38 % higher in women than in men and 400 % higher in children age <1 year than in adults (Adapted from Ref. [51], Redrawn from: BEIR VII, 2006)

children, while improving soft tissue imaging. CMR can also provide detailed anatomic and functional information in patients with CHD and adult CHD and is a cornerstone of the care of these patients [57]. With the classic epidemiology approach (requiring thousands of patients followed up for decades to detect increased incidence of cancer), it was recently shown in a retrospective cohort study that cumulative ionizing radiation doses from 2 to 3 head CTs could almost triple the risk of brain tumors and 5–10 head CTs could triple the risk of leukemia [58]. With the molecular epidemiology approach (requiring hundreds of patients evaluated cross-sectionally with intermediate endpoints and long-term predictors of cancer such as chromosome aberrations and micronuclei in circulating lymphocytes), it was shown that cardiac catheterization procedures performed in infants with congenital heart disease induce an acute increase of DNA double-strand breaks [59] and are associated with a 200 % long-lasting increase in circulating micronuclei, few decades after the exposure [60]. There is little question that with the restoration of radiological awareness, stress echocardiography will become the technique of choice in children, and—when used in tandem with CMR—will help patients to achieve the benefits of the highest diagnostic standards without the long-term oncogenic risks of radiation exposure [61].

37.8 Pitfalls

Suboptimal image quality due to restricted acoustic window is associated with postoperative changes in pediatric and adult CHD, and ultrasound contrast is commonly needed to obtain interpretable images [62].

A focused competence for the pediatric population should ideally be an integral part of the high-volume stress echocardiography laboratory. Diagnostic questions raised by children are extremely variable and require a versatile approach of highly trained personnel. Pediatric stress echocardiography is best performed in teamwork—between an adult cardiologist trained in stress echocardiography and a pediatric cardiologist directly involved in the treatment of the patient. Together, the two cardiologists discuss the indications, perform the examination, and use the results in the light of the clinical context (Table 37.2).

Table 37.2 Stress echocardiography in children vs. adults

	Adults	Children
Stress	Exercise > pharmacologic	Pharmacologic > exercise
Evidence available	Established	Initial
Safety concerns	+	+++
Vulnerability to radiation damage	+	++++
Use of cardiac scintigraphy	Declining	Disappearing
Complementary technique	CMR	CMR

CMR cardiovascular magnetic resonance

Table 37.3 Application of stress echo in children and adults with CHD

	A	M	R	COR	LOE	References
LVOT obstruction syndromes						
Isolated subaortic stenosis						
Exercise stress echo with resting mean gradient <30 mmHg in otherwise equivocal indication to intervention		√		IIa	C	*ACCF*, 2008 [3]
Aortic coarctation						
Exercise (or dobutamine) stress echo with suprasternal notch CW Doppler coarctation gradient, including the diastolic profile		√		IIa	C	*ACCF*, 2008 [3]
Dextro-transposition of the great arteries after arterial switch operation						
Adult survivors should have noninvasive ischemia testing every 3–5 years	√			I	C	*ACCF*, 2008 [3]
ALPACA						
For adult survivors of repair, noninvasive stress testing is indicated every 3–5 years	√			I	C	*ACCF*, 2008 [3]
Detection of cardiac allograft vasculopathy in children with heart transplant	√			I	C	*ISHT*, 2010 [27]
Kawasaki disease						
Coronary lesion severity class IV, V	√			I	C	*JCS*, 2010 [18]
Coronary lesion severity class I, II, III		√		II	C	

A appropriate, *M* may be appropriate, *R* rarely appropriate, *ALPACA* anomalous left coronary artery from the pulmonary artery, *COR* class of recommendation, *LOE* level of evidence

37.9 Clinical Guidelines

Since the advent of neonatal repair of complex lesions in the 1970s, an estimated 85 % of children with congenital heart disease (CHD) today usually survive into adult life, and in the next decade, almost 1 in 150 young adults will have some forms of CHD [3]. Guidelines recommend that diagnostic imaging procedures should be performed in a regional adult CHD center with appropriate experience in CHD and in a laboratory with appropriate personnel and equipment [2, 3]. In general, we need stronger evidences to support a more widespread use of stress echo in these patients, who can benefit most from the unique assets of the method, especially its radiation-free nature and versatility of the information provided. The main applications are summarized in Table 37.3. Adults with CHD often need repetitive imaging, making them vulnerable to radiation-induced cancer; hence, modalities using ionizing radiation should be minimized [51, 56].

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Part V

Comparison with Other Imaging Techniques

Stress Echocardiography Versus Stress Perfusion Scintigraphy

38

Thomas H. Marwick and Eugenio Picano

38.1 Nuclear Cardiology: The Imaging Paradigm

Nuclear cardiology is the time-honored offspring of the marriage between nuclear technology and coronary physiology [1]. Several imaging paradigms later endorsed by stress echocardiography were first understood, proposed, and popularized by nuclear cardiology: the merit of imaging cardiac function during stress, in lieu of the simple electrocardiogram; the value of the pharmacological alternative to physical exercise for stressing the heart; the need to assess viability in segments with resting dysfunction; the advantage of routine use of digital handling for data acquisition, storage, and display; and the prognostic impact of extent and severity of stress-induced ischemia [2]. Although the comparison of nuclear cardiology and echocardiography previously involved a fundamental philosophical issue between the diagnosis of coronary disease based on perfusion (hence the possibility of influencing these data on the basis of small vessel disease, hypertrophy, and other causes of abnormal coronary flow reserve) and evidence of ischemia (hence less sensitivity to mild disease that may engender submaximal attainment of flow without ischemia), recent advances have made it possible for both techniques to offer function and coronary flow reserve data [3]. Each technique has adopted various technical advances, which include a "methodological drift" to incorporate information previously used by the other; thus, gated single-photon emission computed tomography (SPECT), ventriculography, and attenuation correction have been added to SPECT [4], while harmonic imaging, pulsed Doppler coronary flow reserve, diastolic and valvular evaluation, myocardial contrast, and real-time three-dimensional (3D) imaging have been added to echocardiography [5]. These technical advances have provided particular benefits to subpopulations, although it seems unlikely that the few percentage point changes to overall sensitivity and specificity will render obsolete the general conclusions derived from comparison of the methods over the last 30 years, upon which this chapter is based.

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38.2 SPECT, PET, and PET–CT Imaging: Advantages and Limitations

SPECT imaging in combination with 201 thallium or 99mTc tracers is a powerful technique for the detection of perfusion abnormalities during hyperemia induced by pharmacological or physical stress, and it also allows assessment of viability [6]. The mechanism of this test – based on the detection of relative hyperemia – is a fundamental distinction from stress echocardiography, which is dependent on the induction of ischemia in a functional and metabolic sense. Hyperemia may be induced directly (by coronary vasodilators) or indirectly (whereby endogenous vasodilators are produced in response to exercise or dobutamine). The presence of preexisting coronary vasodilation induced by antianginal therapy, or limitation of the vasodilator response due to drug therapy or submaximal exercise, may blunt the difference between rest and stress, impairing the detection of less severe stenoses and contributing to lower sensitivity [7]. Nonetheless, antianginal drug therapy has a greater effect on the results of echocardiography [8, 9] because it prevents the development of ischemia.

38.2.1 Advantages

SPECT and positron emission tomography (PET) have a high technical success rate and are relatively operator independent. SPECT has excellent sensitivity (usually 85–90 %) and good-to-moderate specificity (70–80 %) for the detection of angiographically assessed coronary artery disease. The accuracy of PET is probably greater, especially in the posterior circulation and in obese subjects, where the inherent attenuation correction of PET is advantageous [10]. The extent and severity of stress-induced perfusion defects have important prognostic implications, now supported by a huge evidence base with SPECT [11, 12] and a smaller evidence base with PET [13].

38.2.2 Limitations

The major limitations of SPECT and PET are economic cost, environmental impact, and high radiation dose. For a cardiac imaging test, with the average cost (not charges) of an echocardiogram equal to 1 (as a cost comparator), the cost of a SPECT study is 3.27×, of PET 14×, and of PET–CT around 20× higher [14]. For stress imaging, compared with the treadmill exercise test equal to 1 (as a cost comparator), the cost of stress echocardiography is 2.1×, of stress SPECT scintigraphy 5.7× [15], and of stress SPECT–CT around 20× higher. This cost assessment does not include the indirect additional costs of radiation-induced cancer, the environmental impact of radioactive tracer production and waste, and the manufacturing, transportation, and maintenance costs of large equipment [16]. The older problem of limited availability of PET has been superseded by the problem of greater numbers of scanners but their heavy commitment to oncology work. In addition, PET

perfusion imaging has been dependent on expensive cyclotron facilities (or rubidium-82 generator) as PET tracers have a short half-life.

38.2.3 PET–CT Imaging

PET and SPECT scanners have been linked to computed tomographic (CT) scanners, which are digital radiological systems that acquire data in the axial plane, producing images of internal organs of high spatial and contrast resolution. The combination of PET or SPECT and CT as a single unit provides spatial and pathological correlation of the abnormal metabolic or flow activity, allowing images from both systems to be obtained from a single instrument in one examination procedure with optimal coregistration of images [6]. The resulting fusion images facilitate the most accurate interpretation of both PET and SPECT and CT studies (Fig. 38.1). The recent White Paper on Multimodality Imaging of the European Society of Radiology and the European Association of Nuclear Medicine puts forward two indications on multimodality imaging [10]. (1) Diagnosis of coronary artery disease: the major advantage of the integrated approach to the diagnosis of coronary artery disease is the added sensitivity of PET and SPECT and CT angiography. With integrated PET/SPECT–CT systems, the limitations of both techniques can be overcome, leading to improved diagnostic capability. (2) Guiding management of coronary artery disease: Not all coronary artery stenoses are flow limiting, and PET or

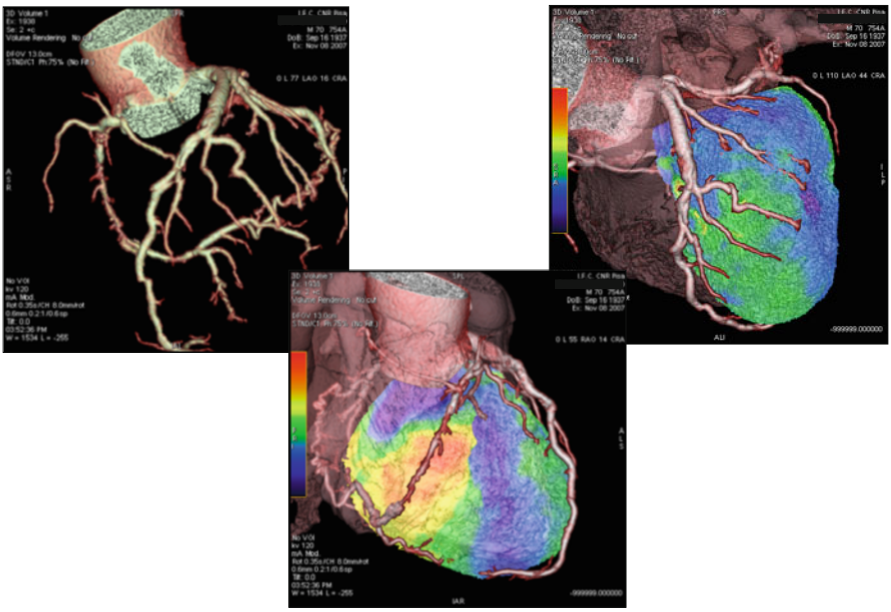

Fig. 38.1 An example of hybrid PET–CT imaging, with simultaneous representation of coronary anatomy (*left*) and perfusion (*right and middle panels*) (Courtesy of Dr. Danilo Neglia, Cardiac PET Lab, Pisa, Italy)

SPECT stress perfusion imaging complements the anatomical CT data by providing functional information on the hemodynamic significance of such stenoses, thus allowing more appropriate selection of patients who may benefit from revascularization procedures. However, while there are no questions about the diagnostic accuracy and the beauty of SPECT and, even more staggering, of combined PET–CT scans, the need for this technology in other than selected patients is difficult to accept. In addition to relatively high cost, combined radiation burden, and environmental impact, for *most* patients, several nonionizing imaging techniques (such as ultrasound and magnetic resonance imaging) offer comparable information.

38.3 MPI Versus Stress Echo

Stress echocardiography and myocardial perfusion imaging (MPI) have a very similar pathophysiological rationale and methodological approach (with assessment of perfusion and function) (Table 38.1). From a diagnostic standpoint, comparisons have been based on evaluation against anatomic evidence of "significant" coronary disease (Fig. 38.2). Although this metric is imperfect, it is likely to be as imperfect for both methods, and the literature points toward diagnostic accuracy being equivalent. They are, more or less, equally reliable "gatekeepers" for more invasive, risky, and costly procedures and have a recognized similar diagnostic and prognostic value [17–22].

38.3.1 Accuracy for Coronary Artery Disease

The sensitivity and specificity of both tests are in the 80–85 % range, with greater sensitivity for SPECT (especially for single vessel and left circumflex disease) and greater specificity for stress echocardiography (especially in women, left ventricular hypertrophy, and left bundle branch block).

Table 38.1 Myocardial radionuclide perfusion imaging: advantages and limitations

	Advantages	Limitations
Operator independent	++	
Radiation dose		−−−
Long-standing experience	+++	
Environment impact		−−−
Convincing display	++	
Low specificity (LBBB, HPT)		−−−
Extensive prognostic database	+++	
High-cost, variable availability		−−−

Advantages are scored as + good, ++ very good, +++ excellent advantage. Limitations are scored as − mild, −− moderate, −−− severe limitation
LBBB left bundle branch block, *HPT* hypertension

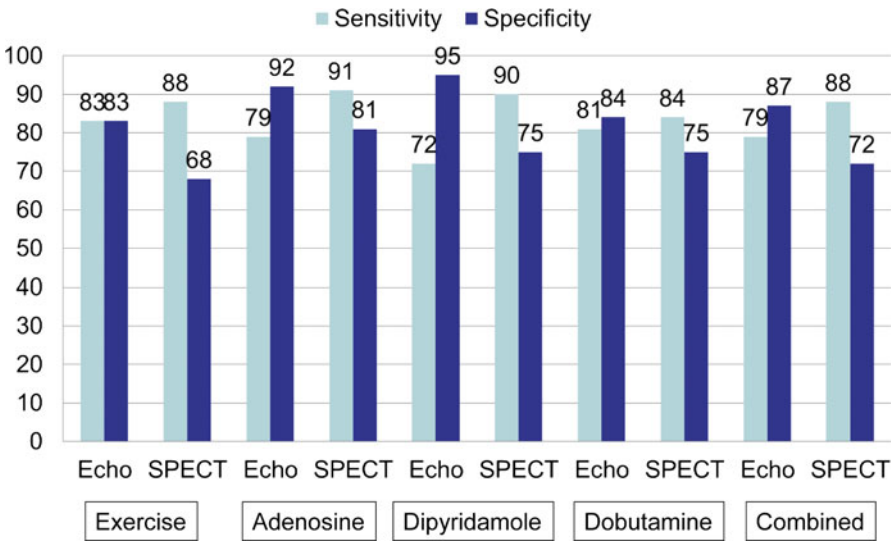

Fig. 38.2 Summary of pooled sensitivity and specificity of stress echocardiography and SPECT in combination with various stressors, from a random effects meta-analysis [17]

The equivalence between stress echocardiography and MPI is often considered surprising in light of the "ischemic cascade," which suggests that because perfusion disturbances precede ischemia, perfusion imaging should be more sensitive than wall motion imaging for the detection of ischemia. However, the results of these noninvasive tests are governed not only by the underlying physiology but also by their imaging characteristics. The imaging strengths of echocardiography (spatial and temporal resolution, independent assessment of segmental wall motion) may therefore compensate for its current dependence on ischemia.

38.3.2 Beyond Sensitivity and Specificity

The modern application of functional testing has moved on from simply the diagnosis of coronary artery disease to assisting in decision-making, especially regarding the presence, location, and extent of ischemia. In these respects, the sensitivity and specificity for the diagnosis of coronary disease are of limited relevance – for example, in postinfarction patients, this analysis does not discriminate between the diagnoses of scar and ischemia.

The regional accuracy of stress echocardiography and perfusion scintigraphy may be important with respect to decision-making about revascularization. Breast and diaphragmatic attenuation are not the cause of artifacts with echocardiography but should be readily recognized with nuclear imaging. The posterior wall poses a problem for perfusion scintigraphy (due to lower counts) and the lateral wall with echocardiography (due to overlying lung). Scintigraphy may be more accurate than echocardiography in these segments [17].

Although the assessment of the extent of ischemia is analogous, this is considerably easier with SPECT. Stress echocardiography has a problem in defining the presence of multivessel coronary artery disease, with nuclear imaging being significantly more sensitive for recognizing the involvement of more than one coronary vascular territory. The reliability of ischemia quantification with SPECT underpins the use of this technique for selection of patients for revascularization or medical therapy on prognostic grounds [22]. Likewise, the detection of ischemia in combination with infarction is simpler with scintigraphy than echocardiography.

38.3.3 Prognostic Value for Coronary Artery Disease

The prognostic value of stress echocardiography has been well defined. Comparison of the predictive value of a negative test result using echo and nuclear techniques has shown them to be similar (Table 38.2). Although additional detail about pretest risk has always to be considered in these comparisons, reported populations have similar age [19, 21]. Cardiac death is uncommon in individuals with stable chronic coronary disease. While ischemia and scar detected by either SPECT or stress echocardiography are predictive of cardiac events, the predictive value of a positive test result has generally been below 20 %. For both echocardiography and nuclear tests, the next step in a patient with a positive test result is to substratify the level of risk. Clinical features such as age, diabetes, and symptoms of congestive heart failure are predictive of outcome in stable coronary artery disease and may be used to select patients for more extensive testing combined with imaging assessment. Similarly, the results of stress testing – expressed, for example, as the Duke treadmill score – are of use in selecting patients for either test. Moreover, in patients at intermediate risk of events, both stress echocardiography and myocardial perfusion SPECT appear to be both useful [20] in separating these into low- and high-risk subgroups.

Table 38.2 Myocardial infarction and cardiac death after negative stress imaging tests

Exercise imaging modality and events	*n*	Follow-up (m)	Age (yrs)	Women (%)	Event rate after a negative test (%, 95 % CI)	Annualized event rate (%)
MPI	8,008	36	54	34	1.21 (0.98–1.48)	0.45
Thallium	868	45	57	32	3.11 (2.05–4.53)	0.70
Sestamibi	1,802	32	58	35	1.28 (0.81–1.92)	0.34
Thallium/ sestamibi	4,938	23	61	39	0.83 (0.60–1.13)	0.45
Tetrofosmin	400	43	57	28	1.5 (0.55–3.26)	0.42
Echo	3,021	33	56	46	1.56 (1.14–2.07)	0.54

Modified from Metz et al. [19]

Although very different practice patterns are today present in high-volume centers, MPI and stress echocardiography are better used as alternative rather than redundant techniques.

Interestingly, a cost-effectiveness study showed that outcomes of groups with comparable levels of risk were similar but the imaging and downstream costs of SPECT were greater in the low- to intermediate-risk patients. Because of the higher sensitivity of SPECT, this technique was the most cost-effective strategy in intermediate- to high-risk patients (e.g., those with known coronary artery disease) [23]. Interestingly, the recent report of a randomized trial showed that the majority of patients undergoing functional testing for the evaluation of chest pain subsequently underwent coronary angiography, irrespective of test results [24]. This implies that the use of downstream testing remains inefficient with all modalities.

38.3.4 Merits of SPECT and Stress Echocardiography

The advantages of stress perfusion imaging include less operator dependence, higher technical success rate, higher sensitivity, and better accuracy when multiple resting left ventricular wall motion abnormalities are present [15]. The advantages listed in guidelines for stress echocardiography over stress perfusion scintigraphy include a higher specificity and a greater availability, versatility, and greater convenience [15]. The lower specificity of SPECT may reflect problems of posttest referral bias with an established test technique and false-positive rates related to image artifacts. It should be recognized that recent technical advances, including gated SPECT and attenuation correction, have improved the specificity of SPECT.

Finally, echocardiography provides important anatomic and functional information that is either not provided or is provided poorly by scintigraphy. Valve diseases such as aortic stenosis or ischemic mitral regurgitation are important comorbidities of coronary artery disease and may merit dynamic evaluation in some circumstances [24]. Likewise, exertional dyspnea may be an important presenting symptom of coronary artery disease [25, 26], but may also be due to diastolic dysfunction. The ability to measure left ventricular filling pressure with exercise may be a useful adjunct to exercise echocardiography [27].

The performance of both stress imaging tests is of dubious efficiency. A concordantly positive result is highly predictive of a critical coronary artery stenosis and clears the pathway toward an ischemia-driven revascularization. More often, a discordant result is found with stress echocardiography negativity (typical of a high specificity technique) and perfusion imaging positivity (typical of a high sensitivity technique). Such patients may have normal coronary arteries or mild-to-moderate coronary artery disease. Proceeding to coronary angiography, with unavoidable escalation of costs, risks, and revascularization, has a very questionable prognostic benefit.

38.4 The Elephant in the Room: Radiation Safety

The radiation burden of stress SPECT and PET ranges from the dose equivalent of 200–2,000 chest X-rays [5, 28] (Table 38.3).

The additional extra risk of a cancer is around 1 in 1,000 (for a middle-aged man performing a sestamibi scan) but can be as high as 1 in 300 for a 35-year-old woman undergoing a thallium scan [3, 25]. Many patients undergoing MPI receive repeat MPI testing, with high cumulative estimated doses often exceeding 100 mSv (5,000 chest X-rays) [29]. In terms of population burden, the almost 10 million scans performed each year in the USA translate into a population risk of about 8,000 new cancers per lifetime [30]. The great number (>30 %) of inappropriate examinations [31], the frequent lack of awareness of dose and risks by the referring physician and the practitioner [32, 33], and the provision of limited radiation safety information to the patient [34] may raise uncomfortable ethical and legal issues, amplified in research-oriented applications especially in children.

A number of strategies can be used to minimize dose in cardiac nuclear imaging:

Use of Tc-99m Sestamibi or tetrofosmin agents as preferred radioisotopes in SPECT and the use of stress-first/stress-only protocols in patients with low pretest probability of disease.

Use of new SPECT detectors with cadmium zinc telluride technology can be used to considerably decrease the effective dose (from 9 to 1.5 mSv) and acquisition time for myocardial perfusion SPECT with preserved image quality.

Selection of stress-first imaging. The radiation dose from stress-first imaging is lower than in two-injection Tc-99 m studies. In single injection studies, not only radiation but also study time is low, and more patients can be imaged per gamma camera per day. This approach can be optimized by communication of clinical information between the referring physician and the nuclear laboratory in

Table 38.3 The radiation dose for common nuclear cardiology examinations

Procedures	Effective radiation dose (mSv)	Equivalent no. of chest radiographs
SPECT ^{99m}Tc-sestamibi (1,100 MBq, 1 day) stress/rest	9.4	470
SPECT ^{99m}Tc-tetrofosmin (1,500 MBq, 1 day) stress/rest	11.4	570
SPECT ^{201}Tl stress/rest reinjection (185 MBq, 2 injections)	40.7	2,035
SPECT ^{201}Tl stress/redistribution (130 MBq, 1 injection)	22	1,100
Cardiac PET ^{18}F–FDG (400 MBq, viability)	8	400
Cardiac PET ^{13}*N*-ammonia stress/rest (1,100 MBq)	2.4	120
Cardiac PET ^{15}*O*-water stress/rest (2,200 MBq)	2.5	125
Cardiac PET ^{82}Rubidium stress/rest (3,700 MBq)	4.6	230

From Picano et al. [28]

sufficient detail to facilitate accurate pretest risk stratification and selection of patients for stress-first/stress-only protocols.

Minimization of radiation dose to that needed to obtain adequate image quality needed for confidence in reporting, and has to be lowered in smaller patients.

Hydration of the patient after imaging and encouragement of early voiding – although technetium tracers are not excreted by the kidneys and hydration has no significant effect on radiation exposure.

Because of the short half-lives of tracers, PET studies potentially offer a lower patient radiation dose compared to SPECT and may result in more favorable patient dosimetry.

Probably the most important step to limiting radiation dose is to avoid unnecessary and inappropriate procedures, by following the guidance provided by appropriate use criteria. It has now been shown that tracking appropriate use is feasible and may result in reduction/elimination of inappropriate testing and unwarranted radiation exposure [28, 35].

The practice of nuclear cardiology (volumes, tracers, protocols, cameras) is different in the USA and Europe. The number of MPI studies performed in Europe is very low as compared with the number of procedures performed in the USA, possibly related in part to regulatory issues (in most jurisdictions, cardiologists do not handle radionuclides) and reimbursement policy (the cardiologist cannot get reimbursement from nuclear cardiology studies) [28, 35]. In Europe, most PET centers are focused on oncology, not cardiology. Stress-only protocols are the standard in Europe, when initial stress images are normal. In the USA, nuclear cardiology accounts for >50 % of all nuclear medicine procedures and 85 % of the entire cumulative effective dose due to nuclear medicine, which accounted for 26 % of the overall medical exposure of patients in 2006 [28, 35]. A strategic target of the nuclear cardiology community is that for the population of patients referred for SPECT or PET myocardial perfusion imaging, on average, a total radiation exposure of <9 mSv can be achieved in 50 % of studies by 2014 [35].

Perhaps in part related to competing technologies, reimbursement problems, and radiation issues, the number of perfusion scans in the USA has begun to decline, with a dramatic downward trend in MPI utilization, which fell (−51 %) in the 2006–2011 time period, when stress echo utilization remained stable [36] (Table 38.4).

38.5 Radiation Safety for the Cardiac Sonographer

Patients who have had a nuclear imaging study with radioactive tracers become, themselves, radiation emitters (“hot” patients). The dose to surrounding persons can be relevant when patient injected with radiotracers (for cardiology or oncologic studies) is sent to perform other diagnostic examinations (i.e., echo, during which the sonographer/cardiologist has to stay very close to patients for a long time therefore increasing health professional exposure to radiation). At one and a half hour after administration of technetium-99 m, the dose equivalent measured right at the anterior chest wall was 0.37 mSv, while the right chest wall dose equivalent was

Table 38.4 Head-to-head comparison between myocardial perfusion imaging (*MPI*) and stress echocardiography

	MPI	Stress echocardiography
Diagnostic parameter	Perfusion (WM)	WM (CFR)
Relative cost	3	1
Sensitivity	Higher	High
Specificity	Moderate	High
Radiation burden (CXr)	200–2000	0
Patient friendliness	Low	High
Operator friendliness	Low	High
Environment friendliness	Low	High

WM wall motion, *CFR* coronary flow reserve, *CXr* chest X-ray

0.58 mSv. Sonographers might have a potential dose equivalent as high as 0.16 mSv (lower if sonographer was left-handed and scanning on the left) during a 24-min echo. A transport worker might face a dose equivalent of 0.02 mSv during a 10-min patient transfer [37].

Cardiac sonographers are frequently asked to perform examinations in patients undergoing multiple procedures in rapid succession, and the study of these radiation emission can lead to considerable radiation exposure for the cardiac sonographer working in close contact with the radioactive patient. In this setting, the radiation protective apparel (such as lead aprons) are of limited value, since high-energy photons emitted by radioisotopes are only partially shielded by lead, which blocks 90 % of X-rays but is ineffective against high-energy positron-emitting tracers (such as 18 F–FDG and ^{13}N-ammonia), modestly effective against intermediate energy ^{99m}Tc tracers (such as sestamibi and tetrofosmin), and really effective only against low-energy photons of ^{201}Tl. The best protection for the sonographer is increasing the time between isotope administration and the ultrasound procedure, with the echocardiographic study performed after 1 day in case of PET or SPECT study with ^{99m}Tc tracers and after 1 week in case of a ^{201}Tl study, characterized by a much longer half-life of a few days. As recommended by the American Society of Echocardiography, sonographers should self-educate with respect to the basic principles of radiation safety and take personal responsibility to ensure their own safety [38].

38.6 Pitfalls

The major pitfalls of stress echocardiography relate to the subjectivity of the technique (and consequent need for training) and the likelihood of false-negative scan results in patients treated with antianginal therapy [7]. In recent ESC guidelines, the main disadvantage of SPECT technique is considered to be radiation exposure, balanced by advantages of high access and extensive data available [39]. Additional disadvantages of PET technique are limited access and high cost.

Table 38.5 Indications to cardiac stress imaging

Recommendations	COR	LOE	Reference
An imaging stress test is recommended as the initial test for diagnosing SCAD if the PTP is between 66 and 85 % or if LVEF is <50 % in patients without typical angina	I	B	ESC 2014 [40]
An imaging stress test is recommended in patients with resting ECG abnormalities which prevent accurate interpretation of ECG changes during stress	I	B	ESC 2014 [40]
Exercise stress testing is recommended rather than pharmacologic testing whenever possible	I	C	ESC 2014 [40]
An imaging stress test should be considered to assess the functional severity of intermediate lesions on coronary arteriography	IIa	B	ESC 2014 [40]
Noninvasive imaging to detect myocardial ischemia and viability is reasonable in HF and CAD	IIa	B	ESC 2014 [40]
Viability assessment is reasonable before revascularization in HF patients with CAD	IIa IIa	C B	ACC/AHA [41, 42]

COR class of recommendation, *LOE* level of evidence

38.7 Clinical Guidelines

Nuclear perfusion imaging and stress echocardiography show common pathophysiological roots and produce similar clinical fruits. They share a bipartisan imaging strategy to replace an anatomy-driven with a more physiologically oriented approach, referring for coronary angiography for ischemia-driven revascularization only patients with uncontrolled symptoms or a high-risk pattern of stress imaging. Appropriate indications to MPI as stipulated by recent European and US guidelines [40–42] are listed in Table 38.5.

If we put the choice of cardiac stress imaging in the wider context of medical imaging, the European Commission recommendations and the recent European Society of Cardiology position paper clearly state that a nonionizing test should always be preferred when the information is grossly comparable to an ionizing test and both are available [28, 43]. For diagnostic purposes in patients in low to intermediate risk, whenever a stress imaging test is clinically indicated, stress echocardiography is the first-line test; when stress echocardiography is not feasible or yields ambiguous response, if contrast-enhanced stress echocardiography does not salvage the technically difficult stress echocardiography, stress CMR is an excellent radiation-free option. If stress CMR technology and expertise are not available, stress MPI can be considered. In the high-probability patient or the setting where extent of ischemia will be an important component of a revascularization decision, the benefits of quantitation with MPI may be attractive. The value of this approach will be examined prospectively in the ISCHEMIA trial (https://www.ischemiatrial.org/).

A good MPI is better than a bad stress echocardiography study, and a good stress echocardiography study is better than a poor MPI – but it is equally obvious that the

capability to perform good echocardiography is one of the indicators of the quality of a cardiology division and that the choice between stress echocardiography and MPI should be made in the context of the environmental, biological, and economic effects.

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Stress Echocardiography Versus Cardiac CT

39

Paolo Marraccini and Eugenio Picano

39.1 Cardiac Imaging in the CCTA Era

With the arrival of multislice coronary computed tomography angiography (CCTA), noninvasive imaging of coronary anatomy has become possible. The introduction of multidetector-row computed tomography in 1999 led to a significant improvement in the temporal and spatial resolution allowing the visualization of small and rapidly moving structures, such as coronary arteries [1]. CCTA has the potential for offering important information, without catheters, on established cardiovascular risk factors, such as epicardial fat and coronary calcifications, coronary anatomy, and general cardiac morphology and function, including aorta and pulmonary circulation and in addition myocardial perfusion (Fig. 39.1). Moreover, conceptually, CCTA allows one to track the natural history of coronary artery disease with the earliest possible marker, providing unprecedented noninvasive insight into the coronary anatomy and coronary wall structure changes, which anticipate by years and sometimes decades the onset of myocardial perfusion or functional changes during stress, which are the cornerstone of current noninvasive diagnosis of coronary artery disease by stress scintigraphy or stress echocardiography (SE) [2, 3] (Fig. 39.2).

At present, the informations derived from CCTA in clinical setting, even if very high, are generally limited to coronary and atherosclerotic plaque morphology. In any case, this kind of information is higher than invasive angiography, possibly equivalent to gray-scale intravascular ultrasound plus angiography (Fig. 39.3). Invasive coronary angiography can identify obstructive as well as complex lesions, but it is restricted to the coronary lumen and is unable to depict the coronary wall. Thus, features such as vessel remodeling or plaque composition are missed. CCTA depicts not only a coronary luminogram as coronary angiography does but also the thickness of the wall and the plaque composition to some extent as ultrasound does [3]. This is especially important in the early diagnosis of coronary artery disease, since the earliest stage of atherosclerosis is the initial positive remodeling with preserved lumen, as plaque accumulates [4] (Fig. 39.2). Several studies showed an increased level of inflammatory markers, high lipid cores, and pronounced medial

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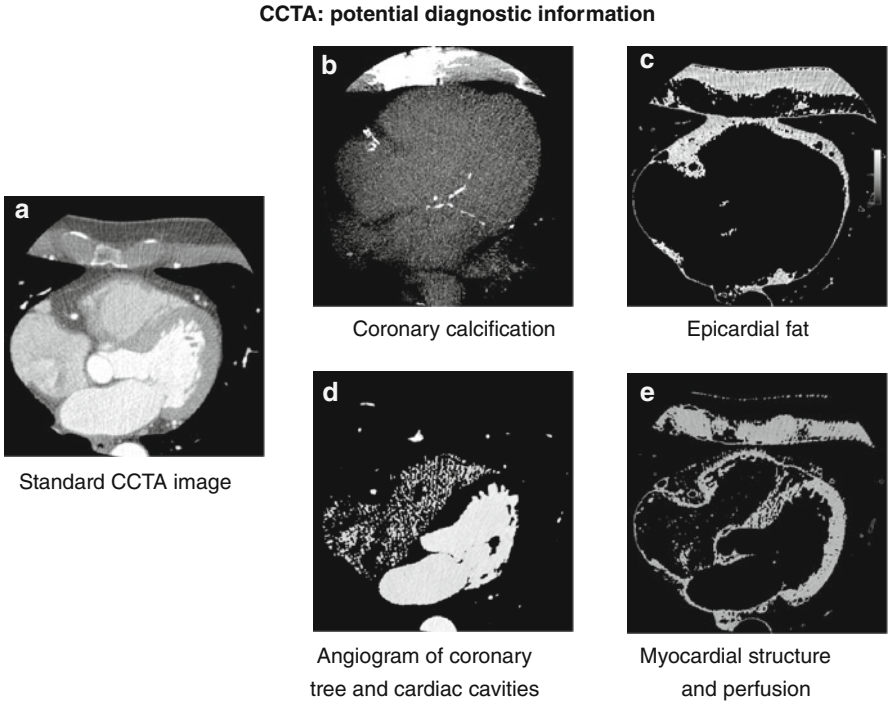

Fig. 39.1 The picture shows the potential information present inside the CCTA: changing the window level of the standard image (**a**), it is possible to enhance the presence of coronary calcification (**b**), the epicardial fat (**c**), the contrast medium inside the cavities and the coronary tree (**d**), and the distribution of the contrast medium in the myocardium (**e**)

thinning in positively remodeled vessels [5]. Some of the initial acute presentations of the disease may occur when the adaptive remodeling mechanisms are exhausted and a threshold mass of plaque (depending on vessel diameter) starts to breach toward the lumen. CCTA can also offer insight into the structural composition of plaque which – for any given plaque size – contributes to plaque vulnerability [5], with lipid-rich, high-risk plaques (hypoechoic by ultrasound and hypodense by CT) more prone to rupture and subsequent thrombotic occlusion than calcium-rich, low-risk plaques (hyperechoic with shadowing by ultrasound and hyperdense by CT). This conceptual breakthrough translated into a scientific and commercial explosion with the newer generations of multidetector CT scanners, which significantly improved the diagnostic performance for the assessment of coronary artery disease, and decreased the proportion of nonassessable segments (Fig. 39.3). This determined a surge of scientific and clinical interest in the method. The message is clear and simple and comes straight from scientific journals and lay press [6]: beautiful, easily obtained images of coronary artery stenoses, which otherwise would go undetected, provide an opportunity to intervene early enough, and put an end to sudden death, without hospital stay, without catheters inserted into the body, and without heaps of consent forms to be signed informing the patient about the risk of death

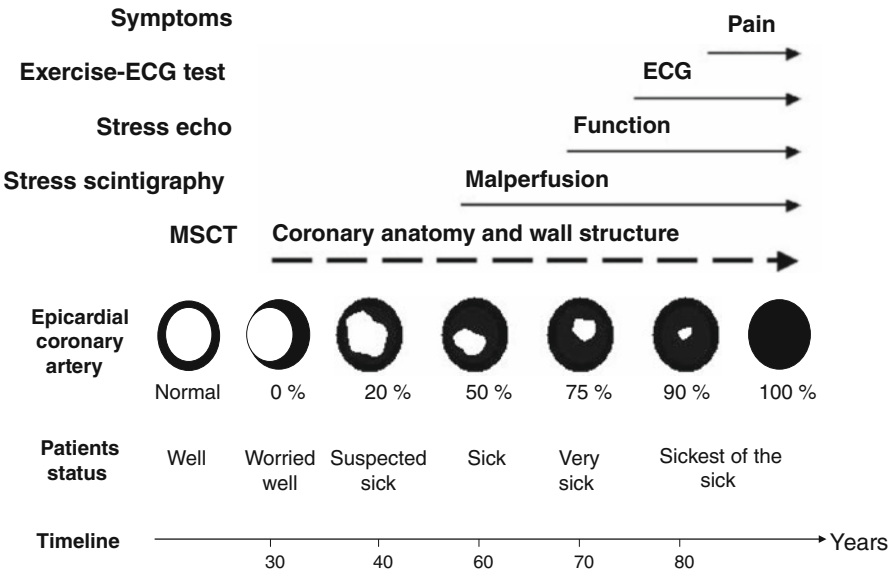

Fig. 39.2 The timeline of atherosclerosis and the disruptive opportunity offered by CTA to image coronary atherosclerotic disease, directly, decades before stress-induced changes in function and perfusion are detectable during SE and stress scintigraphy. The information on initial positive remodeling of arterial wall and plaque composition of the plaque is off-limits for invasive coronary angiography and can be obtained with intracoronary ultrasound (Redrawn and adapted from Erbel and Gorge [3])

and myocardial infarction, as is the case with invasive cardiac catheterization [6]. However, if inappropriately used, cardiac CT may become a double-edged sword, with potential to create a huge reservoir of tens of thousands of future cancers in a not-too-distant future [7, 8]. At this point, the pros and cons of each imaging technique need to be carefully incorporated in the clinical decision-making – also shared with the patient – so that the combination of the various techniques may yield the greatest benefit to the individual patient [9].

39.2 Advantages of CCTA

CCTA has wide availability, and – compared with invasive coronary angiography – shorter examination time with better patient adherence and lower temporal and spatial resolution [1] (Fig. 39.4). The patient radiation exposure using updated CT equipments and examination protocols may be lower than invasive coronary angiography (3 vs. 7 mSv), and, moreover, the exposure of operators is avoided. The presence, extent, and severity of coronary artery disease assessed with CCTA have clear prognostic impact [10, 11]. It is also possible with CT to assess the presence and extent of coronary calcification. The amount of coronary calcium correlates moderately closely to the overall atherosclerotic plaque burden and has prognostic impact, also additive to that of coronary anatomy [12, 13].

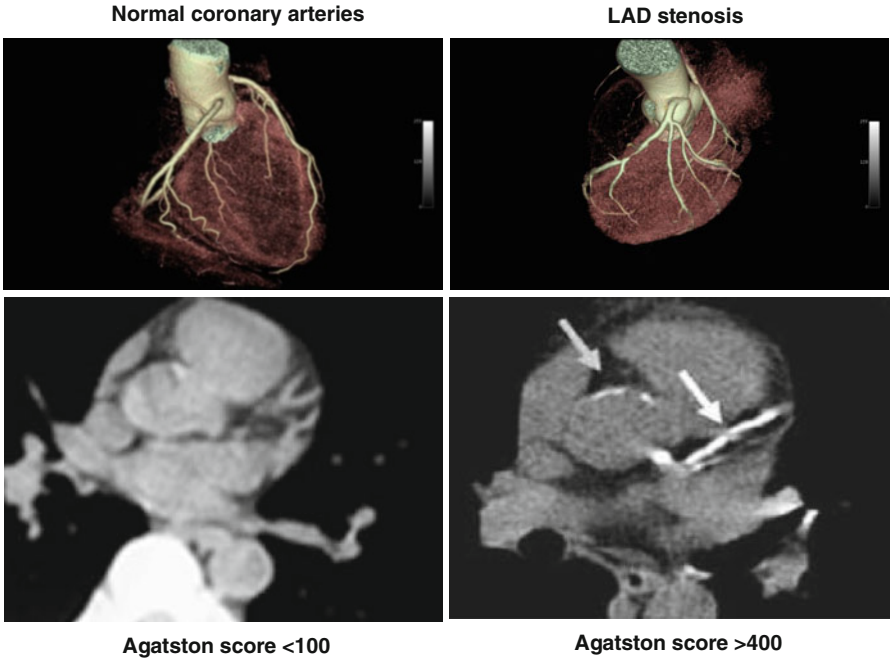

Fig. 39.3 Normal CCTA with normal coronary arteries and calcium score <100 (*left*) and abnormal CCTA with left anterior descending coronary artery stenosis and calcium score >400 (*right*) (Courtesy of Dr. Paolo Marraccini, Pisa)

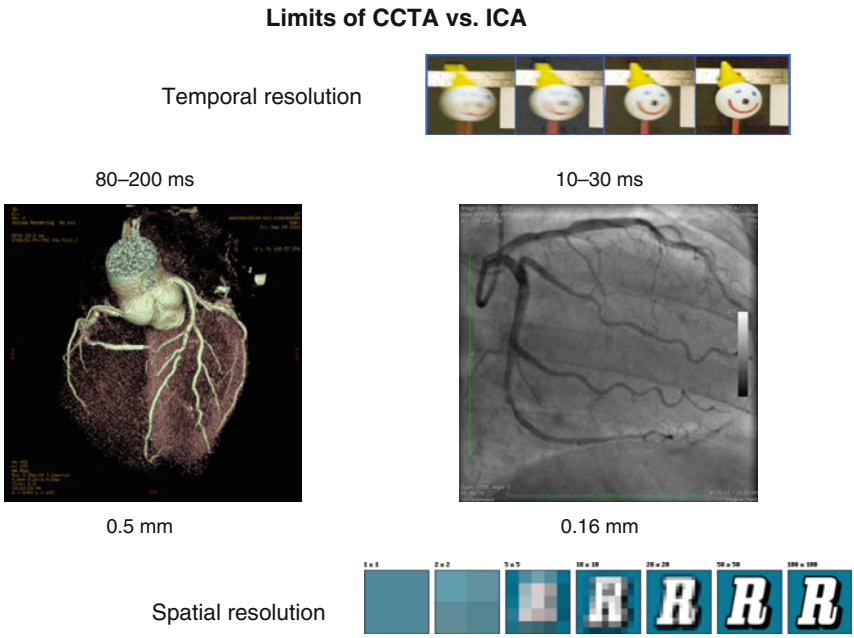

Fig 39.4 The two major limitations of CCTA versus ICA are highlighted, i.e., temporal and spatial resolution

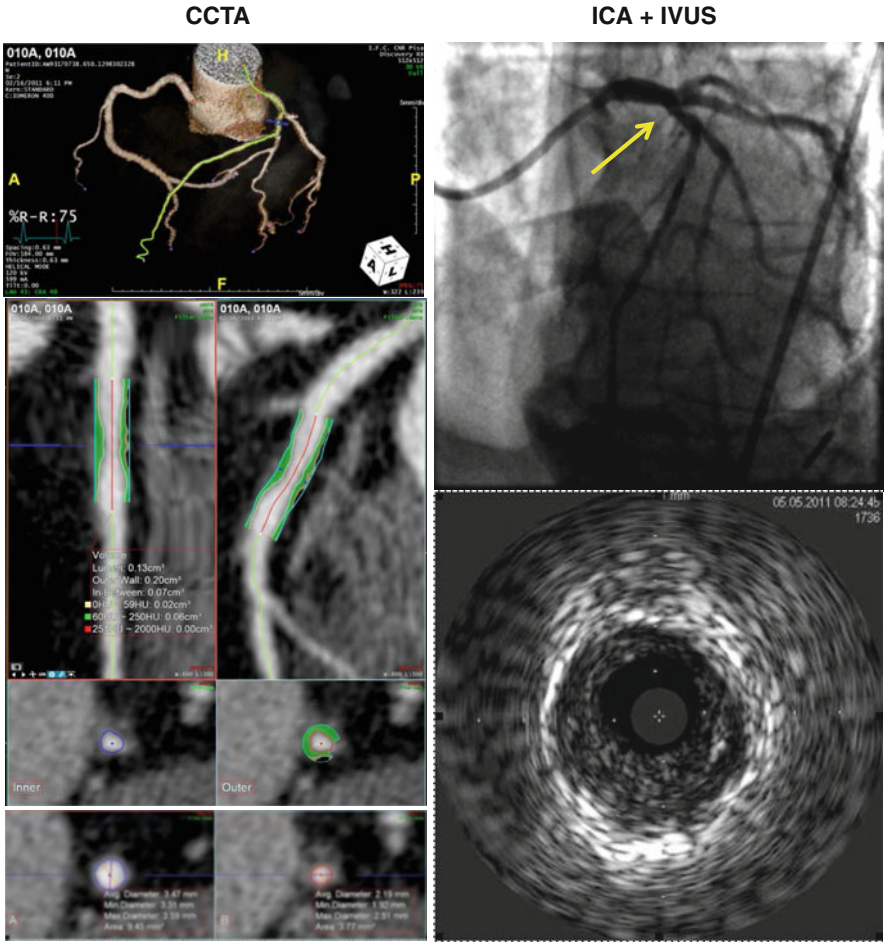

Fig. 39.5 CCTA versus ICA plus IVUS: the *left top panel* shows volume rendering of coronary tree (*top*), with reconstruction of middle LAD with an example of vessel and plaque analysis. The *left bottom panel* represents axial analysis of lumen and plaque. *Right panel* shows the left coronary angiography in the same patient. *Top*: *yellow arrow* highlights the middle LAD lesion; *bottom panel* shows an IVUS image at the level of the same coronary lesion

The test has high negative predictive value especially in patients with low pretest probability [14]. The versatility of the information provided may allow a triple rule out (coronary artery disease, pulmonary embolism, aortic dissection) in the emergency setting of acute chest pain, although the evidence supporting routine use for diagnosis of pulmonary embolism and aortic dissection is insufficient to date [15]. Plaques demonstrating positive remodeling and low attenuation are associated with thin-cap fibroatheroma and macrophage infiltration by optical coherence angiography, suggesting the potential of CCTA to identify vulnerable, high-risk plaques – although this information is not yet ready for clinical use and clearly less reliable than the tissue characterization provided by intravascular ultrasound [16, 17] (Fig. 39.5).

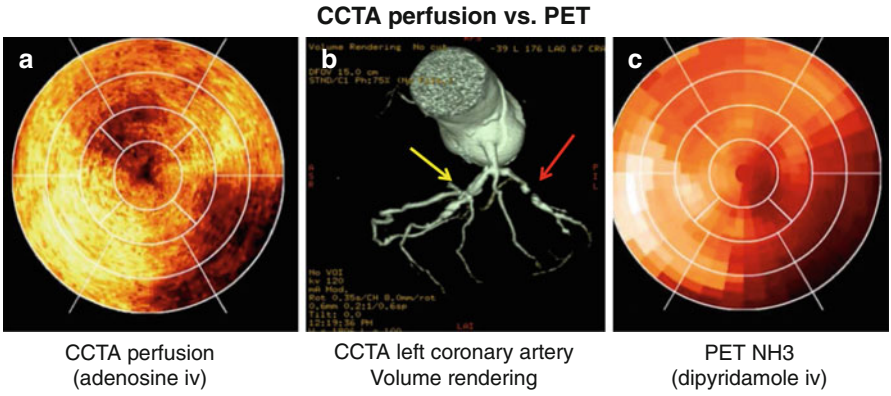

Fig 39.6 The 3D volume rendering (panel **a**) shows a panoramic view of coronary arteries in a 65-year-old man. *Red arrow* indicates a sub-occlusive stenosis of left circumflex artery; *yellow arrow* indicates a calcific lesion of the proximal left anterior descending coronary artery. Panels **a** and **c** show the perfusion map, respectively, by CCTA (*left*) and PET (*right*). An obvious perfusion defect is present in the inferoposterior segments with both techniques, but CCTA also shows an anterior defect, in the territory dependent upon a calcified artery

There is the potential of CCTA to calculate fractional flow reserve for each stenosis, thereby integrating anatomic information with physiologic assessment currently restricted to the catheterization laboratory [18]. Although at present this is only possible in a time-consuming manner off-site, new simplified algorithms allowing on-site application within clinically viable time frames are under development at a rapid pace [19]. CCTA-based FFR provides functional information of coronary stenosis severity, which is particularly important in intermediate lesions. The addition of FFR-CT may help reclassify false-positive patients as true negatives, and this key functional information can be obtained with no extra radiation, differently from myocardial CT perfusion. The only commercially available product received US FDA clearance in November 2014.

CCTA may also allow the evaluation of myocardial perfusion through the analysis of distribution of contrast medium inside the myocardium. The technique is interesting and may allow images comparable to SPECT or PET (Fig. 39.6). At present, however, CCTA perfusion has several limitations: first of all, the need of two scans (basal condition and under vasodilation) that significantly increase the radiation exposure and, in addition, the relevant number of false-positive evaluations as reported in the CORE 320 trial [20]. The use of CCTA perfusion remains, at present, objective of research programs; its widespread application is related to the progress in appropriate hardware and software of vendors, standardization of protocols, and extensive clinical validation.

39.3 Stress Echocardiography Versus CCTA

SE and CCTA have completely different – and therefore potentially complementary – pathophysiological rationale, methodological approach, and clinical results, as summarized in Table 39.1. The most important difference is the separation

Table 39.1 Head-to-head comparison between CCTA and SE

	CCTA	SE
Approach	Anatomic	Functional
Direct alternative	Invasive CA	Stress CMR or MPI
Radiation exposure	Yes	No
Stress required	No	Yes
Nephrotoxic iodinated contrast	Yes	No
Relative cost	1	1
Therapy masking effect	No	Yes
More efficient pretest probability	Low	Intermediate

CA coronary angiography, *MPI* myocardial perfusion imaging

between the anatomic and the functional approach. Comparative studies have demonstrated that anatomic imaging with CCTA may provide information complementary to the traditionally used techniques for functional assessment. From these, studies can be derived that only approximately 50 % of significant stenosis on CCTA is functionally relevant; a large proportion of significant (>50 %) lesions on CCTA do not result in perfusion and/or functional abnormalities [21]. Alternatively, many patients with normal perfusion and function show considerable atherosclerosis on CCTA. The most frequent source of CCTA–SE mismatch is represented by patients with negative SE and positive CCTA findings [22]. Therefore, the combined use of these techniques may enhance the assessment of the presence and extent of coronary artery disease. Whether this can be cost-effective and risk effective remains to be established and will likely depend on the clinical presentation and specific diagnostic questions. Compared to SE, patients undergoing CCTA first in a non-acute setting were more likely to undergo subsequent invasive cardiac procedures and have higher CAD-related spending than patients who underwent stress testing [23]. This is likely due to the fact that CCTA may detect atherosclerotic plaques that are not hemodynamically significant and may lead to additional tests and procedures until the inappropriate indication for coronary catheterization and revascularization, thereby increasing expenditures and risks.

These considerations underline the importance of a redefinition of the diagnostic process of the ischemic heart disease following the introduction in clinical setting of CCTA. In particular, randomized trials comparing SE versus CCTA are eagerly needed [24]. In symptomatic patients with suspected CAD who required noninvasive testing, a strategy of initial CCTA as compared to functional testing (with SE or other imaging techniques) did not improve clinical outcomes over a median follow-up of 2 years, as shown by the PROMISE randomized trial on over 10,000 patients [25].

The aggressive use of CCTA for mass screening in asymptomatic subjects will also possibly lead to irresistible triggering of coronary stenting, irrespective of the symptomatic status, functional significance of the stenosis, or any form of prognostic evaluation [26]. Yet we know now that in chronic stable angina – and even more in asymptomatic patients – an anatomic stenosis associated with negative stress testing and normal function has a very low risk and should be left untreated, whereas a similar coronary stenosis with high-risk stress test positivity dictates an

ischemia-driven revascularization with maximal prognostic benefit [27, 28]. Taken together, the appropriateness of the explosive growth in revascularization procedures by the use of PCI, possibly further fuelled by diagnostic carpet bombing with CCTA, is under question. Concerns will only increase if the radiation side of the risk–benefit balance of imaging and interventions is included in the appropriateness assessment, as currently recommended by practice guidelines [29, 30].

39.4 Pitfalls

CCTA is a radiologic technique, and any effort is required for maintaining image quality with the lowest possible exposure. With updated equipments and personalized acquisition protocol, the dose of CCTA may be reduced until 1–3 mSv, i.e., lower than an ICA (about 7 mSv) and similar to a calcium scoring. However, the published data report a wide inter-institutional variability in the dose administered and a mean exposure of 15 mSv [29, 31–33] (Table 39.2).

The coronary anatomy assessment is limited with extensive coronary calcification or previous stent implantation, image quality limited with arrhythmias and high heart rates that cannot be lowered beyond 60–65/min, and low negative predictive value in patients with high pretest probability. In the individual stenosis, CCTA assessment tends toward overestimation and cannot determine physiologic significance of lesions – although recent developments, not yet ready for clinical use, may allow the calculation of fractional flow reserve without the need for extra imaging or drug administration and myocardial perfusion. In the individual patient, the expected benefit should be weighed against the acute (dye allergic reaction), subacute (dye nephrotoxic effects), and chronic (long-term cancer risk) risk of CCTA. Any intended use of the CCTA technique to follow up serially the atherosclerotic burden or the revascularization outcome should be restrained by consideration of the cumulative radiation burden resulting from serial studies.

It is true that the use of calcium score has quite convincing (non-randomized) outcome impact over years, but it is equally true that the question remains open on how much incremental information can be obtained by CCTA. It is also unclear whether the extra information provided by calcium score assessment is better than that provided by simpler, radiation-free atherosclerosis imaging biomarkers such as carotid intima-media thickness or cardiac calcification score (including mitral annulus calcification, aortic root, and aortic valve leaflet calcification) by ultrasound scan (see Chap. 2) [34, 35].

Table 39.2 The average radiation dose of CCTA

	Effective dose (mSv)	Equivalent number of chest X-rays
Calcium score	3 (1–12)	150 (50–600)
64-slice CCTA	15 (3–32)	750 (150–1600)

Adapted from Picano et al. [29]

CCTA is a purely diagnostic test that does not provide an option for immediate intervention. Because the temporal resolution is low, motion artifacts can occur. Predictable visualization of the coronary arteries is not possible at present in patients with atrial fibrillation or frequent ectopy. The coronary lumen is generally not well observed in the region of a coronary stent [30]. Coronary artery segments with substantial calcification may not be evaluable with respect to the presence of a hemodynamically relevant stenosis. There may be overdiagnosis of stenoses in patients with the Agatston scores of >400, and ESC guidelines 2013 suggest to call a CCTA "unclear" if severe focal or diffuse calcifications prevent an unambiguous identification of vessel lumen. With these caveats in mind, CCTA may be considered an alternative to ischemia testing, especially in patients with chest pain symptoms at pretest probabilities lower than 50 % [27].

39.5 Clinical Indications

Table 39.3 lists current indications for performing CCTA. They closely mirror those of SE in many subsets [27, 28]. Although it is tempting to obtain in the same patient both anatomic (with CCTA) and functional (with SE) insight to have a more

Table 39.3 Use of CCTA for stable coronary artery disease

Recommendations	A	M	R	COR	LOE	Reference
Symptomatic, intermediate pretest probability of CAD, ECG uninterpretable or unable to exercise	√					[28]
CCTA should be considered as an alternative to stress imaging techniques for ruling out SCAD in patients within the lower range of intermediate PTP for SCAD in whom good image quality can be expected		√		IIa	C	[26]
CCTA should be considered in patients within the lower range of intermediate PTP for SCAD after a non-conclusive exercise ECG or stress imaging test or who have contraindications to stress testing in order to avoid otherwise necessary invasive coronary angiography if fully diagnostic image quality of coronary CCTA can be expected		√		IIa	C	[27]
Symptomatic, low pre-test probability of CAD, ECG uninterpretable OR unable to exercise		√				[28]
Coronary calcium detection by CT is not recommended to identify individuals with coronary artery stenosis			√	III	C	[27]
CCTA is not recommended in patients with prior coronary revascularization			√	III	C	[27]
CCTA is not recommended as a "screening" test in asymptomatic individuals without clinical suspicion of coronary artery disease			√	III	C	[27]

M may be appropriate, *R* rarely appropriate, *COR* class of recommendation, *LOE* level of evidence

integrated pathophysiological and prognostic picture, this practice is today unsupported by the available evidence and will act as a dangerous multiplier of costs and risks.

American (ACCF and AHA) guidelines consider appropriate CCTA in symptomatic patients with intermediate pretest probability of coronary artery disease, ECG uninterpretable, or unable to exercise [28]. The development of radiation-sparing technology capable of abating by tenfold the current exposure levels of CCTA will play a key role in improving the risk–benefit profile of CCTA [32], shifting the threshold of application of CCTA toward less sick and possibly worried well patients.

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Stress Echocardiography Versus Stress CMR

40

Juerg Schwitter and Eugenio Picano

40.1 Coronary Artery Disease Detection by CMR

Recently, cardiovascular magnetic resonance (CMR) imaging has emerged as a new noninvasive imaging modality providing high-resolution images in any desired plane of the heart, combined with the potential to assess and monitor left and right ventricular function [1, 2]. Although early attempts to use stress CMR, combined with dipyridamole [3] or dobutamine [4] stress, with standard (low-temporal resolution) gradient-echo techniques date back to the early 1990s, the scientific and clinical interest in stress CMR rose strikingly in the last 5 years as a consequence of technological improvements (Table 40.1). To assess cardiac function, cine MR imaging is performed with gradient-echo pulse sequences. Between 20 and 30 frames with a temporal resolution of 50 ms or less are usually sufficient to evaluate the entire cardiac cycle and are displayed in a cine loop, allowing a dynamic read with the same format, projections, segment assignment (17-segment model), and reading criteria (from 1 = normal to 4 = dyskinetic) as for stress echocardiography [5]. Gradient-echo images provide an excellent contrast between intracavitary blood and the endocardium without the use of contrast medium and provide an accurate delineation of the endocardium and epicardium.

Wall motion can be assessed by CMR at rest and during stress. Over the years, the initial standard cine gradient-echo images changed into the tremendously improved temporal resolution of new steady-state free precession (SSFP) pulse sequences. Together with technical improvements in patient monitoring within the magnet as well as due to the reduction in imaging time with accelerated pharmacological stress protocols, stress CMR with wall motion analysis has become more feasible and more accurate. In addition a novel and very powerful acquisition and reconstruction strategy is evolving the so-called compressed sensing which samples in the sparsity domain of information to be iteratively reconstructed. This technique accelerates conventional SSFP techniques by a factor of 10 without a significant penalty in quality allowing coverage of the entire LV in 3D within a single

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Table 40.1 Versatility of CMR for coronary artery disease detection

	Parameter				
Method (image mode)	WM rest	WM stress ischemia	Viability	Hyperemia optional: rest	Coronary artery anomalies
Cine SSFP acquisitions					
Conventional	√	√			
Compressed Sensing	√				
Late gadolinium enhancement (LGE)			√		
Low-dose dobutamine CMR			√		
First-pass perfusion CMR					
Conventional				√	
Compressed sensing				(√)	
Rest 3D acquisitions with navigators					√
Liver navigator					√
Self-navigation (on the heart)					√

WM wall motion, *SSFP* steady-state free precession, *LGE* late gadolinium enhancement (imaging 15–20 min after contrast medium injection depending on dose injected)

breath-hold [6]. This concept is applicable in theory to most CMR applications, and future studies will assess its usefulness in stress CMR.

CMR also has the potential of assessing myocardial perfusion, by visualizing the first pass of a conventional gadolinium-based MR contrast medium (perfusion CMR) [7, 8].

In perfusion CMR, the acquisition is performed during CMR injection while hyperemia is induced pharmacologically (generally by means of adenosine or dipyridamole). This is methodologically and conceptually different from the late gadolinium enhancement (LGE) technique for scar detection, which is performed at rest (no stress required) and several minutes after contrast medium injection, since the redistribution phase in the tissue (and not the first-pass effect in the vessels) is the diagnostic target. CMR visualizes directly myocardial scar as hyperenhanced areas in T1-weighted images [9–11] (Fig. 40.1). The high spatial resolution of contrast-enhanced MR imaging now makes it possible to visualize microinfarcts associated with successful percutaneous coronary intervention, as well as the detection of subendocardial infarcts, which do not exhibit a wall motion abnormality (Fig. 40.2) but still may have prognostic significance [12]. Newer developments for respiratory motion correction will hopefully also allow for the assessment of coronary anatomy with an accuracy similar to multislice computed tomography – and without radiation burden or sensitivity to calcium artifacts. In the past respiratory motion correction was based on navigators on the liver dome which were correlated with the heart position. As this correlation is not constant over a time, results of this

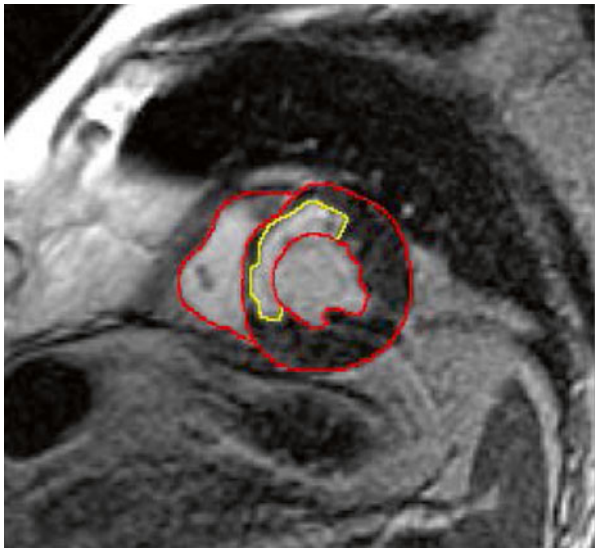

Fig. 40.1 A delayed enhancement image showing a subendocardial scar in the septal and anterior region

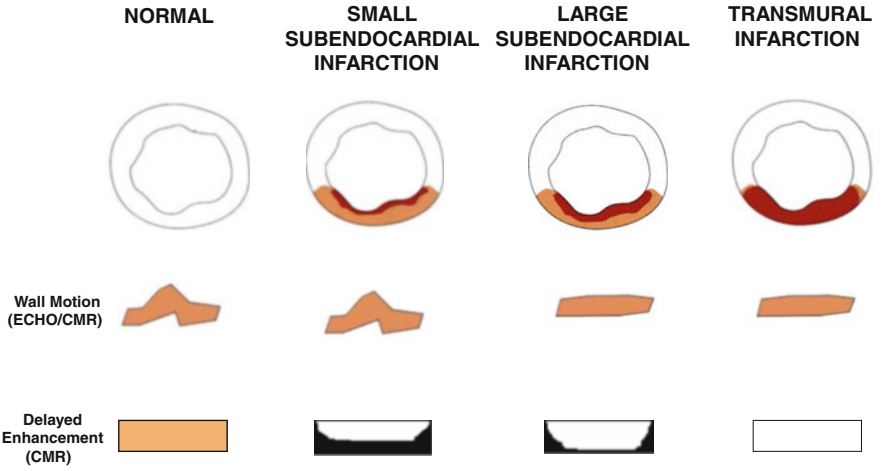

Fig. 40.2 Different levels of transmural myocardial scar induce different levels of echocardiographic and CMR (wall motion) and CMR-specific (delayed enhancement) changes. For 10–30 % subendocardial scar involvement, scar is detectable only by CMR and remains functionally silent on the basis of standard conventional regional wall motion changes

strategy were variable. Recently, novel "self-navigation" techniques became available where the instantaneous position of the heart is extracted from the cardiac data themselves which yields coronary visualization with high robustness [13]. Further development is needed to achieve diagnostic quality to assess coronary stenosis, whereas this technique is already in daily routine in patients with congenital heart disease to assess proximal coronary anatomy preoperatively [14]. To date, clinically

useful imaging of the coronary arteries by CMR is restricted to identification of the origin and course of anomalous coronary arteries and of bypass grafts [15].

40.2 Stress CMR: Advantages and Limitations

Major advantages of CMR are the radiation-free, nonionizing nature and the tremendous versatility (Table 40.2) of the information supplied, also independent of acoustic window. Another major asset, especially valuable today in research-oriented contexts, is the possibility of quantification of volumes, global function, and scar mass. Due to the high spatial resolution of CMR scar imaging, the transmural extent of scar is easily quantifiable. In some research laboratories, software is available also for regional function quantification [16, 17]. Perfusion quantification is currently still demanding with more robust approaches, which also worked in larger studies using, for example, the upslope of the myocardial signal during first pass as a perfusion-linked parameter [7, 18], while absolute quantification of perfusion in ml/min/g tissue is not yet established for coronary artery disease detection by perfusion CMR [7, 19, 20].

The main limitations of CMR include time-consuming data acquisition and analysis and the fact that not all patients can be studied, since pacemakers and metallic clips are still a contraindication for CMR. Additional concern arose regarding the use of contrast medium in patients with impairment of renal function. Paramagnetic contrast media have long been considered absolutely safe and well tolerated, and the incidence of acute, usually mild side effects (nausea, vomiting, acute systemic allergic reactions) remains well below 0.5 % [21]. In 2007, the FDA ordered a "boxed warning" on the safety of gadolinium-containing contrast agents, on the basis of 200 cases of nephrogenic systemic fibrosis (NSF) that occurred in patients with kidney failure after administration of some types of gadolinium-based contrast

Table 40.2 Stress CMR: advantages and limitations

	Advantages	Limitations
Nonionizing energy	+++	
Availability		–
Costs		(–)
Expertise, skills of operators, personnel		(–)
Independent of acoustic window	++	
Claustrophobia, metallic foreign bodies		––
MR-conditional pacemakers, ICD's, etc.	++	
Quantification possible for volumes, global function, scar	++	
Second-generation contrast medium toxicity (NSF) in renal failure		(–)

Approximately 250 cases confirmed out of approximately 140 million contrast medium applications. Cyclic contrast medium for magnetic resonance appears not to cause nephrogenic systemic sclerosis (as of 2014)
NSF nephrogenic systemic fibrosis

media. In NSF, patients develop tight and rigid skin making it difficult to bend joints and may also result in fibrosis of body organs resulting in the inability of body organs to work properly and can lead to death [21]. The putative association of NSF with first-generation gadolinium contrast agents prompted the development of guidelines to limit their use in at-risk patients such as those with advanced chronic kidney disease, and NSF has decreased dramatically following application of these guidelines [21]. Cost and safety concerns should lead to a prudent use of contrast media, especially in patients with kidney failure. Availability of CMR is still a limitation, but the role of CMR continues to expand in evaluation of CAD and heart failure patients, with simpler methods for assessment of myocardial deformation and extracellular fibrosis, with more advanced pulse sequences for tissue characterization to detect inflammation, edema, amyloidosis, or iron overload [22]. Accordingly, CMR is now more widely used, particularly in Europe as demonstrated by the European Cardiovascular MR Registry [23]. This registry also documented the safety of stress CMR examinations with 0.1 % of mild complications in the group of patients with suspected coronary artery disease to 0.42 % in patients undergoing CMR for detection of myocardial viability in the setting of left ventricular dysfunction and known coronary artery disease [24]. No moderate and no severe adverse events were observed in this cohort of >17,000 patients [24].

40.3 Stress Echocardiography Versus Stress CMR

The recent experience with stress CMR for coronary artery disease detection with state-of-the-art technology has been characterized by the attempt to evaluate wall motion (stress dobutamine CMR) [4, 25] and perfusion imaging (stress adenosine or dipyridamole CMR) [3, 7, 26, 27] or both [28, 29]. It is well known from cardiac stress imaging experience over the last 20 years that wall motion and perfusion provide partially different information, and each one has its strengths and weaknesses [30]. Regional wall motion abnormalities as assessed by stress echocardiography are more specific, identify troublemakers in the short run, require true subendocardial myocardial ischemia, and are best suited to assess the effects of medical anti-ischemic therapy (Fig. 40.3). Perfusion or flow heterogeneity is more sensitive; can identify troublemakers in the long run; does not require true subendocardial ischemia but only perfusion heterogeneity, which may frequently occur with mild-to-moderate coronary stenosis or even with normal coronary arteries and concomitant microvascular disease; and is less affected by concomitant anti-ischemic therapy at the time of testing [30] (Fig. 40.4). The two approaches, i.e., perfusion CMR and dobutamine stress CMR in the same patients with coronary artery disease, were tested to predict outcome over a follow-up of 3 years [27]. In patients without ischemia, the outcome was excellent and not different for the dobutamine stress CMR and perfusion CMR with event rates (cardiac death and nonfatal myocardial infarction) of 0.8 and 1.1 %/year, respectively [27]. CMR evaluates perfusion by means of contrast medium first-pass kinetics and stress echocardiography coronary flow reserve through Doppler flow velocity. CMR requires paramagnetic

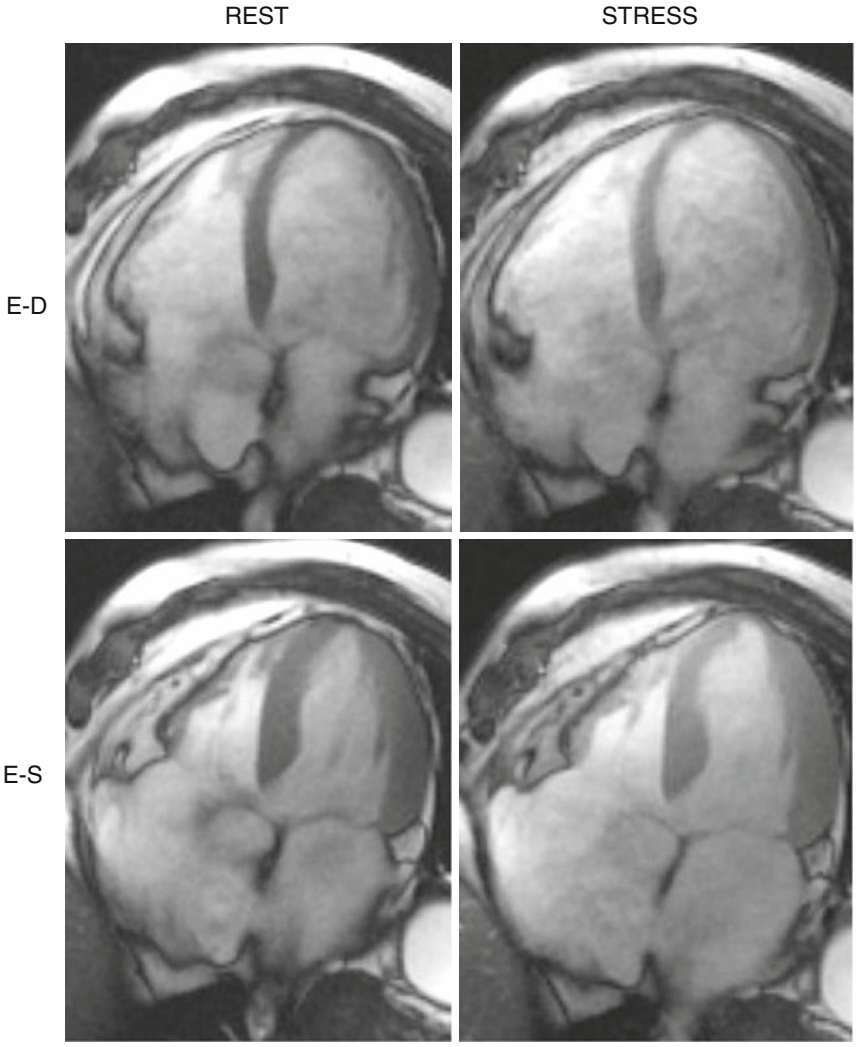

Fig. 40.3 A positive wall motion study by stress CMR, with apical dyssynergy during dipyridamole stress (Courtesy of CMR Pisa Lab 2007, modified from Pingitore et al. [29]). *E-D* end-diastole, *E-S* end-systole

contrast medium, whereas ultrasound contrast medium is often not needed with stress echocardiography. A perfusion reserve approach is typically applied when flow is measured in a vessel for which the supply territory is not known, thereby providing some measure of indexing by normalizing hyperemic flow with resting flow. If perfusion in the tissue is measured as, for example, by perfusion CMR, the supply territory is known, as the volume is known in which perfusion is measured (x- and y-resolution time slice thickness). Consequently, "normalization" by resting flow appears unnecessary, and in fact it adds substantial confounding factors which

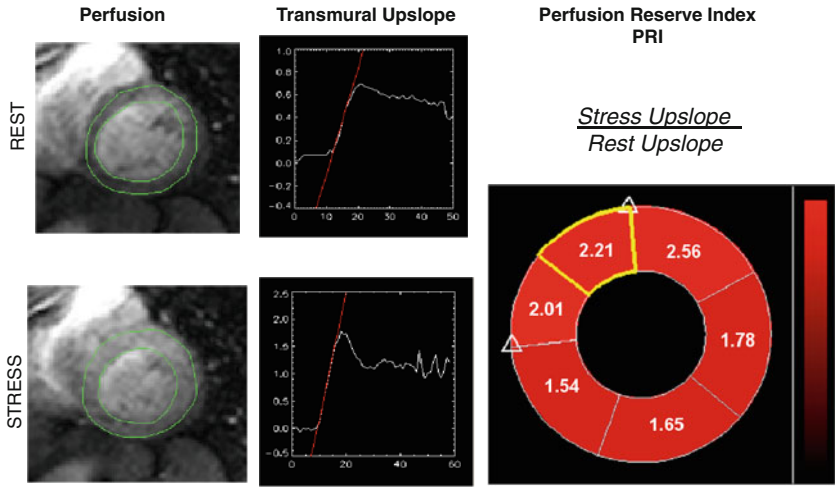

Fig. 40.4 A positive perfusion study with stress CMR, with blunted increase in perfusion in the anteroseptal region (Courtesy of CMR Pisa Lab 2007)

govern resting perfusion (and for which no correction is available) [31]. Not surprisingly, PET perfusion studies repeatedly showed closer correlations between area stenoses in coronary arteries and hyperemic flow than with flow reserve [32, 33]. Other serious concerns regarding a flow reserve approach would need absolute quantification of perfusion, which is currently not possible by CMR, and, in addition, geometrical match of myocardial tissue for stress and rest situation (with large differences in heart rate and therefore filling) is difficult. In addition, the multicenter perfusion CMR trials, all with high diagnostic yield, used hyperemic perfusion data only [26, 33]. Direct comparative studies will be needed to answer the questions of whether stress only or stress–rest protocols should be used for perfusion CMR.

An important difference between CMR and echocardiography regards the use of stresses. Ideally, one would like to catch "two birds with one stone," i.e., to assess function and perfusion with only one stress. As a matter of fact, usually dobutamine is used for function assessment and dipyridamole (or adenosine) for perfusion assessment. With echocardiography, high doses of dipyridamole given with a fast, accelerated infusion protocol allow one to have the same sensitivity as high-dose dobutamine [30] and also to simultaneously assess coronary flow velocity with a maximal hyperemic stimulus [30]. This has been less used with CMR, probably also for a methodological reason, since perfusion CMR is sensitive for motion during data acquisition. This problem can be mitigated by acquiring data during phases of minimal cardiac motion (end diastole and end systole) but would become a limiting factor if perfusion data acquisition should take place at high heart rates [7, 33]. The high prognostic yield of perfusion CMR [27, 34] and dobutamine stress CMR [35] reported in single-center studies was recently confirmed in a large registry population of 1,706 patients in the setting of the European Cardiovascular MR

Registry with an event rate of <1.0 %/y (for all cause death, aborted SCD, and non-fatal myocardial infarction) [23].

In front of largely comparable diagnostic and likely prognostic information, which tends to be better for CMR in patients with difficult acoustic window especially in challenging segments such as the inferior wall [36], there are differences between the two techniques. Echocardiography can be combined with any form of physical (such as exercise) and pharmacological stress, whereas exercise stress (which is the first choice in coronary artery disease patients able to exercise and the only choice for stress testing in valvular heart disease patients) is currently not feasible in a clinical setting with CMR. The cost of CMR is considerably higher than for echocardiography [1], and the availability is certainly lower for CMR. Stress echocardiography is portable and can be made at the bedside, and this is a crucial advantage in some clinical settings such as patients with acute chest pain. The safety is certainly excellent, for any given stress, in the echocardiography laboratory, since the online imaging and hand contact of the sonographer and nurse with the patient in an unrestricted environment, with ECG and blood pressure monitoring, allow for early detection of complications and instantaneous treatment. In the stress CMR laboratory, ischemia during stress is detectable in early stages due to the generally good imaging conditions; however, in the case of emergencies, the scanner environment necessitates special equipment and training of all personnel, and thus, efforts to ensure safe studies in the MR scanner are substantial [37] especially with dobutamine, which is known to be associated with threefold more frequent life-threatening complications compared with dipyridamole or adenosine (1 in 300 vs. 1 in 900) [38, 39]. The safety and cost gap in favor of stress echocardiography are further enhanced by the strict need of paramagnetic contrast in the case of stress perfusion CMR to evaluate coronary artery disease. However, for stress echocardiography the contrast is rarely used for enhancement of left ventricular border detection or coronary flow reserve assessment of the left anterior descending artery, and contrast perfusion imaging is not a viable clinical option today for stress echocardiography. A major advantage, especially in research-oriented environments and for scientific protocols, is that stress CMR is much better equipped for a convenient quantification of tissue structure – even in a transmural sense, separating subendocardial from subepicardial layers. For assessment of myocardial function by CMR, reliable (semi)automatic quantification is still not available, but newer methods, particularly tagging techniques, hold promise for achieving this goal in the near future [16, 17]. Regarding quantification of myocardial perfusion by CMR, it should be kept in mind that hemodynamically relevant stenosis can be detected with state-of-the art CMR today, implicating that changes in myocardial perfusion in the range of several ml/min/g tissue are detected, for instance, by calculating “upslope” maps and comparing them with normal data [7, 19]. No larger trials are currently available to demonstrate that smaller changes in perfusion, such that might be caused by microcirculatory alterations, are detectable by perfusion CMR, and therefore at least for a clinical application no reliable quantitative CMR methods are available. These quantifications are theoretically possible with echocardiography, for instance, with myocardial velocity imaging, but de facto impossible and/or irreproducible in

Table 40.3 Stress CMR vs. stress echo

	CMR	Stress echo
Cost	Higher (2x)	Lower
Availability	+	+++
Portability	No	Yes
Wall motion	Yes	Yes
Perfusion (CMR)/flow (echo)	Yes	Yes (LAD only)
Contrast material (perfusion/viability)	Yes	Usually no
Stress: inotropic	Dob	Ex, dob, dip
Stress: hyperemia	Ado, dip	Dip, ado
Safety profile	Good	Good
Imaging time	About 1 h	<30 min
Operator dependence	Yes	Substantial
Dependence on acoustic window	No	Yes
Quantification: LV volumes, global function	Very accurate	Accurate
Quantification: RV volumes, scar	Accurate	Difficult
Absolute quantification: regional function, perfusion	Possible, not (yet) well validated	Difficult
Transmurality visible (perfusion, function, scar)	Established	Not possible

Ado adenosine, *Dip* dipyridamole, *Ex* exercise, *LV* left ventricle, *RV* right ventricle

a clinical setting – although recently developed angle-independent techniques such as speckle tracking or real-time three-dimensional stress echocardiography show some potential in this regard (Table 40.3).

40.4 Clinical Implications

In a high-volume tertiary care referral center for cardiac imaging, stress CMR may play a clinically relevant role today witnessed by the growth of demand in this specific field. Looking at the guidelines of the European Society of Cardiology, published in 2006 and summarized in Table 40.4, CMR techniques were not yet included for clinical utilization. However, at the time of data collection for these guidelines, the relevant comparative CMR trials were not yet available. In the past few years, several multicenter perfusion CMR trials, in particular the multicenter, multivendor MR-IMPACT I and II [26, 40], demonstrated an excellent performance in detecting coronary artery disease. As these MR-IMPACT trials are also the largest multicenter single-photon emission computed tomography (SPECT) trials utilizing state-of-the-art technology and radioactive tracers, perfusion CMR can be compared with SPECT. In both trials, perfusion CMR outperformed SPECT, and it appears reasonable to recommend perfusion CMR, provided the institution features adequate expertise in this technique, as a first-line technique when myocardial perfusion (a high sensitivity, high negative predictive value gatekeeper) is the desired diagnostic

Table 40.4 Stress CMR and stress echo appropriateness ratings

	Stress echo	Stress CMR
Appropriateness criteria for symptomatic patient		
ECG interpretable and able to exercise	M	R
Low pretest probability of CAD		
ECG uninterpretable or unable to exercise	A	M
Intermediate pretest probability of CAD		
ECG uninterpretable or unable to exercise	A	A
Guidelines		
ESC guidelines – stable CAD (2013)		
Patient with intermediate PTP	Class I, LOE B	Class I, LOE B
PTP 15–65 % and LVEF ≥50 %	Class I, LOE B	Class I, LOE B
PTP 66–85 % and LVEF <50 %		
ESC guidelines – revascularizations (2014)	Class I, LOE B	Class I, LOE B
Symptomatic and PTP 15–85 %	Class I, LOE A	Class I, LOE A
AHA/ACC guidelines (2012):		
Patient with intermediate to high PTP	Class IIa, LOE B	Class I, LOE B
Patient able to exercise, ECG uninterpretable	Class IIa, LOE B	Class I, LOE B
Patient unable to exercise		
ESC guidelines – heart failure (2012)	1 C	
Ischemia testing	Class I, LOE C	Class I, LOE C
Appropriateness criteria for asymptomatic patient		
Intermediate global CAD risk	M	R
ECG uninterpretable or unable to exercise	M	R
High global CAD risk	M	M

A appropriate, *M* may be appropriate, *R* rarely appropriate, *LOE* level of evidence; *PTP* pre-test probability

end point. When regional wall motion abnormality (a high specificity, high positive predictive value gatekeeper) is the preferred diagnostic option, functional CMR can still be an excellent option with accuracy comparable to stress echo and even better in patients with suboptimal echo image quality. A similar approach can also be used for the assessment of myocardial viability. In many patients a simple resting transthoracic echocardiography study can show signs of scar, in the presence of a thinned, hyperechoic, and dyskinetic wall [30]. In patients with preserved end-diastolic thickness, low-dose dobutamine can show a regional and global inotropic reserve of established prognostic value in predicting a good response to medical therapy, revascularization, and cardiac resynchronization therapy [30]. However, in patients with difficult echocardiography studies or ambiguous response, LGE can be an excellent diagnostic option [41], does not require any stress, and today is probably the true gold standard for viability identification and quantification. Low-dose dobutamine CMR can also be performed with the same methodology and interpretation criteria as low-dose dobutamine echocardiography [42]. Rest and stress CMR can also be used as a one-stop shop, with a comprehensive stress CMR examination

including cine (wall motion), perfusion, and late gadolinium enhancement, allowing to assess with the same stress – vasodilator or dobutamine – simultaneously function and perfusion. This comprehensive approach widens the spectrum of stress responses from wall motion and perfusion negativity (excellent prognosis), to intermediate severity response (usually perfusion defect with preserved function) up to most severe concordant perfusion and highly specific wall motion abnormalities during stress [43–50]. Stress echo and stress CMR can easily be integrated for a comprehensive approach for a radiation-free diagnosis of coronary artery disease (Fig. 40.5) with CMR applied as a second-line test to patients with unfeasible or ambiguous stress echo response.

A similar integrated approach can be used for the diagnosis of myocardial viability (Fig. 40.6), allowing to identify in virtually all patients the presence and extent of viable myocardium, without exposure to ionizing radiation.

Compared with stress echocardiography, stress dobutamine CMR is more costly and complex and probably less safe. It is, however, less operator and patient dependent and shares with echocardiography the radiation-free nature. For functional (wall motion) stress imaging, dobutamine CMR should not be used as a "rich doctor's super stress echocardiography," as a first-line tool to evaluate left ventricular

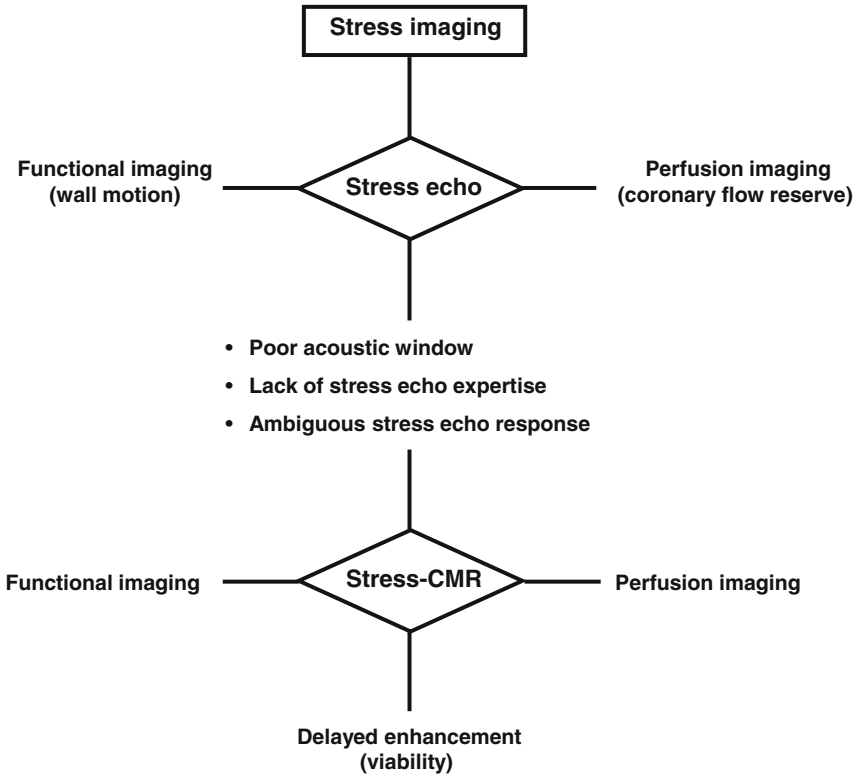

Fig. 40.5 The proposed diagnostic algorithm for the diagnosis of coronary artery disease

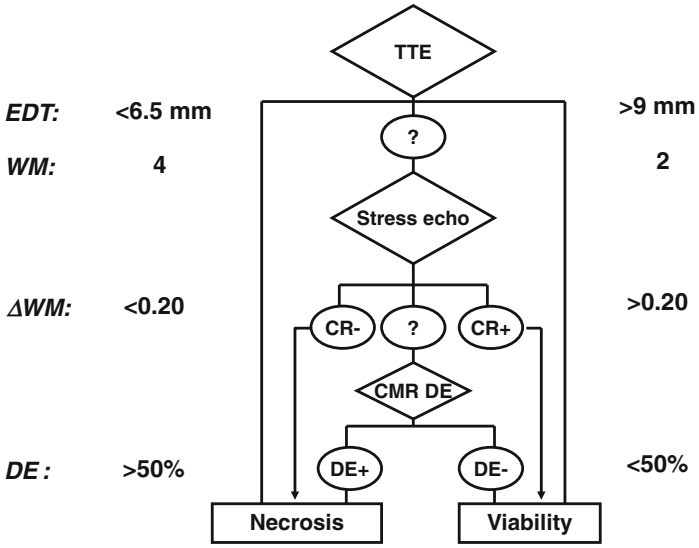

Fig. 40.6 The proposed algorithm for the diagnosis of myocardial viability. *CR* contractile reserve, *DE* delayed enhancement, *EDT* end-diastolic thickness, *WM* wall motion (from 1 = normal, 2 = hypokinetic, 3 = akinetic, 4 = dyskinetic)

function under stress: this would be a waste of resources, in many cases, with no benefit for the patient and the system. It should be used, rather, as the "smart cardiologist's second choice" when stress echocardiography is not feasible and/or yields ambiguous results. For perfusion imaging, stress CMR (with adenosine or dipyridamole) can already be used as "the smart cardiologists' super-SPECT." In fact, when compared with stress SPECT, stress CMR has no radiation exposure and higher accuracy. Regarding viability assessment, low-dose dobutamine echocardiography is well established as a specific test to predict recovery of function. In ambiguous situations, particularly with high interventional risk due to severely reduced global left ventricular function, LGE of CMR can add valuable information to predict outcome after surgery [51].

Costs for coronary artery disease management were estimated to reach 60 billion Euros in 2009 within the European Union [52]. Accordingly, models were developed to estimate the potential cost savings of a CMR-guided strategy to diagnose coronary artery disease in comparison to invasive strategies [53]. In order to decide on coronary revascularization, both, ischemia burden and coronary anatomy, must be known. Stress perfusion CMR can reduce costs when used as an up-front test in patients with suspected coronary artery disease which is followed by invasive coronary angiography in ischemia-positive patients. In populations with low to intermediate disease prevalence (i.e., below 65 % prevalence), the CMR-based strategy is cost saving compared to an invasive strategy which starts with X-ray coronary angiography followed by fractional flow reserve testing in intermediate stenoses [53]. In line with these results, the economic analysis of the CE-MARC trial yielded strategies starting with CMR as the most cost-effective strategies of all tested [54].

40.5 Pitfalls

CMR has clear advantages recognized by guidelines such as absence of radiation and high soft tissue contrast including precise imaging of myocardial scar but also disadvantages such as limited access in cardiology and contraindications (such as claustrophobia, metallic foreign bodies, etc.). Fortunately, major efforts over the past decade were successful to develop MR-compatible pacemakers and defibrillators [55]. In addition, devices designed for the MR environment are low of ferromagnetic material and allow for high-quality CMR examinations in >84 and >93 % of patients for visualization and functional analysis of the left and right ventricle, respectively [55]. Other potential limitations are functional analysis in patients with a high incidence of arrhythmias and limited 3D quantification of ischemia [55].

40.6 Clinical Guidelines

When compared to previous 2006 guidelines [2], in the 2013 ACCF/AHA Multimodality appropriate use criteria for the detection of stable ischemic heart disease, ratings for stress CMR significantly increased toward more appropriate indications [56]. In the latest document, ratings for stress CMR were more often in accord with the ratings for stress radionuclide imaging and stress echo. A similar rating was present in the ESC 2013 guidelines, which recommend noninvasive testing in patients with suspected stable CAD and an intermediate pretest probability with stress imaging preferred (echo, CMR, SPECT, PET) if local expertise, availability, and resources permit [57]. The main concordant and discordant ratings for stress CMR and stress echo are reported in Tab. 40.4. Thus, the newest guidelines reflect the growing body of evidence supporting the utility and accuracy of stress CMR [7, 19, 56–61].

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Appropriateness in the Cardiac Imaging and Stress Echo Laboratory

41

Roxy Senior and Eugenio Picano

Health-care payment is a subject on the mind of virtually every citizen today. Are there areas where expenses can be cut without undermining the quality of care provided? One of these areas is certainly the misuse and overuse of medical imaging [1]. Imaging is a major culprit for several reasons. For instance, diagnostic imaging tests are performed to protect against malpractice exposure, a high-cost diagnostic procedure is used for patients at low risk for the condition, a diagnostic test is applied despite no expected impact on the course of the treatment, or there may simply be a lack of communication and inadequate exchange of information among physicians. As a result, more than 95 million high-tech scans are done each year in the USA, and medical imaging (including CT, MRI, and PET scans) has ballooned into a $100 billion a year industry in the USA, with Medicare paying for $14 billion of that [1].

Cardiovascular imaging has become the focus of intensive efforts on the part of public and private payers, since it has substantially increased the escalating health-care costs in the last 20 years, and payment to cardiologists for imaging services represented 8.7 % of total payments for all physician services in 2006 [2]. According to recent estimates, 20–50 % of all examinations are partially or totally inappropriate, i.e., risks and costs outweigh benefits [3, 4]. Following the definition of the American College of Cardiology Foundation, an appropriate imaging study is one in which the expected incremental information, combined with clinical judgment, exceeds any expected negative consequences by a sufficiently wide margin for a specific indication that the procedure is generally considered acceptable care and a reasonable approach for the indication [3] (Fig. 41.1). Negative consequences include the risks of the procedure itself (i.e., radiation or contrast exposure) and the downstream impact of poor performance such as delay in diagnosis (false-negative results) or inappropriate diagnosis (false-positive results). This implies potential harm for patients undergoing imaging (who suffer the risks of an imaging study without a commensurate benefit), excessive delay in the waiting lists for other patients needing the test, and an exorbitant cost for society, with no improvement and possibly with a reduction in care quality [3]. Although echo and stress echo are

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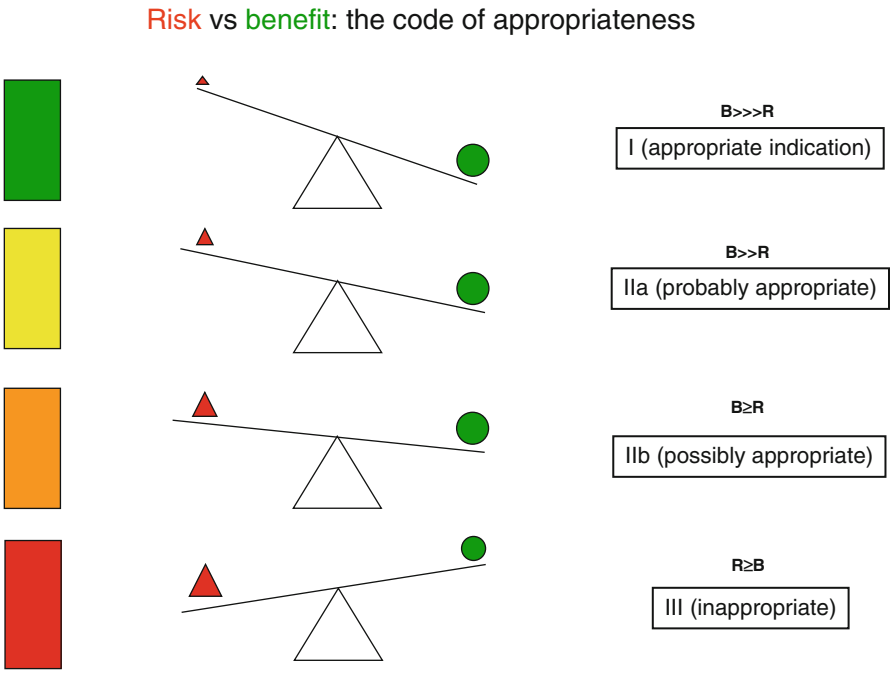

Fig. 41.1 The balance between risks (*red triangle*) and benefits determining the appropriateness score of testing. The three angles of the red triangle represent acute, subacute, and long-term (radiation) risks. Acute risks occur within seconds and minutes (for instance, death or myocardial infarction during stress or cath), subacute risks within days or weeks (for instance, iodinated contrast-induced nephropathy), and long-term risks (due to cumulative exposure to ionizing radiation) after years or decades (AHA-ACC-ESC Guidelines 2007)

less costly and risky than other competing techniques, they have also contributed substantially to imaging waste. Stress imaging tests in particular have increased at an annual rate of 6.1 % since 1993 in individuals covered by Medicare, and we deal with a stress imaging market of ten million exams in the USA alone, with an increase in utilization rate (from 1998 to 2006) of 20 % for stress echo and 215 % among cardiologists for an MPI procedure [5]. Diagnostic imaging has increased more rapidly than any other component of medical care, and echocardiography is the single most frequently used test in the Medicare population, except for laboratory tests [6]. Although the diagnostic and prognostic information provided by these tests is not without a cost, some studies have shown that the use of noninvasive imaging in appropriately selected patients translates into savings because of more appropriate selection of even more expensive procedures [7, 8]. However, these studies involved patients who were appropriately selected for testing; and the trade-off between costs and benefits will not be the same when studies are performed less appropriately [9]. In order to limit the detrimental consequences of the pandemic of inappropriateness and diagnostic obesity, the European Commission in 2001 [10] and more recently the European Society of Cardiology [11] and the American

College of Cardiology Foundation/American Society of Echocardiography [12] have prepared guidelines on the appropriateness of general or specialized imaging testing, including stress echocardiography [13]. The ultimate goal of these documents is to define the appropriate test for the appropriate indication in the appropriate patient: a difficult and elusive target which is, however, one of the new features, and not the least important, of good-quality medical care.

41.1 The Ulysses Syndrome in the Cardiac Imaging Laboratory

The Ulysses syndrome was first described in 1972 by Canadian physician Dr. Mercer Rang, who applied it to the ill effects of extensive diagnostic investigations conducted because of a false-positive or indeterminate result in the course of a routine laboratory screening [14]. Ulysses left Troy in full physical and psychological health. Equipped with a safe ship and a competent crew, he was sure he would return home quickly; instead, it turned out that he lost all his crew and his ship, and he was able to make it home only after a long journey full of hardship. Today, the most frequent diagnostic investigation is a cardiac imaging test. Mr. Ulysses, a typical middle-aged "worried-well" asymptomatic subject with an A-type coronary personality, a heavy (opium) smoker, and leading a stressful life, would be advised to have a cardiological checkup after 10 years of war (Fig. 41.2). The family physician directly refers the patient to the cardiologist (step 2), who suggests a transthoracic echocardiogram (step 3), which is perfectly normal, but with poor visualization of segment 17, the true apex. The patient is again sent to the echo lab to repeat the transthoracic echo with echo contrast injection (step 4): the apex is perfectly visualized and looks normal. However, just to be on the safe side, the cardiologist suggests a multislice computed tomography (step 5) study. Ulysses accepts enthusiastically since he read the front page and cover story of *Time* magazine (September 5, 2005) explaining that in this way, you can detect asymptomatic life-threatening coronary artery stenosis. The scan shows only minor luminal irregularities of very uncertain pathological meaning. At this point, thallium stress perfusion scintigraphy (step 6) is performed. A very mild, questionable hypoperfusion of the infero-basal wall is documented. The stress echocardiography (step 7) is performed, and a very mild apical hypokinesis is observed at peak exercise in the presence of marked systolic blood pressure rise. At this point, the cardiologist requests further examinations and Mr. Ulysses is becoming increasingly anxious. One after another, Ulysses undergoes a PET adenosine stress (step 8: marginally positive finding at basal lateral wall) and magnetic resonance imaging with adenosine and gadolinium contrast (step 9: marginally positive finding on the basal inferior septum). The patient is eventually referred for coronary angiography (step 10); the island of Ithaca is crowded with nonsignificant coronary stenoses, unrelated to perfusion defects or wall motion abnormalities, which may however trigger the oculo-stenotic reflex [4] leading to the vicious circle of angioplasty (obviously with drug-eluting stent), imaging test for the diagnosis of silent

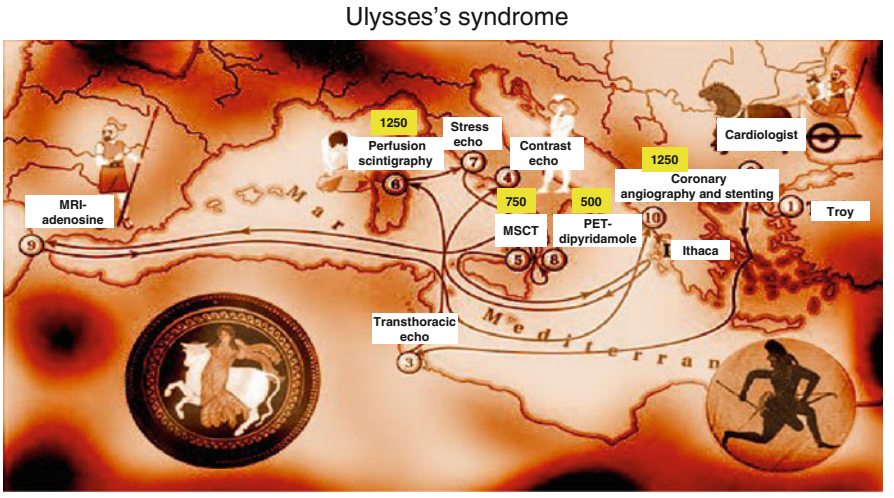

Fig. 41.2 Ulysses' voyage as a metaphor for the diagnostic pathway of the patient with suspected coronary artery disease. At the end of the first round of this odyssey, the cumulative cost is more than 100 times that of a simple exercise electrocardiography. The cumulative radiation dose is that of more than 4,000 chest x-rays. The cumulative damage (including acute, subacute, and long-term risks) will cause a serious health detriment (including infarction, renal insufficiency, or cancer) in about 5–10 % of patients

restenosis, presence of perfusion or wall motion defects, re-angiography, and so on and so forth.

None of these examinations are free, and they all imply a financial cost and a risk. Referring to 2012 Medicare fee schedule for selected cardiovascular tests, for a cardiac imaging test, compared with the treadmill exercise test considered as equal to 1 (as a cost comparator), the cost of CT angiography is 2.5×, of stress echo 2.9×, of a stress scintigraphy 4.8×, of MR 5.4×, and of a diagnostic cath 13× higher [13] (Fig. 41.3). Costs may vary depending on who pays, and site of service and patterns of downstream costs, costs of environmental impact per procedure, and cost of acute and long-term complications or potential cost savings should be considered implicitly [15, 16].

There are non-negligible acute risks in several noninvasive imaging techniques (Fig. 41.4). These risks are composite and can be separated according to the type of

Fig. 41.4 The order of magnitude of composite risks of cardiac imaging. On the *x*-axis, the different types of imaging risks, due to stress administration, contrast injection, and radiation exposure, which appear, respectively, within seconds, days, and years. Contrast injection can be associated with acute risks, such as allergic reactions, and/or subacute risks, such as contrast-induced nephropathy with iodinated contrast agents used in invasive fluoroscopy or noninvasive CT. On the *y*-axis, the magnitude of associated risks. An overall risk-benefit assessment in the individual patient should include the composite assessment of all risks in the risk side of the equation

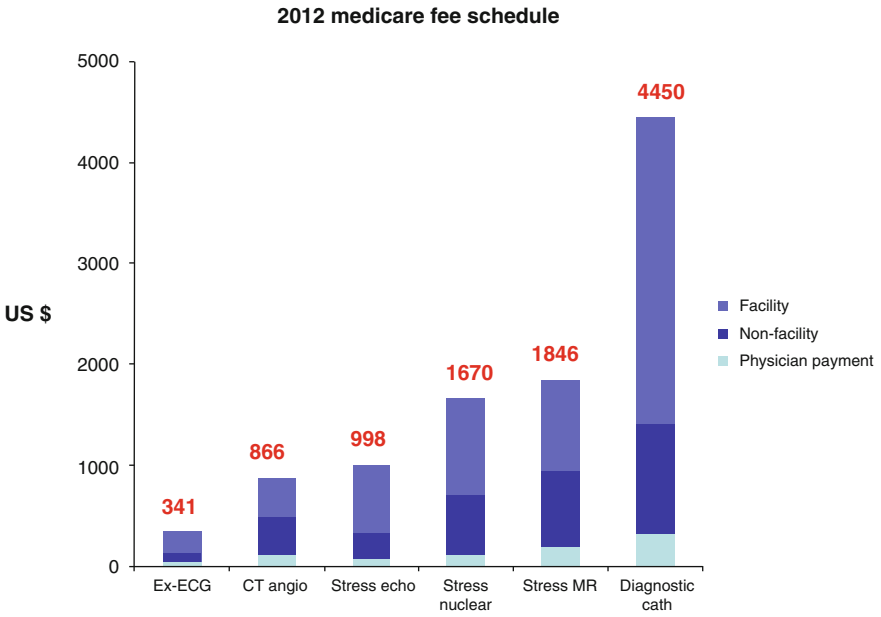

Fig. 41.3 The relative costs of different cardiac imaging techniques (From the data of 2012 Medicine fee schedule presented in Wolk et al. [13])

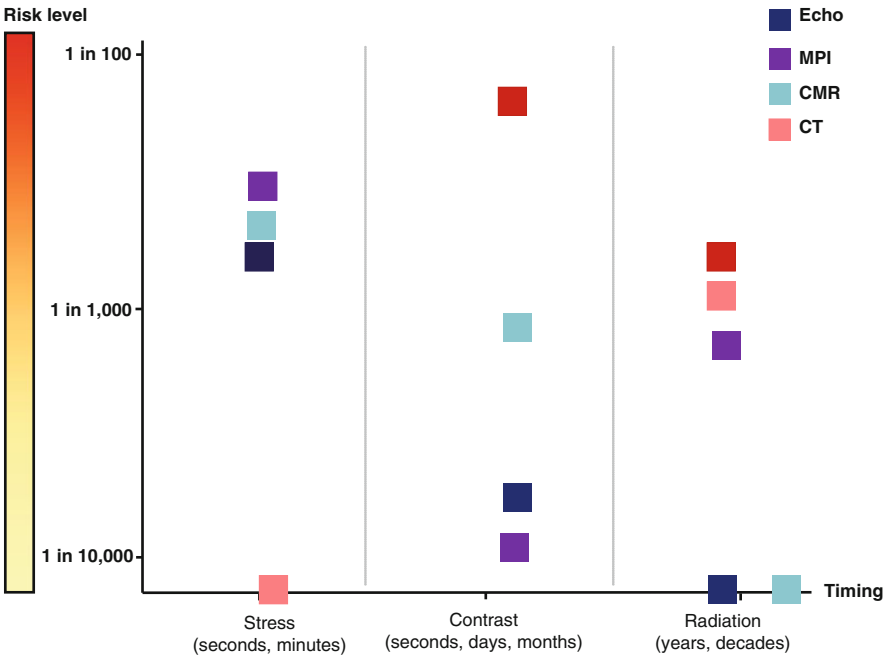

Table 41.1 Acute, subacute, and long-term risks in noninvasive cardiac imaging

	Acute	Subacute	Chronic
Most frequent cause	Stress administration	Iodinated contrast	Radiation
Imaging type	SE, MPI, CMR	CT	MPI, CT
Examples	Myocardial infarction	Renal failure	Cancer
Target organ	Myocardium	Kidney	Lung, breast, etc.
Risk per exam	1 in 500–1 in 1000	1 in 50–1 in 200	1 in 500–1 in 2000
Cumulative nature	No	No	Yes

risk (stress-related, contrast-related, and radiation-related) and the timing of appearance (acute, within seconds/hours; subacute, within days/weeks; chronic, within years or decades) (Table 41.1).

Stressors imply the highest risk of death or myocardial infarction or other serious adverse reactions.

Exercise testing entails a very small but definite risk, and there is up to 1 myocardial infarction or death per 2,500 tests [17]. Major, life-threatening side effects (sustained ventricular tachycardia, ventricular fibrillation, and myocardial infarction) occur in about 1 out of 300 dobutamine echocardiography exams and 1 out of 1,000 dipyridamole echocardiography tests [18, 19]. In general, exercise is safer than pharmacological stress, in which major complications are three times more frequent with dobutamine than with dipyridamole [20, 21].

Computed tomography and invasive coronary angiography require administration of an iodinated contrast agent. Serious adverse reactions including pulmonary edema, severe hypotension, and loss of consciousness occur in 0.04 % patients with nonionic contrast agents [22]. Contrast agents used in stress echocardiography to improve the endocardial border of the left ventricle and for evaluation of myocardial perfusion have a much lower risk of serious adverse events, around 3/10,000 according to the overall post-marketing experience with a perflutren lipid microsphere (Definity) [23]. The "safety" profile is also excellent with CMR contrast agents, although gadolinium-based contrast agents have been associated with nephrogenic systemic fibrosis, a potentially lethal disease which has never been seen in patients with normal kidney function [24].

The use of nephrotoxic contrast agents in large doses with CT imaging is a major concern, since it induces an acute worsening of renal function – not always reversible – in about 1 % of patients. The rate of complications is obviously higher with invasive imaging procedures. For instance, coronary angiography has a cumulative risk of 1–2 % of major complications (including myocardial infarction and stroke) and 1 in 1,000 risk of death [25]. Contrast-induced nephropathy is the third most common cause of hospital-acquired renal failure, ranging between 3 and 14 % in patients with cardiovascular pathology undergoing angiography procedures [26]. All of these risks may be fully acceptable in presence of a proper indication but become unacceptable if the indication is less than appropriate. More than ten million stress imaging procedures [5] and more than one million coronary angiographies [25] are performed every year in the USA alone. The small individual risk multiplied by a million procedures thus becomes an important population burden [27].

In other words, at the end of the first round of examinations shown in Fig. 41.2, Ulysses paid about 100 times the cost of a simple exercise electrocardiography test – probably all that he needed. He received a 5 % cumulative risk of major short-term adverse events (from renal insufficiency to myocardial infarction). He received a cumulative radiation dose exposure of about 4,000 chest x-rays, corresponding to an extra risk of cancer of 1 in 150. The invasive and interventional procedures that he underwent did not improve his quality of life since he was asymptomatic at the beginning of his cardiological history and the anatomy-driven revascularization will not increase his life expectancy [28]. Periodic follow-up examinations with imaging testing will be scheduled – mostly inappropriately – and the odyssey will probably last forever.

41.2 Appropriateness in the Stress Echocardiography Lab

The proliferation of cardiac stress imaging may represent an added value when appropriate and an added cost when inappropriate. Unfortunately, the criteria of appropriateness are obvious in theory but not so straightforward on practical grounds. Unlike prevention and treatment strategies supported by evidence-based practice guidelines, the evidence base for imaging is anecdotal, fragmented, and lacking in prospective clinical trials [3]. As a consequence, the process for developing appropriateness criteria is only partially evidence based and is heavily weighted by expert consensus [3]. There is, therefore, also an urgent requirement of prospective studies to unravel appropriateness of a test. However, as it stands, the appropriate criteria of some modalities have been tested clinically and by and large found to be adequate [29–31]. On an arbitrary scale of 1 (most inappropriate) to 9 (most appropriate), indications are classified as "appropriate" (score > 7, test is generally acceptable and is a reasonable approach for the indication), "uncertain" (score between 4 and 6, test may be generally acceptable and may be a reasonable approach for the indication), and "inappropriate" (score < 3, test is not generally acceptable and is not a reasonable approach for the indication). The most frequent appropriate, uncertain, and inappropriate indications encountered in the clinical practice of high-volume laboratories are listed in Table 41.2 [12, 13]. Following these criteria, only two out of three stress echocardiography tests are appropriate, with similar numbers observed in disparate geographic, cultural, and economic situations – from Europe to Australia to the USA [29–34] (Fig. 41.5a). Of interest, the vast majority of inappropriate studies were restricted to only a few patient indications, with the three most frequent inappropriate indications listed in Table 41.2 accounting for 79 % of inappropriate indications in ambulatory patients [29] (Fig. 41.5b). These indications included symptomatic patients with low pretest probability of coronary artery disease having an interpretable ECG and ability to exercise, asymptomatic patients who had undergone angioplasty less than 2 years before, and asymptomatic patients with low risk [29]. An inappropriate test also provides negligible prognostic information when compared to an appropriate test and is per se – independently of test positivity or negativity – associated with lower rate of positive results and better survival as compared with appropriate and uncertain indications [29, 31].

Table 41.2 Most frequent appropriate/uncertain/inappropriate indications in CAD detection and/or risk stratification

	Appropriate	Uncertain	Inappropriate
ECG uninterpretable or unable to exercise, or prior stress ECG equivocal	√		
Coronary artery stenosis of unclear significance (CT or angiography)	√		
Postrevascularization not in the early post-procedure period, with change in symptoms	√		
Pre-surgery, high-risk non-emergent, poor exercise tolerance <4 METS	√		
Viability (dobutamine) ischemic cardiomyopathy, known CAD, patient eligible for revascularization	√		
Asymptomatic or stable symptoms, repeat stress echo after >5 years		√	
Asymptomatic <5 years post-CABG or <2 years post-PCI		√	
Asymptomatic, low risk			√
Preop, intermediate risk surgery, good exercise capacity			√
Symptomatic, low pretest probability, interpretable ECG, able to exercise			√
Asymptomatic <1 year after PCI/CABG or stable with recent abnormal stress			√
Pre-op low risk surgery			√

Similar rates of inappropriateness apply to the simplest imaging examinations, such as chest x-ray, and to most complex, costly, and risky such as myocardial perfusion scintigraphy, computed tomography, coronary angiography, and percutaneous coronary intervention [35]. This repetitive pattern of inappropriateness points to a need for quality improvement and educational programs to achieve measurable improvement in results [1, 2]. This task remains difficult to achieve, also because appropriateness ratings may change rapidly over time as the body of evidence grows. For instance, when compared to the previous 2010 release, the 2014 ACCF assigned higher ratings to stress CMR, more often in accord with the ratings for stress echo and stress RNI [13]. It also assigned higher ratings for stress echo among symptomatic patients with low pretest probability to exercise and an interpretable ECG [12, 13] and to CCTA following an abnormal stress imaging study [13]. Similarly in the recent ESC guidelines for stable angina, stress exercise imaging is considered appropriate even in patients with interpretable ECG [11]. Furthermore, recent data suggest that stress imaging for patients admitted with suspected acute coronary syndrome increased downstream costs compared to no testing strategy [36]. This finding is likely to impact on the appropriateness criteria for stress imaging. Last but certainly not the least, all the guidelines and appropriateness criteria are based on younger population. With growing elderly population, clinical trials are now imperative to develop appropriateness criteria in the aging population.

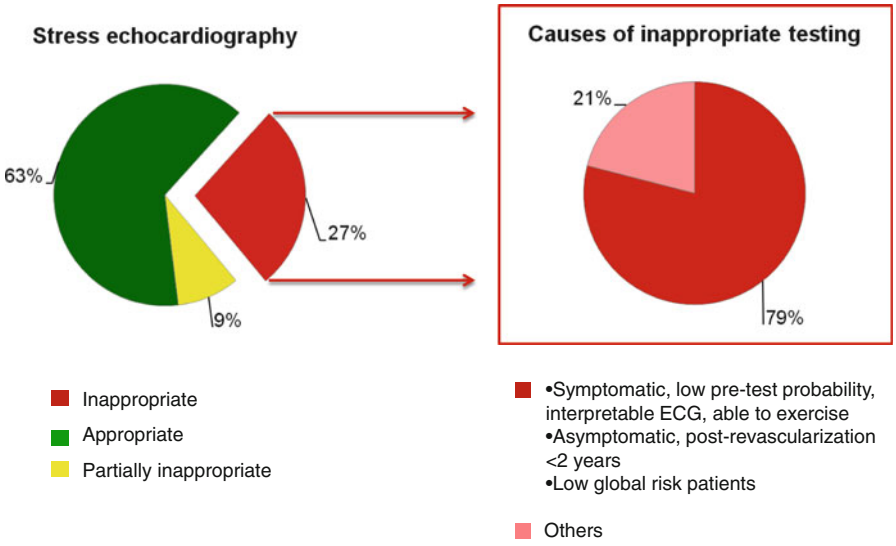

Fig. 41.5 The inappropriateness rate of outpatient stress echo activity in a tertiary care center (*left panel*) and the main reasons for inappropriate indications (*right panel*) (Adapted from Refs. [32] and [29])

In addition, the very same indication can be rated differently by a different group of experts: for instance, a stress imaging test in a symptomatic patient with ECG interpretable and capable of exercise and with low (between 5 and 10 %) pretest probability of disease "may be appropriate" for ACCF 2014 [13], whereas for ESC guidelines, patients with "low" (<15 %) probability have no indication for imaging testing [11].

41.3 How to Improve Appropriateness

The "paradox of plenty" is a major challenge for contemporary health-care delivery: more resource use may lead to poorer measures of care [37]. More is not necessarily better and in fact may be worse [38]. A substantial abatement of inappropriateness could be achieved through targeted action on a number of factors that include but are not limited to physician test ordering practice, diagnostic imaging funding mechanisms, and assurance and accreditation practices. Upstream from the examination, the booking system should be remodeled. In many places, this is a passive administrative channel between the patient and a secretary. The lower levels of inappropriate testing in an environment where there is a screening or consultation step suggest that this more active, time-consuming, but critically important filter between the referring and the practicing physician is effective. Local guidelines for testing might be developed and implemented on the basis of general guidelines adapted to local expertise and technology available and possibly also implemented on the basis of specific audit and training courses [39]. In fact, lack of communication and

imperfect exchange of information are often at the root of inappropriateness in this rapidly evolving field.

Downstream from the examination, current systems pay for cardiac procedures regardless of their appropriateness. New payment models should be developed to pay physicians more for providing clearly appropriate procedures and substantially less for procedures of limited value. Although it is certain that this is more easily said than done, there is no doubt that a system paying for the quality, not only the quantity, of the procedures would be an enormous boost to appropriateness.

Education efforts alone – such as ground rounds and newsletters, pocket cards, and sample letters for distribution – are remarkably ineffective in reducing inappropriateness levels [30], unless education is provided to physicians in the context of losing coverage for testing [40]. In the USA, more than 90 % of the largest private payers have contracted with a radiology benefit manager, who requires prior authorization of imaging as a front-end safeguard for managing resources, a method that has been successful at reducing costs [40], although it requires additional administrative resources, with an estimated 7500 US dollars per cardiologist per year necessary to accommodate a radiation benefit manager. With a different, more physician-centered approach, it has been shown that a computerized point-of-order decision support system can reliably track physician behavior, improve appropriateness, and reduce inappropriateness, even with a waiver of radiation manager preauthorization [41]. In this way, a transparent and educational mechanism can guide imaging utilization and reduce costs. Clinical decision support systems provide real-time guidance to the physician and can be accessed through computerized order entry systems or web portals or via electronic health records so that they become a part of the normal workflow. It has also been suggested that, as a part of maintaining quality standards, laboratories should ensure that staff understand appropriate use criteria and develop a process to reduce the number of inappropriate referrals [42]. An important contributor to excessive use of advanced imaging may be a physician "knowledge gap" regarding the state-of-the art knowledge of updated guidelines, the safety (especially regarding dose and risks of radiation exposure), and the cost of the tests. This knowledge gap has far-reaching consequences, since physicians are responsible for weighing the risks, costs, and benefits of medical tests, a difficult task if they ignore costs and risks. With clinical decision support systems embedded in computerized physician order entry systems providing for each test the corresponding appropriateness, cost, and radiation exposure information, the decision of the physician is generally steered toward tests with similar appropriateness, lower cost, and less or no radiation exposure [43]. Although radiation risk "per se" does not reduce the level of appropriateness of a particular test compared with other tests (e.g., tests that impart ionizing radiation should not necessarily receive a lower score than tests that do not), the ALARA (as low as reasonably achievable) principle should be used to guide both test choice and test protocols emphasizing dose-reduction techniques while preserving diagnostic image quality [10, 11, 13, 44]. At the end, the communication of an increased culture of appropriateness and safety ("carrot") combined with the abandoning of a pay-per-volume policy, with reduced chances of reimbursement for inappropriate testing ("stick"), will eventually lead to less overuse and misuse of cardiac imaging.

41.4 Take-Home Message: Our Responsibility to Change

Appropriateness in health care, like quality, can be a moving target and not easy to define. More than 30 years ago, a *Lancet* editorial complained of the "flooding of laboratory testing" requested by clinicians who believe that "all seems to be for free" and often ask for "diagnostic carpet bombing" instead of carefully targeted, clinically driven testing [45]. After 30 years, the same pattern seems to apply to cardiac stress imaging testing. Several factors may influence the ordering of an inappropriate test such as financial incentives, lack of physician confidence in clinical assessment skills, patient insistence, pro-technology bias, lack of a filtering order system, and knowledge gap of the prescribing physician regarding cost and radiation doses (Table 41.3). Much imaging practice is driven by habit or anecdote, new methods enter the clinical practice with limited testing of their contribution to improving health, and – most importantly – evidence basis for using imaging is incomplete [46], and we urgently need comparative effectiveness randomized trials of imaging-guided strategies to reliably guide health-care coverage and medical necessity decisions in the prevalent population [2]. It is also difficult to convince patients with cardiac conditions that routine cardiac imaging is no longer needed and is in fact harmful [47]. The major question that needs to be posed to both the physician and the patient when ordering test is whether that particular test is likely to bring about change in management. If not, that test cannot be appropriate under the circumstances. Therefore, the "Choosing Wisely" campaign was started in 2009 by the American Board of Internal Medicine Foundation in partnership with Consumer Reports to spark discussion about the need and lack thereof for many frequently ordered tests and treatments with low-value (but often high-cost) services [48]. The list developed in collaboration with the American College of Cardiology included cardiac imaging, particularly stress test or advanced recommended imaging, among the "five things physicians and patients should question" [48].

As with many quality measures, the very act of having appropriateness criteria and measuring your own appropriateness performance is likely to improve the

Table 41.3 The road to appropriateness in cardiac imaging lab

	What we have	What we need
Philosophy	Moral suasion	"Carrot and stick"
Audit	"Prejudicial to our reputation"	A legal duty
Payment	Pay per volume	Penalty for inappropriateness
Authorization	Specialist self-referral	Radiology manager pass
Indication	Guidelines and "experience"	Web decision support system
Cost and radiation dose	Physician knowledge gap	Embedded in order forms
Patient education	Early screening and intensive follow-up	Choosing Wisely
Economic climate	Affluent society	Sustainable society
Starting point	High tech (imaging first)	High touch (patient first)
Industry	Pro-technology bias	Cost-effectiveness evidence
Physician mantra	More is better	Less is more

quality of what is being measured [49]. What is even more important, in a changing economic climate, if we as cardiologists do not play a proactive role in implementing appropriateness, others will do it for us – as is already happening with dramatically decreasing trends of utilization in recent years for techniques that are more costly and associated with radiation exposure, such as MPI (Fig. 41.6) [50, 51]. Although patients, institutions, and physicians all share the goal of delivering effective and high-quality medical care, "in too many instances financial pressures, structural inefficiencies, imperfect information, and irrational patterns of traditional practice, resource allocation and use defeat or deflect the achievement of these ends." The possible countermeasures are a better alignment of payment incentives for physicians and hospitals, transparency of performance measures and cost data, and incentives for promoting more appropriate and responsible delivery of care [52]. Cardiac stress imaging procedures – be it nuclear stress testing or stress echo – are two to six times more frequent among patients seen by physicians who provide and bill for these procedures than by those not billing [53], clearly showing the persistence of financial conflicts of interest as a driver of utilization [54]. The quest for appropriateness is a priority for the echocardiography community to improve the quality of our profession, to address the legitimate existing concerns of those who pay for these services, and to optimize the immense benefits our patients can derive from the appropriate practice of cardiac imaging and stress echocardiography.

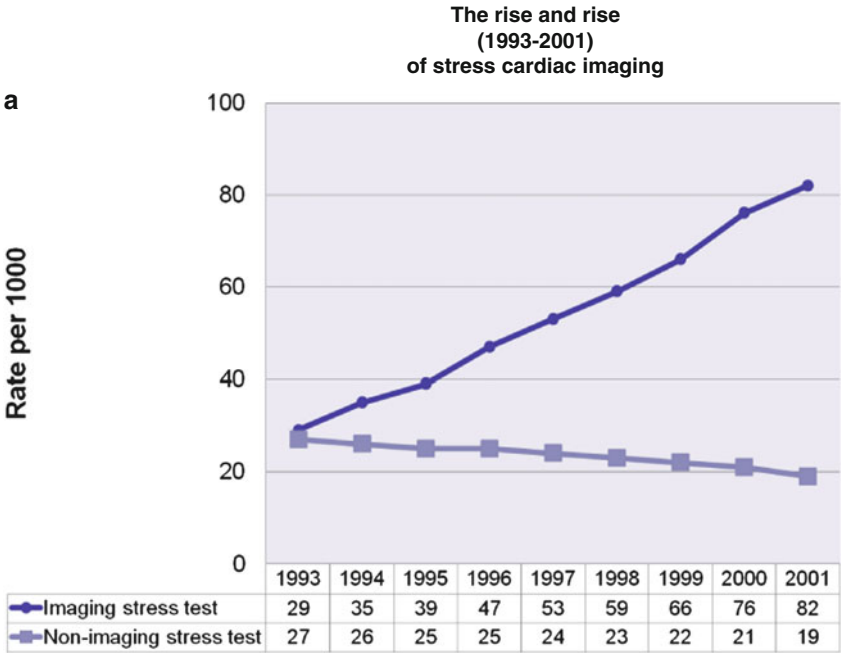

Fig. 41.6 The temporal trends in utilization of cardiac stress imaging in the USA. (**a**) The continuous steep rise from 1993 to 2001 (From Ref. [9]). During this period, the average annual increase of imaging stress test is accompanied by a decrease of non-imaging stress test. (**b**) Utilization trends for MPI from 2000 to 2006 are +41 % and from 2006 to 2011 −51 %. In the same 2006–2011 period, stress echo remained stable and CT increased by 100 % from McNulty et al. [50]

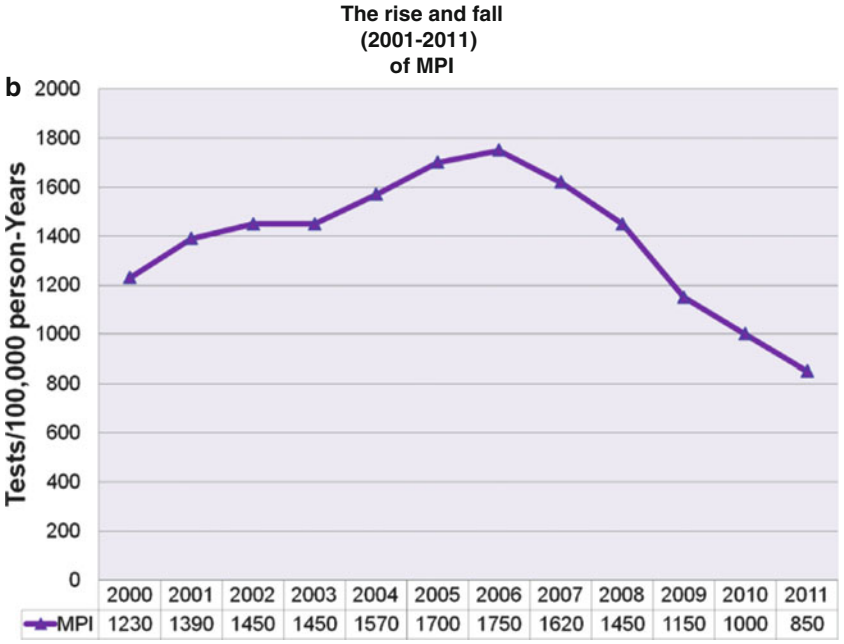

Fig. 41.6 (continued)

Table of Contents Video Companion

See also, in the section selected presentations: The appropriate and justified use of medical radiation.

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