Stress Echocardiography
From Pathophysiological Toy to Diagnostic Tool

Eugenio Picano, MD

The Red Queen to Alice: “Here, you see, you have to run with all your might to stay in the same place. To go somewhere else, you have to run at least twice as fast.”

Lewis Carroll
Through the Looking Glass

Stress echocardiography today enters the clinical arena as a safe and efficient option for diagnostic imaging of myocardial ischemia in the nineties. It is no longer considered an esoteric research tool in the hands of few high-tech laboratories but rather an extension of daily echocardiographic diagnosis.1,2 This article will briefly review the basic features of this new method: the pathophysiological rationale, the echocardiographic signs of transient myocardial ischemia, the development of pharmacological stress to overcome the technical limitations of exercise echocardiography, the physiological basis of pharmacological stresses, the clinical results, and the diagnostic impact and the possible clinical role in cardiology practice today.

Rationale of Stress Echocardiography

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.” In ischemia, the cell minimizes expenditure of energy into cardiac work and uses whatever is left for the maintenance of cellular integrity: Accordingly, the impairment of regional contractile function is an early sign of ischemia.3

The decrement of regional contractile function is directly related to the decrease in regional subendocardial blood flow, both with acute progressive stenosis and during stress-induced ischemia.4,5 Experimental data therefore support the possibility that the contractile defect may provide a sensitive and semiquantitative marker of regional ischemia. At the clinical level, myocardial ischemia results in a typical cascade of events in which the various markers are hierarchically ranked in a well-defined time sequence, with regional dyssynergy being a very early marker followed only at a later stage by electrocardiographic changes, global left ventricular dysfunction, and pain.6 The clinical appeal of regional dyssynergy as a marker of ischemia obviously increased tremendously in the echocardiographic era.

Echocardiographic Signs of Myocardial Ischemia

The cardinal marker of transient myocardial ischemia is regional dyssynergy (or asynergy) in its three degrees: hypokinesis (reduction of systolic movement), akinesis (absence of systolic movement), and dyskinesis (paradoxical systolic movement). Obviously, these descriptive terms identify arbitrarily three discrete points in the continuous spectrum of mechanical changes induced by ischemia. Clinically, the reliability of hypokinesia is decreased by a greater intraobserver and interobserver variability.

Another marker of ischemia is reduced regional systolic wall thickening, which is theoretically more sensitive than regional movement, because thickening is necessarily an active process, whereas motion can be passively transmitted from nearby normocontracting segments. From the practical standpoint, both motion and thickening should be evaluated for each myocardial segment, both in resting conditions and during stress.

Other signs of myocardial ischemia have been described, but they are ancillary markers of the extension of regional dysfunction rather than accurate indicators of myocardial ischemia.7 They include left ventricular cavity dilation and Doppler signs of global systolic or diastolic dysfunction. Transaortic Doppler flow monitoring can show a reduction in aortic peak flow velocity and flow velocity integral, whereas the main sign of ischemia in transmitral Doppler flow is a decrease in the ratio of postdiastolic and presystolic peak flow velocity. Color Doppler is particularly suited for imaging acute mitral valve insufficiency, which appears to be related to the amount of jeopardized left ventricular muscle rather than to the site of ischemia or to the involvement of papillary muscles.

Different from the electrocardiogram, the same echocardiographic signs can be found in transient ischemia and acute infarction. The difference is in the time sequence of mechanical changes, because myocardial ischemia (from an echocardiographic viewpoint) is a “reversible” myocardial infarction. Regional dyssynergy is the most sensitive and specific sign of myocardial ischemia,4–6 the only one that allows a diagnosis of site and simple visualization.

Stress Echocardiography:
A Drug-Dependent Technique?

Although dynamic exercise is the paradigm of all physiological stresses and the most popular provocative
test of myocardial ischemia, it makes imaging by two-dimensional echocardiography difficult.\(^8\)

Several exercise protocols have been proposed in combination with two-dimensional echocardiography: supine or upright bicycle and treadmill.\(^9\) The proposed techniques of echocardiography monitoring are also different: during exercise or immediately after exercise.\(^1\)

The advantage of postexercise imaging is to improve image acquisition rates by minimizing the many factors degrading the echo quality during exercise: respiratory interference, excessive tachycardia, and chest wall movement. Although a very high feasibility has been reported with postexercise studies,\(^1\) the success rate is often based on good-quality imaging of a single cardiac cycle in only one projection. In a patient with a known or suspected infarction, no echocardiographer would make the diagnosis of presence, site, and extension of dysynergy on the basis of a single cardiac cycle in one view from only one approach: The dysynergy can be highly localized, and some regions can be adequately visualized only in some projections. The rationale of postexercise imaging lies in the evidence that the recovery of systolic function after ischemia is linked to the duration of ischemia.\(^9\) The longer the myocardium is deprived of blood, the longer it takes for that myocardium to recover its function. Although postexercise imaging reduces echocardiographic limitations, it suffers greater cardiological drawbacks. In the presence of milder degrees of ischemia, wall motion changes induced by exercise reverse quickly upon cessation of exercise. Even when wall motion abnormalities are observed after exercise, the phenomenon of reversal suggests that the magnitude of stress-induced abnormality may be greatly underestimated, limiting its use as a measure of extent and severity of the disease. Finally, postexercise imaging completely misses the level of cardiac work eliciting ischemia during exercise, which is directly related to physiological impairment and to prognosis.

In striking contrast to exercise, pharmacological stresses are the ideal partners of echocardiography for a series of technical, economical, and pathophysiological reasons. Technically, pharmacological stresses allow minimization of factors that make the ultrasonic examination difficult during exercise: The patient can lie comfortably in the position more suitable for echocardiography monitoring without excessive chest wall movement, hyperventilation, or tachycardia interfering with the ultrasonic imaging.

Economically, pharmacological stresses do not need additional expense and apparatus required by some stresses. Exercise will require a treadmill or a tilting bed; pacing will require intravenous or transesophaegal catheterization, which will obviously increase the personnel involved, the time required for preparation, the cost of the procedure, and the discomfort to the patient. Pharmacological stresses require only the placement of an intravenous line and the availability of a low-cost drug.

Pharmacological stresses allow continuous monitoring throughout the stress and therefore exact assessment of the timing of the dysynergy, which carries the single most important information for the anatomic and prognostic stratification of these patients.\(^10\)\(^11\)

At present, the two most popular tests in stress echocardiography are dipyridamole\(^10\)\(^11\) and dobutamine,\(^12\)\(^13\) which have the potential to induce myocardial ischemia in the territory dependent on a critical coronary stenosis acting through completely different biochemical and hemodynamic mechanisms.

**Physiological Basis for Pharmacological Stress Testing**

Dipyridamole inhibits adenosine cellular uptake and provokes inappropriate endogenous adenosine accumulation, whereas dobutamine acts through adrenoceptor stimulation (Table 1). They can induce ischemia through two separate mechanisms: 1) an increase in oxygen demand, exceeding the fixed supply (the prevailing mechanism with dobutamine), and 2) flow maldistribution resulting from inappropriate coronary arteriolar vasodilation (the main mechanism after dipyridamole). In the presence of a fixed reduction in coronary flow reserve, both these mechanisms can provoke subendocardial ischemia necessary to induce the regional dysynergy.

**Increase in Demand**

This mechanism can be easily fitted into the familiar conceptual 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 an increase in demand of different entity and through different mechanisms.

In resting conditions, myocardial oxygen consumption is mainly dependent on heart rate, inotropic state, and the wall stress (which is proportional to the systolic blood pressure)\(^14\) (Figure 1). During exercise, the increase in heart rate and, to a lesser extent, blood pressure and

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Flow Maldistribution

In the presence of coronary atherosclerosis, an inappropriate arteriolar dilation can paradoxically exert detrimental effects on regional myocardial perfusion, determining an 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.

In “vertical steal,” the anatomic requisite is the presence of an epicardial coronary artery stenosis, and the subepicardium “steals” blood from the subendocardial layer.16,17 The mechanism underlying vertical steal is a fall in poststenotic pressure secondary to the increase in flow across the stenosis. The flow increase is made possible by the existence of a residual vasodilatory reserve in the territory of the stenotic vessel. The depressurization of the microcirculation induces a collapse of subendocardial vessels because extravascular resistance is higher in the subendocardium, thus causing an absolute reduction—compared with resting conditions—of subendocardial flow.16,17

The “horizontal steal” requires the presence of collateral circulation between two vascular beds: the victim of the steal is the myocardium fed by the more stenotic of the two vessels.18 The arteriolar vasodilatory reserve must be at least partially preserved in the nonstenotic vessel and abolished in the vessel receiving collateral flow. After vasodilation, the flow in the collateral circulation is decreased in comparison with resting conditions because the arteriolar bed of the nonstenotic vessel competes with the arteriolar bed of the stenotic vessel that has no vasodilatory reserve (Figures 2 and 3).

The stresses provoking this flow maldistribution act through a “reverse Robin Hood effect”11: Unlike the British hero who stole from the rich to give to the poor, 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 usually is the inappropriate accumulation of adenosine, which is the main physiological modulator of coronary arteriolar vasodilation.19,20 Inappropriate adenosine accumulation can be triggered by a stimulus either metabolic (such as exercise or pacing) or pharmacological (such as dipyridamole) (Figure 4). 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 dipyridamole-induced ischemia, and a relatively minor, although possibly significant, role in exercise-induced ischemia.19,20 In the experimental model of exercising dogs with critical coronary stenosis in which the mean coronary blood flow exhibits lack of vasodilator reserve, during exercise subendocardial myocardial blood flow falls, whereas subepicardial flow rises slightly above the resting level.4 Therefore, also during exercise the transmural maldistribution of flow marks the development of ischemia and mechanical dysfunction in the region

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**Figure 1.** Bar graph shows the major determinants of myocardial oxygen consumption in resting conditions (left, REST) and during some stresses (right) commonly used with echocardiography. The relative contributions of systolic blood pressure (BP), heart rate (HR), and inotropic state (INO) to myocardial oxygen demand are represented. They are approximate and not derived from a specific population. During dipyridamole or adenosine, there is a mild increase in oxygen consumption caused by increase in the inotropic state or heart rate, respectively. The rise in oxygen demand is even more marked during exercise, which causes an increase in heart rate as well as in inotropic state and systolic pressure (redrawn and modified from J. Ross Jr.14).

**Figure 2.** Schematic drawing of hydraulic model illustrating coronary horizontal steal. For this example, the right coronary artery (RCA) is the supply artery, with the vascular distribution of the left anterior descending (LAD), which is severely stenotic, being supplied by collaterals from the RCA. Coronary steal after 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 pressure drop along the supply artery. Asterisks (*) indicate dipyridamole-induced arteriolar dilation. Distal perfusion pressure to the collateral vessels therefore falls, because collateral flow depends primarily on the driving pressure gradient (between distal perfusion pressure of the supply and collateralized vascular bed) (redrawn and modified from Demer et al19).
subserv by the stenosed artery. Theoretically, dobutamine might also induce flow maldistribution (of moderate degree?) by stimulating $\beta_2$-adrenergic receptors, which mediate coronary arteriolar vasodilation.²¹

It is important to recognize that although a potential limitation of pharmacological stresses is that they provoke ischemia through nonphysiological mechanisms absent in everyday life, clinical studies document that

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**FIGURE 3.** Echocardiographic images of collaterals 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) were obtained in basal conditions and after dipyridamole administration. After dipyridamole, the apex is dyskinetic; coronary angiography shows an almost total disappearance of the collateral vessels (arrows) (redrawn and modified from E. Picano¹⁰).

**FIGURE 4.** Diagram shows biochemical pathways possibly leading to inappropriate arteriolar vasodilation in different stresses (redrawn and modified from E. Picano⁷).
ischemia induced by pharmacological stresses closely reproduces the site and extent of ischemia produced by physiological stresses such as exercise.\textsuperscript{22}

\textbf{Clinical Results of Pharmacological Stress Echocardiography}

Despite the different underlying biochemical and coronary hemodynamic mechanisms, both dipyridamole and dobutamine tend to induce ischemia in the same myocardial territory fed by a critically stenosed region apparently with a similar sensitivity and specificity for the detection of angiographically assessed coronary artery disease.\textsuperscript{23-25} These clinical data only apparently conflict with the experimental findings obtained in nine dogs by Fung et al.\textsuperscript{17} showing a higher sensitivity of dobutamine versus dipyridamole testing (100\% versus 56\%, \textit{p}<0.05). In fact, Fung et al used submaximal doses of dipyridamole (0.56 mg/kg, which yields a substantially lower sensitivity than the high dose of 0.84 mg/kg over 10 minutes, now currently used for echocardiographic testing\textsuperscript{16}). Furthermore, the two-dimensional echocardiography sampling was made at 5 minutes after the end of dipyridamole infusion, when the peak ischemic effect of the lower dose may have disappeared. Antianginal therapy (especially with \textit{\beta}-blockers) may exert asymmetrical effects on dobutamine and dipyridamole, and the spectrum of coronary anatomy found in patients (including multivessel disease and collateral circulation) is broader than a one-vessel stenosis evaluated in dogs.

Limiting side effects occur rarely with both drugs (Table 1), although arrhythmic events (ranging from atrial fibrillation to ventricular tachycardia) are more frequent with dobutamine than with dipyridamole.

Dipyridamole may provoke bronchospasm in patients with lung disease because adenosine is a bronchoconstrictor in asthmatics; dobutamine, which may induce bronchodilation through its \textit{\beta}-adrenergic activity, should be preferred in these patients.

Dipyridamole requires a shorter infusion time than dobutamine (Table 1). Its safety record\textsuperscript{11} and prognostic yield in different patients subsets (chronic coronary artery disease,\textsuperscript{26} early postinfarction,\textsuperscript{27} postangioplasty,\textsuperscript{28} and major vascular surgery\textsuperscript{29}) have been widely documented. Preliminary experience with dobutamine is also encouraging for perioperative risk assessment\textsuperscript{30} and prognostic stratification in early postinfarction patients.\textsuperscript{31} Dipyridamole has proved effective for evaluation of efficacy of antianginal therapy\textsuperscript{32}; both dipyridamole\textsuperscript{33} and dobutamine\textsuperscript{34} are capable of detecting jeopardized myocardium after thrombolysis. Both drugs have the potential to distinguish a viable from a necrotic area. Unlike infarcted myocardium, viable tissue retains contractile reserve, which can be unmasked by an inotropic challenge, either catecholaminic (such as dobutamine\textsuperscript{35}) or flow mediated (such as dipyridamole\textsuperscript{36}).

Most importantly, with both drugs echocardiographic recordings remain interpretable during stress in virtually all studies, although about 10\% of dobutamine studies can be of reduced quality, mostly because of excessive cardiac motion at peak stress, which renders some segments uninterpretable.\textsuperscript{13}

\textbf{Stratification of a Positive Response by Stress Echocardiography}

Conventional sensitivity/specificity analysis is usually used to describe the relation between stress test results and arteriographic disease. This method requires binary classification of both stress test (positive versus negative) and arteriographic (normal versus diseased) results. However, coronary disease is not an all-or-none condition: Binary classification requires arbitrary threshold criteria and creates artificial distinctions in coronary artery disease that, in actuality, has a continuous spectrum of severity.\textsuperscript{18} As a matter of fact, the diagnosis of myocardial ischemia by stress echocardiography is not only made after a binary (yes or no) response but rather according to a complex stratification along spatial and temporal coordinates. During stress echocardiography, the anatomic and functional impairment is proportional to the area subtended by a system with three coordinates representing the circumferential (horizontal) extension of ischemia (x axis), the transmural (vertical) extent of ischemia (y axis), and the duration of the "ischemia-free" stress time (z axis).

\textbf{Transmural Extent of Ischemia}

The progressive decline of regional subendocardial blood flow is paralleled by a decline of regional myocardial function. On the 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 causes regional wall thickening to decrease by about 40\%; and an 80\% reduction in subendocardial blood flow causes akinesis.\textsuperscript{4,5} The severity of regional wall dysfunction offers important information on the underlying severity of the regional perfusion defect.

\textbf{Circumferential Extent of Ischemia}

As with all diagnostic tests exploiting imaging techniques, stress echocardiography offers information on the geographic localization and spatial extent of ischemia. This has obvious clinical relevance because it allows identification of the area at risk in the individual patient and also possibly the ischemia-producing vessel in patients with multivessel disease who are candidates for coronary angioplasty. In terms of correlation with coronary anatomy, there are two mechanical patterns that pathognomonically identify multivessel disease: 1) multiple dysynergies in territories fed by different coronary arteries in patients with normal resting function; this pattern is relatively rare, if one interrupts the test whenever an obvious asynergy has been clearly documented; 2) remote (heterozonal) positivity in patients with a resting dysynergy; this pattern is relatively frequent in patients with a previous myocardial infarction, and it must be clearly separated from homozonal positivity, in which the asynergy develops in the asynergic although still viable region. Both the transmural and the circumferential extent of ischemia can be combined in the Wall Motion Score Index, which supplies an integrated semiquantitative and computer-independent estimation of the sensitivity and extent of the dysynergy.\textsuperscript{37}
Ischemia-Free Stress Time

The ischemia-free stress time (i.e., the time from onset of stress as exercise or drug infusion to development of a regional asynergy) is conceptually similar to exercise time, i.e., the time from onset of exercise to development of 0.1 mV of ST segment depression. This similarity is fairly obvious for exercise echocardiography, but it is substantiated by several lines of evidence also for dipyridamole echocardiography, the results of which have been compared with anatomic (extent of angiographically assessed coronary disease; lesion geometry in one-vessel disease), physiological (exercise tolerance in ischemic patients), and prognostic standards. Both with exercise and dipyridamole stresses, the ischemia-free stress time is inversely related to the extent of coronary disease, and in patients with one-vessel disease with the severity of coronary stenosis. Also, the prognostic impact of stress echocardiography positivity is clearly worse with shorter ischemia-free stress time. Preliminary data suggest that a stratification of severity of coronary artery disease is possible with dobutamine as well, basing on the dose required to induce the dyssynergy and/or the heart rate achieved during stress, slower frequencies and lower dobutamine doses being associated with more severe and/or extensive disease.

Time and space coordinates of stress-induced ischemia should always be considered in the evaluation of the test response, and the temporal and spatial allocation of the stress-induced dyssynergy are even more important than its presence. The echocardiographic response during physical and pharmacological stresses can be expressed not only in a black or white code but also, in the positive tests, by a grey scale capable to integrate the severity and extent of dyssynergy with the ischemia-free stress time.

Stress Echocardiography in the Clinical Arena

Stress echocardiography has not yet been accepted and used as an established diagnostic tool, despite the sound scientific foundations. The spread of the technique remains balanced between opposing forces—facilitatory and inhibitory.

Limitations of Stress Echocardiography

The qualitative and subjective nature of the diagnosis of transient wall motion dyssynergy bears scrutiny and tightly links the level of diagnostic performance to the observer’s expertise. A laboratory performing stress echocardiography only in limited volume, or for a short time, will undoubtedly obtain disappointing results.

Another reason for the skepticism of the cardiological community toward stress echocardiography is the lack of large-scale multicenter trials supplying the necessary information for an unrestricted acceptance of any new diagnostic procedure. To date, no study exists representing for stress echocardiography what the GISSI study was for the peripheral thrombolytic therapy in acute myocardial infarction; i.e., the turning point between a sporadic, subjective, and controversial use and an accepted, established, and universal procedure in daily practice.

The third factor slowing the diffusion of stress echocardiography pertains to organization. The explosive growth of resting echocardiography in recent years has overcrowded the echocardiography laboratories, whose resources are used intensively. Often, there is the willingness to do stress echocardiography, but the lack of space, personnel, and dedicated instrumentation prohibits implementation. On the other hand, the costly hardware and the sophisticated knowhow of nuclear cardiology—developed when there was no reliable alternative for imaging myocardial ischemia—do exist and are profitable.

Growth Factors of Stress Echocardiography

From the scientific viewpoint, the development of an array of pharmacological stimuli overcame the feasibility problems of exercise echocardiography, further reducing the difficulty of the technique and the need for additional apparatus. The level of training required to correctly perform stress echocardiography is now standardized, and it is not dissimilar from the one required to learn the Doppler technique. A qualitative, subjective reading is currently applied, for instance, in the evaluation of regional wall motion by contrast ventriculography: In this case, too, the reliability and reproducibility of the information are clinically acceptable after adequate training. Up to now, the quantitative assessment of regional function is limited by the need for computerized systems, the tedious and inherently inaccurate border definition, the lack of a universally accepted functional parameter, the scarcity of reference values in resting conditions and during stress, the temporal nonuniformity of contraction, and the complexity of cardiac movement. Conversely, the human eye naturally integrates space and time, and its discriminatory power is very difficult to match and virtually impossible to surpass. Although it is also true that different individuals have different eyes, at the present state of technology and knowledge, the visual evaluation of motion remains not only the simplest but the most accurate method of regional wall motion analysis.

The theoretical and practical training in echocardiography is now an essential component of the cardiology teaching. This leads to the spreading of echocardiographic culture and therefore increases the receptivity for stress echocardiography.

Large-scale multicenter studies are in progress for stress echocardiography, and they should ultimately provide the “phase IV” information for the final validation of the technique. For instance, the Echo-Persantine International Cooperative Study is collecting the experience of more than 30 echocardiographic laboratories, mostly in Italy but also in other countries of Europe and South America, that are currently applying the high-dose dipyridamole test for clinical purposes in daily diagnostic practice. The test protocol was standardized and the clinical features as well as the test results are stored in a central data bank in the Institute of Clinical Physiology in Pisa. It is expected that this large-scale trial, which enrolled over 7,000 tests in the first year, will provide, in a reasonable amount of time, the information required to assign a priority for dipyridamole echocardiography testing in the diagnostic cardiological armamentarium. Similar data should be systematically collected also for other tests before widespread clinical use is considered.
From the technological viewpoint, new techniques of generation and analysis of the ultrasonic image, coupled with the diffusion of transesophageal echocardiography, will certainly shrink the percentage of cases in which an ultrasonic examination is either unfeasible or of poor quality. Finally, on the strictly economic side, growing attention is being paid to cost-benefit analysis in medicine, and increasing awareness exists of the need for a rationalization of diagnostic protocols.

**Nuclear or “Clean” Energy for Imaging Myocardial Ischemia?**

From the theoretical viewpoint, perfusion myocardial scintigraphy and stress echocardiography recognize different physiological end points. The positivity of perfusion scintigraphy is based on the detection of a relative difference in perfusion between myocardial regions supplied by different arteries. Ischemia is not, therefore, a diagnostic end point. For stress echocardiography, on the contrary, ischemia is the diagnostic end point, detected through the highly specific marker of a regional dyssynergy. Ideally, in this case the arbitrary cut point for the detection of coronary artery disease should be the level of stenosis that not only blunts reactive hyperemia, but has also the potential for inducing myocardial ischemia in the presence of an adequate stress. From the pragmatic viewpoint, perfusion myocardial scintigraphy and stress echocardiography show a grossly similar diagnostic accuracy either with exercise or dipyridamole stress. The slightly higher sensitivity for nuclear perfusion imaging is, at least in a selected population referred to perfusion imaging for diagnostic purposes, balanced by a much better specificity of stress echocardiography.

Both imaging techniques can identify the site and extent of coronary disease, but the temporal allocation of the onset of ischemia during stress is impossible with perfusion scintigraphy, which therefore misses a parameter of crucial importance for stratifying the severity of ischemia.

Antianginal pharmacological therapy markedly reduces the sensitivity of stress echocardiography, which requires ischemia for test positivity, whereas the effects of drugs on myocardial perfusion scintigraphy seem to depend on the type of drug and the kind of vasodilator stress used. Pretreatment with isosorbide dinitrate improves T wave uptake on exercise scintigraphy and thus diminishes sensitivity. Reports on the influence of \( \beta \)-blockers on sensitivity and specificity of exercise T scintigraphy are conflicting, although they probably diminish sensitivity to some extent.

Regarding dipyridamole stress, concordant experimental and clinical data show that \( \beta \)-blockers do not influence the coronary hyperemic response or the diagnostic accuracy of dipyridamole scintigraphy. Therefore, the sensitivity of dipyridamole echocardiography—not of dipyridamole scintigraphy—can be affected by medical therapy. This implies that the sensitivity gap in favor of perfusion scintigraphy can further increase in populations studied under antianginal therapy, whereas on the other hand, stress echocardiography is more suitable for assessing the effects of antianginal therapy.

The possibility to immediately stop the stress when an obvious transient dyssynergy is detected makes echocardiography a potentially safer diagnostic tool in comparison with perfusion scintigraphy, which “sees” ischemia in real time only by unreliable markers such as chest pain and ECG changes, during which a possible early injection of the tracer must be followed by several minutes of exercise before completion of the imaging.

In comparison with nuclear perfusion imaging, the two major limitations of stress echocardiography are the dependence on the acoustic window as well as on the operator’s experience. The quality of perfusion imaging is not affected by exercise. Thallium perfusion imaging provides information on the viability of an asynergic segment expressed by the tracer uptake at delayed redistribution or after reinjection. The possibility of obtaining similar information by pharmacological stresses after the inotropic challenge of either a catecholaminic stimulus or increased flow also has been documented.

In the face of equal information from stress echocardiography versus nuclear scans, the cost/benefit balance often shifts toward stress echocardiography in view of the markedly lower cost, the use of nonionizing energy, the ubiquitous availability of instrumentation, and the shorter time required for preparation, performance, and interpretation of the test. The choice of an imaging technique in a given patient should follow clinical reasoning tailored to the individual needs: the type of stress chosen (exercise being more suitable for nuclear imaging and pharmacological stresses for echocardiographic imaging); the safety priority (in some patients, such as early post–acute myocardial infarction or unstable angina, echocardiography is preferred due to the possibility of stopping the stress whenever ischemia develops); the quality of the acoustic window in that patient (95% of patients have an acceptable acoustic window but the image quality, and therefore the reliability of the stress echocardiography information, is obviously highly variable); the need to assess the efficacy of medical antianginal therapy (which can be done by dipyridamole echocardiography, not by dipyridamole perfusion imaging); and the availability and the reliability—tested personally, not derived from the literature—of the referral echocardiography and nuclear medicine laboratories.

With Doppler, the expansion of the echocardiography diagnostic domain eroded the territory of invasive diagnosis; with the introduction of stress echocardiography, ultrasound diagnosis will invade the nuclear medicine domain. In fact, it is unacceptable, as a rule, to apply several imaging techniques in the same patient because they will provide data that are redundant rather than complementary. The rejection of stress echocardiography makes a nonelectrocardiographic diagnosis of myocardial ischemia totally dependent on nuclear cardiology. Today, the question is “when and how,” not “whether,” to perform stress echocardiography, which allows the broad territory of myocardial ischemia to be included in the diagnostic domain of echocardiography. Only by following the advice given by the Red Queen to Alice will echocardiography play a key role despite the growth of other imaging techniques.
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