Review

Recent Advances in Dobutamine Stress Echocardiography

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Summary: Dobutamine stress echocardiography (DSE) is a reliable cardiac risk stratifier that has widespread applicability because of its clinical accuracy and cost effectiveness. Dobutamine has positive inotropic and chronotropic effects and is commonly used in patients who cannot exercise or achieve an adequate heart rate response with exercise. Recently available long-term results from several independent clinical trials, combined with enhancements in image quality, have improved the ability to detect significant coronary artery disease and determine myocardial viability. Dobutamine stress echocardiography has an excellent safety profile with clinical results superior to regular exercise electrocardiography and comparable with exercise echocardiography and radionuclide perfusion stress imaging. Low-dose dobutamine response can accurately predict dysfunctional yet viable myocardial regions that may improve with revascularization. Clinical studies are now available refining the common use of DSE preoperatively in female patients with valvular disease, as well as in the emergency department. Dobutamine stress echocardiography does have some limitations in discriminating particular regions of ischemia when multiple ventricular segments are involved and when the imaging is suboptimal. It can be applied using minimal additional resources in an otherwise functioning echocardiography laboratory and, with appropriate training, can result in clinical results comparable with those of large-scale multicenter trials. Ongoing improvements in technology and the de-

velopment of new reagents such as myocardial contrast agents hold promise for further advancement in the near future.

Key words: echocardiography, stress testing, dobutamine, diagnostic testing, coronary artery disease

Introduction

Recent years have seen the rapid advancement and refinement of cardiovascular stress testing to its current status as an essential and readily available component in the practice of adult medicine in the United States. The particular modality of stress testing (e.g., treadmill, bicycle, pacing, dobutamine, dipyridamole, adenosine, or arbutamine) or method of measuring ischemia [e.g., electrocardiography (ECG), echocardiography, nuclear perfusion or positron emission tomography] depends on patient requirements, diagnostic efficacy, local availability, and expertise. Rather than being viewed as a congeries of increasingly complex technologies, the variety of contemporary cardiac stress testing is more a tribute to its diagnostic and prognostic utility; that is, determining inadequate coronary blood flow, however produced or measured, yields interpretable and reproducible clinical information.

This review focuses on dobutamine stress echocardiography (DSE) because of recent refinements in its application as well as the technique's increasingly widespread availability in hospitals and outpatient settings. Since DSE has been the subject of several excellent prior reviews,^{1–4} the focus here is the recent literature of the past 3 years. As an example of this information proliferation, from January 1997 through June 1999, 404 articles are accessed with the keywords "dobutamine stress echocardiography" with a PubMed query to the National Center for Biotechnology Information (<www.ncbi.nlm.gov>).

As early as 1935, Drs. Tennant and Wiggers⁵ described the effects of stenotic coronary lesions on left ventricular wall motion as "a progressive enfeeblement of contraction to the extent that within a minute the area stretches during isometric con-

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traction, remains relaxed during systolic ejection and shortens quickly during isometric relaxation." In patients in whom the ECG is considered diagnostically inadequate, there are two types of imaging modalities commonly used with pharmacologic stress testing: echocardiography and nuclear perfusion. Dobutamine stress echocardiography diagnoses ischemic coronary artery disease based on development of wall motion abnormalities induced by myocardial ischemia. General advantages of DSE include its widespread availability, portability, lack of radiation exposure, lower cost (than nuclear procedures), and the immediate availability of results. In addition, incidental unsuspected findings may be detected on echocardiography that would not be available with nuclear perfusion imaging. Pellikka *et al.*³ reported on 1,000 consecutive patients undergoing DSE at the Mayo Clinic, 375 of whom had additional findings on echocardiography unrelated to ischemia such as left ventricular hypertrophy (25%), aortic stenosis of mild to moderate severity (5%), dilated cardiomyopathy (3%), mitral valve prolapse (2%), left ventricular aneurysm (2%), mitral stenosis (1%), left ventricular thrombus (1%), and hypertrophic cardiomyopathy (<1%).

Dobutamine Pharmacology

Significant numbers of patients are unable to undergo adequate exercise stress testing because of peripheral vascular disease, orthopedic disorders, pulmonary incapacity, cerebrovascular disease, and so forth. Accordingly, pharmacologic agents such as dobutamine, dipyridamole, arbutamine, and adenosine have been developed for routine use as alternative means of inducing cardiovascular energetic stress. Dobutamine is the most commonly used.

It is a synthetic catecholamine that causes increases in heart rate, wall stress, contractility, and cardiac work, predominantly through beta-adrenergic stimulation in a dose-dependent manner. There is some α_{1-2} -adrenergic stimulation, and afterload is reduced by peripheral artery dilation. These effects, along with dobutamine's half-life of about 2 min, make it useful for cardiac stress testing. Dobutamine has a similar effect on heart rate as exercise, but there is typically less of an increase in blood pressure. Recently Bartunek *et al.*⁶ examined dobutamine physiology in human subjects with discrete coronary stenoses. They found dobutamine did not affect the dimensions of the stenosis but rather maximally dilated coronary flow reserve whether there was ventricular dysfunction or not. Dobutamine increased contractility more than physical exercise and may require a greater amount of energy utilization at comparable workloads. Although dobutamine is a more potent inotropic and chronotropic agent than the primary coronary vasodilators such as dipyridamole and adenosine, these agents are very useful when the hemodynamic response to dobutamine may not be safe, such as with poorly controlled hypertension, cerebral vascular disease, or large abdominal aortic aneurysms. These vasodilators are more commonly used with nuclear perfusion imaging since echocardiographically visible wall motion abnormalities may not be produced.

Echocardiographically, the normal ventricular response to dobutamine is hyperdynamic wall motion as well as increased wall thickening during systole. Abnormal wall motion can be seen either as a lack of hyperdynamic wall motion, relative hypokinesis, or the development of akinesis or dyskinesis in the general distribution of one or more coronary arteries. Of importance is the fact that if only a submaximal heart rate is achieved, some investigators consider the test nondiagnostic because of significant cardiac event rates in patients who do not have an adequate chronotropic response.⁷ Dobutamine stress echocardiography is most commonly indicated in the evaluation of patients with either known or suspected coronary artery disease and is particularly useful when the resting ECG makes stress interpretation difficult. The most common indications for DSE are listed in Table I. Abbreviations are listed in Table II.

Contraindications for DSE include those for cardiovascular stress testing in general and are not specifically reviewed here. An important consideration for DSE is that interpretable echocardiographic images must be readily obtainable. Image quality is more often a problem in patients with significant lung disease, morbid obesity, or chest wall deformities. Inadequate images occur in about 5% of patients and preclude DSE performance. Tachyarrhythmia rates, either ventricular (6%–non-sustained) or supraventricular (7%), can occur during DSE and are more common in patients with significant left ventricular dysfunction rather than in those with coronary artery disease.⁸

TABLE I Common indications for dobutamine stress echocardiography

Patients who cannot exercise adequately
Detection of myocardial ischemia
Myocardial viability determination
Prognosis postmyocardial infarction
Emergency department chest pain evaluation
Aortic stenosis functional severity (especially with reduced systolic function)
Other valvular assessments
Cost effectiveness versus nuclear imaging or cardiac catheterization
Preoperative evaluation (risk stratification)
Typical and atypical cardiac symptom evaluation
Electrocardiographic baseline abnormalities

TABLE II Abbreviations used

DSE = dobutamine stress echocardiography
LHC = left heart catheterization
ECG = electrocardiogram
ESE = exercise stress echo
DNS = dobutamine nuclear stress (thallium or sestamibi)
PTCA = percutaneous transluminal coronary angioplasty
CABG = coronary artery bypass graft
WMA = wall motion abnormality
HR = heart rate
LV = left ventricular

Methodology for Performing Dobutamine Stress Echocardiography

Dobutamine stress echocardiography protocols may be performed with echocardiography equipment from most of the major manufacturers. This routinely includes the ability for rapid acquisition (commonly as cardiac cycle loops), easy storage, and retrieval of images (increasingly digitally). Other requirements are 12-lead ECG monitoring, an automated blood pressure cuff, an infusion pump for dobutamine, and optionally, pulse oximetry. Personnel includes a dedicated echocardiographic sonographer to obtain sequential images according to a set protocol and a technician or nurse to monitor the dobutamine infusion, blood pressure response, pulse oximetry, and ECG. Studies should be supervised directly by a cardiologist. A typical protocol requires four standard echocardiography views: parasternal long-axis, parasternal short-axis, apical 4-chamber, and apical 2-chamber. The dobutamine infusion is started at a low dose (5–10 $\mu\text{g/kg/min}$). At approximately 2.5-min intervals, the infusion is increased by 10 $\mu\text{g/kg/min}$ increments until a maximum dose of 40 $\mu\text{g/kg/min}$ is reached. Intravenous (IV) administration of atropine 0.5–2 mg can supplement the stress test if 85% of the maximal predicted heart rate $[220 - \text{age}] \times (0.85)$ is not achieved. The DSE test is terminated when the target heart rate is achieved, if angina or its clinical equivalent occurs, after significant hemodynamic compromise or arrhythmia when significant ECG changes occur (which, when present, can improve the positive predictive power),⁹ or if diagnostic wall motion abnormalities are observed. If the dobutamine effect needs to be antagonized clinically, an IV beta blocker can be administered (e.g., metoprolol 5 mg IV). Standard DSE images are obtained at rest, with low dose (5 $\mu\text{g/kg/min}$) and peak

dose dobutamine, and after several min of recovery when heart rate has largely normalized. Studies are recorded on high resolution videotape, or representative cardiac cycles are acquired as digital loops, usually in a side-by-side or quad-screen format to allow direct comparisons of similar views during different stages of the stress test. Digital storage can also allow remote transmission for review of studies. Patients are closely monitored until they are asymptomatic and stable. The development of hyperdynamic ventricular wall motion is considered normal. Abnormal responses include the development of new regional wall motion abnormalities (hypokinesis, akinesis, or dyskinesis) or a worsening of a baseline wall motion abnormality. The improvement of a baseline abnormal ventricular segment at lower dobutamine doses (i.e., evidence of contractile reserve) may indicate viability (hibernating or stunned myocardium), that then worsens again at higher doses (the "biphasic response"). Ventricular regions that are akinetic at rest and do not change after peak heart rate is achieved are considered to be infarcted (scarred) myocardium.¹⁰ Although DSE interpretation is subjective, blinded analyses have generally shown good interobserver agreement, with bias being introduced only if ancillary test data or other clinical information are available to the interpreter¹¹ (which, it may be argued, might improve interpretation). This interpretative scheme is presented in Figure 1. Like most useful technologies, there is a learning curve to both performing and interpreting DSE. Recently, the American Society of Echocardiography recommended level 2 training which includes at least 100 over-read stress echocardiograms initially and an independently interpreted volume of at least 15 studies per month. Other general advice includes an initial performance of DSEs on patients already undergoing dobutamine nuclear stress (DNS) imaging to compare the results for quality assurance.

FIG. 1 Schematic for interpreting dobutamine stress echocardiograms. HR = heart rate, LV = left ventricular, WMA = wall motion abnormality, DSE = dobutamine stress echocardiography.

Detection of Myocardial Ischemia

In general, an abnormal DSE must have at least one ischemic ventricular segment unless the basal inferior or septal walls are involved, in which case the presence of an adjacent abnormal segment is required to increase sensitivity.¹² Several classic studies^{13–17} have established DSE as an excellent method for evaluating myocardial ischemia, with published diagnostic sensitivities ranging from 74–89% and specificities from 82–88% (Table III). In the vast majority of these and other investigations, the accuracy of DSE to detect myocardial ischemia is superior to routine stress ECG without imaging. The sensitivity of DSE has been found to be less in single-vessel than in multivessel disease (particularly regarding lateral wall abnormalities).¹⁶ In patients with abnormal regional wall motion at rest, which could represent coronary artery disease but not necessarily ischemia, DSE interpretation is more accurate when a remote (i.e., new) wall motion abnormality is seen. This is as opposed to the worsening of the preexisting abnormality, which is more difficult and subjective to interpret. Other findings that increase the probability of significant ischemia are an impaired blood pressure response or left ventricular cavity dilation with dobutamine.¹⁸

Prognostic Value of Dobutamine Stress Echocardiography

The prognostic accuracy of a positive DSE increases when more than one ventricular segments are involved, with resting wall motion abnormalities, an ischemic ECG response, or an abnormal ejection fraction after dobutamine.¹⁹ On the other hand, ventricular systolic cavity obliteration is an independent predictor of freedom from cardiac events.²⁰ In terms of long-term patient follow-up, an abnormal DSE independently predicts an increased likelihood of coronary events up to 5 years later,^{19–21} and a negative result can predict which patients are at lowest risk for cardiac events²² also up to 5 years after the test.²³ In one trial, a negative DSE discriminated patients with single-vessel coronary disease who did not statistically benefit

from invasive revascularization.²⁴ In a summation analysis of 28 separate studies, the mean sensitivities of DSE for single-, double-, and triple-vessel obstructive coronary disease were 74, 86, and 92%, respectively.¹ It has also been reported that an abnormal DSE in heart transplant recipients can predict allograft coronary artery disease.²⁵

Comparison with Nuclear Perfusion Imaging

Direct comparisons between DSE and dobutamine nuclear stress (DNS) testing have usually shown a comparable ability to detect coronary artery disease with some important differences. In an early trial of 217 patients without any prior myocardial infarction, there was comparable sensitivity between the techniques with a decreased specificity for nuclear imaging in the patients without severe coronary artery disease.¹⁷ Forster *et al.*²⁶ evaluated DSE and DNS in 105 patients being assessed for myocardial ischemia and found the concordance between the imaging modalities to be 84%. The sensitivity of DSE was better for multivessel coronary artery disease. Another analysis of 292 patients who underwent concomitant exercise stress echocardiography and nuclear perfusion scintigraphy found a high degree of concordance (82%).²⁸ In a subset of 112 patients who also underwent coronary angiography, the sensitivity for detecting significant coronary artery stenoses (>70% luminal stenosis) was 85% for single-vessel disease, 86% for double-vessel disease, and up to 94% for triple-vessel disease. Other studies have confirmed similar results for DSE and are summarized in Table III. However, there are reports of DSE with lower sensitivity than DNS in patients post myocardial infarction.²⁷ Such reports must be taken into careful consideration since it is difficult to quantitate potential publication biases toward favorable findings in the medical literature. Also, the clinician must take into account what techniques are performed best in their local situation.

There are specific clinical situations that deserve emphasis. In patients with left ventricular hypertrophy on ECG, the specificity of DSE is 94% compared with 59% for nuclear stress testing.¹⁷ Dobutamine stress echocardiography can determine the ischemic threshold (in terms of blood pressure and

TABLE III Dobutamine stress echocardiography performance in the diagnosis of myocardial ischemia

First author / Ref. No.	% Sensitivity / % specificity	Comparative modality	Comments
Anthopoulos, ¹³ 1996	87/84	DSE vs. LHC	All elderly patients aged > 70 years
Elhendy, ¹⁴ 1996	—	DSE vs. DNS vs. LHC	Biphasic response predicted ischemia as well as viability with DSE
Marwick, ¹⁵ 1993	85/82	DSE vs. adenosine NS vs. DNS	DSE, DNS, and adenosine NS with comparable sensitivity
Sawada, ¹⁶ 1991	89/85	DSE vs. LHC	—
Marwick, ¹⁷ 1993	84/86	DSE vs. DNS vs. LHC	False negatives with submaximal exercise and single-vessel disease

Abbreviations as in Table II.

heart rate) at which wall motion abnormalities occur, which is associated with the severity of coronary artery disease. For example, Segar *et al.*²⁹ found wall motion abnormalities induced at a heart rate of ≤ 125 beats/min have a greater chance of originating from multivessel disease than wall motion abnormalities induced at heart rates > 125 beats/min.

Detection of Myocardial Viability

Dobutamine stress echocardiography is increasingly used to determine hibernating and stunned (i.e., viable) myocardium from scar. With low-dose dobutamine (3–5 mg/kg/min), the increased coronary blood flow and inotropic effect to myocardial areas with chronically reduced blood flow may enhance myocardial function via improved wall motion and thickening. At higher dobutamine doses, left ventricular function may show worsening wall motion abnormalities, the so-called biphasic response. This is particularly useful in ischemic cardiomyopathy with left ventricular dysfunction when a high-risk intervention is being contemplated. The presence of enhanced left ventricular systolic function and improved wall motion at low-dose dobutamine can identify patients with viable myocardium who would potentially benefit from revascularization. Elhendy *et al.*¹⁴ reported that patients with a DSE biphasic response in akinetic ventricular segments had the highest incidence of reversible nuclear perfusion defects; that is, initially akinetic areas that showed some degree of increased left ventricular function with low-dose dobutamine predicted a return to normal function after revascularization [e.g., with coronary artery bypass graft (CABG)] that was comparable to thallium perfusion uptake viability determination.³⁰ Table IV summarizes studies examining DSE and myocardial viability.^{31–37}

In patients with coronary disease and left ventricular dysfunction, Pasquet *et al.*³⁸ recently found that after 33 ± 10 months follow-up it was the demonstration of viable myocardium on DSE prior to revascularization that predicted improved survival with single- or double-vessel disease.

Similarly, low-dose DSE (using transesophageal imaging) showed comparable diagnostic accuracy to F-18 fluorodeoxyglucose positron emission tomography in predicting functional recovery after revascularization.³⁹ In a series of 319 patients with coronary artery disease and left ventricular ejection fractions of $< 35\%$, those with demonstrated myocardial viability by DSE had improved survival over those without myocardial viability.⁴⁰ Several contemporary studies support DSE in predicting left ventricular dysfunction and inducible ischemia in patients who have improved survival after revascularization.⁴¹

Low-dose DSE response in patients with ischemic congestive heart failure has been reported to predict those who improve their functional capacity after moderate exercise training.⁴² A recent series of patients with congestive heart failure from coronary ischemia with significant myocardial viability on low-dose DSE showed a 93% survival advantage after 40 months over similarly revascularized patients without demonstrable viability.³⁷

After Acute Myocardial Infarction

An abnormal DSE post acute myocardial infarction can independently predict future cardiac events whereas a negative DSE decreases such likelihood. Several studies examining DSE performed within 2 weeks of acute myocardial infarction (in patients where this was felt clinically safe) found correlation between cardiac mortality and future infarcts that were proportional to the presence and degree of inducible ischemia⁴³ as well as the size of any nonviable infarct regions.^{44, 45} A less favorable prognosis associated with reversible or worsening ventricular wall motion abnormalities is found whether the infarction was treated with thrombolysis or with primary coronary angioplasty.^{34, 46} Investigators note that caution must be used in interpreting positive DSE findings in a region where there is baseline hypokinesis soon after an acute infarction, since accuracy may be limited by a higher frequency of false positive results.⁴⁷

TABLE IV Predicting contractile recovery after revascularization

First author / Ref. No.	% Sensitivity / % specificity	Revascularization procedure	Comparative modality	Comments
Picano, ³¹ 1996	72/95	PTCA or CABG	Low-dose DSE vs. dipyridamole vs. both	Highest sensitivity with both
Cornel, ³² 1998	89/—	CABG	DSE at 14 months	75% late recovery with biphasic response pre-CABG
Vanoverschelde, ³³ 1996	88/77	PTCA or CABG	Nuclear	DSE predicted viability in 84%
Leclercq, ³⁴ 1997	82/83	PTCA	LHC	Low-dose DSE more sensitive, esp. with hypokinesis
Smart, ³⁵ 1993	86/90	Thrombolytics	LHC	Identifies reversible dysfunction
Cigarroa, ³⁶ 1993	—	PTCA or CABG		Predicted contractile reserve
Senior, ³⁷ 1999	—	PTCA or CABG	Mortality over 40 $\pm$ 17 months	93% mortality reduction when ischemic CHF revascularized

Abbreviations as in Table II.

TABLE V Preoperative assessment using dobutamine stress echos

First author/Ref. No.	Surgery	Conclusions
Lane, ⁵¹ 1991	Noncardiac surgery	⊕ DSE = 21% risk of event
Poldermans, ⁴⁹ 1993	Vascular surgery	⊕ Predictive value = 42%
		⊖ Predictive value = 100%
Poldermans, ⁵⁰ 1995	Vascular surgery	⊕ Predictive value = 38%
		⊖ Predictive value = 100%
Davila-Roman, ⁴⁸ 1993	Vascular surgery	⊕ Predictive value = 40%

Preoperative Evaluation

Dobutamine stress echocardiography is commonly used to define preoperative cardiovascular risk in patients undergoing noncardiac surgery. Davila-Roman *et al.*⁴⁸ studied 98 patients undergoing either aortic aneurysm repair or peripheral vascular surgery and found that an abnormal DSE strongly predicted cardiac events perioperatively (positive predictive value of 40%). Equally important, among the patients with normal DSEs, none had perioperative cardiac complications. Poldermans *et al.*⁴⁹ reported on 136 patients who underwent DSE preoperatively for major vascular surgery and found that all patients who had cardiac complications had an abnormal DSE (100% negative predictive value). The same investigators in a later study⁵⁰ described 302 consecutive patients undergoing major vascular surgery who had a preoperative DSE. There were 72 positive studies, and of the 27 patients who had a perioperative cardiac event (death, nonfatal infarcting, or unstable angina) all were among these positive DSEs. These reports are summarized in Table V.⁴⁸⁻⁵¹

Dobutamine Stress Echocardiography in Women

Dobutamine stress echocardiography has been shown to be a safe and useful noninvasive method for detecting coronary artery disease in both men and women. Secknus and Marwick⁵² looked at dobutamine physiology in 2,748 consecutive patients (44% women) undergoing DSE. The hemodynamic effects on men and women were comparable except for a more rapid heart rate response in women. The accuracy of DSE between male and female patients has been examined by several groups and in general is quite comparable and not plagued with the higher false positive rates seen in women with regular exercise stress testing. Elhendy *et al.*⁵³ reported on 96 consec-

utive women with suspected myocardial ischemia and limited exercise tolerance, all of whom underwent coronary angiography within 3 months of their DSE. Overall sensitivity, specificity, and accuracy were similar between the female and male cohorts. Likewise, Dionisopoulos *et al.*⁵⁴ showed no gender-based differences in sensitivity, specificity, and accuracy of DSE in detecting coronary artery disease in a series of 288 consecutive patients (101 women). The ongoing Women's Ischemia Syndrome Evaluation (WISE) study⁵⁵ recently added a cautionary note, finding DSE more sensitive for multivessel coronary disease than single-vessel disease. Table VI summarizes these results.

Dobutamine stress echocardiography is also valuable in cardiovascular risk stratifying female patients. Cortigiani *et al.*⁵⁶ performed DSE on 151 consecutive women being evaluated for chest pain without known coronary disease and who were then followed for 32 ± 19 months. An abnormal DSE had a strong independent negative prognostic value for spontaneous cardiac events. Equally important, a normal DSE identified a low-risk population for having cardiac events (< 1% over 3-year follow-up).

Emergency Department Evaluation

Telephonic transmission of DSEs performed in the emergency department have been reported to have excellent sensitivity and specificity (89.5 and 88.9%) with a negative predictive value of 98.5% for near-term coronary events.⁵⁷ Increasingly, acute chest pain (or other anginal equivalent) evaluations are attempting to identify patients efficiently who are felt to be of low risk and safe to discharge for an outpatient work-up. Dobutamine stress echocardiography can provide an efficient triage for patients who cannot exercise. Also, echocardiography can identify potential nonischemic chest pain etiologies

TABLE VI Gender differences in stress echocardiography

First author / Ref. No.	Sensitivity /specificity /accuracy in women (%)	Sensitivity /specificity / accuracy in men (%)
Elhendy, ⁵³ 1997	76 / 94 / 82	73 / 77 / 74
Dionisopoulos, ⁵⁴ 1997	90 / 79 / 86	85 / 96 / 88
Secknus, ⁵² 1997	78 / 55 / 71	88 / 46 / 77
Lewis, ⁵⁵ 1999	50 (single vessel) vs. 81 (multivessel) / 80 / —	—

such as cardiac tamponade, pulmonary hypertension, dissection, and so forth.

Dobutamine Stress Echocardiography in Valvular Heart Disease

Stress echocardiography with Doppler interrogation is a noninvasive way of assessing hemodynamic changes with valvular heart disease. Perhaps the most common use is grading aortic stenosis severity in patients with low transvalvular gradients and depressed ejection fractions. Assessment of left ventricular contractile reserve and measuring transvalvular gradients and calculated valve areas during DSE allows discrimination between patients with severe aortic stenosis and secondary systolic dysfunction who could benefit from valve surgery from patients with less severe aortic stenosis and left ventricular systolic dysfunction unrelated to aortic valve disease who would not benefit from such surgery. DeFilippi *et al.*⁵⁸ looked at 18 patients with suspected severe aortic stenosis, significant left ventricular systolic dysfunction, and low transvalvular gradients. Using DSE cautiously, they were able to differentiate in patients both with and without left ventricular systolic dysfunction those who would potentially benefit from valve replacement; that is, patients who at high transvalvular flow rates and cardiac outputs had fixed valve areas consistent with severe aortic stenosis.

American College of Cardiology/American Heart Association (ACC/AHA) Guidelines

The ACC/AHA guidelines for the clinical application of stress echocardiography⁵⁹ were published in 1997. While individual patients obviously require judgment for particular clinical situations, these guidelines are quite useful and are summarized in Table VII.

Limitations of Dobutamine Stress Echocardiography

Dobutamine stress echocardiography interpretations are subjective by their nature and can be quite limited in technically difficult studies. In an interinstitutional study measuring variance in DSE interpretation, the best predictors of observer agreement were the image quality, the degree of new wall motion abnormalities, and the heart rate–blood pressure product obtained.⁶⁰ False positive DSE results have been described with mitral valve prolapse, left ventricular hypertrophy, and asymmetric septal hypertrophy. Patients with a baseline left bundle-branch block (or after cardiac surgery) may have abnormal septal contraction without significant epicardial coronary disease, and septal wall motion abnormalities must be interpreted accordingly. The basal portion of the posterior wall (particularly on short-axis views) may have atypical myocardial thickening relative to other segments and should be inter-

TABLE VII ACC/AHA guidelines for clinical application of dobutamine stress echocardiography^{a 59}

Class I

- In-hospital or early postdischarge assessment for the presence/extent of inducible ischemia when baseline abnormalities are expected to compromise ECG interpretation
- Diagnosis of myocardial ischemia in symptomatic patients
- Assessment of myocardial viability for planning revascularization
- Assessment of functional significance of coronary lesions in planning revascularization
- Assessment for restenosis post revascularization in patients with atypical recurrent symptoms

Class IIa

- In-hospital or early postdischarge assessment of the presence/extent of inducible ischemia in the absence of baseline abnormalities expected to compromise ECG interpretation
- Assessment for restenosis post revascularization in patients with typical recurrent symptoms

Class IIb

- Diagnosis of myocardial ischemia in selected patients with intermediate or high pretest likelihood of coronary artery disease
- Assessment of global left ventricular function with exercise

Class III

- Screening asymptomatic patients with low likelihood of disease
- Periodic assessment of stable patients

^a Class I: the given procedure is useful and effective.

Class II: conflicting evidence about the usefulness/efficacy of the procedure.

Class IIa: weight of evidence in favor of usefulness/efficacy.

Class IIb: usefulness/efficacy less established.

Class III: procedure is not useful/effective.

Abbreviations: ACC/AHA = American College of Cardiology / American Heart Association, ECG = electrocardiogram.

preted conservatively to avoid false positive results (i.e., such a finding is more likely truly abnormal if another contiguous ventricular region is also abnormal). "Tethering" effect of infarcted myocardium can limit the systolic motion of adjacent normal myocardium (particularly when only part of a coronary artery distribution is affected).⁶¹ Of course, off-axis or technically suboptimal imaging will adversely affect interpretation. In general, DSE interpretation is more difficult when there are resting wall motion abnormalities. Whether a ventricular region with abnormal function at rest has deteriorated further with pharmacologic stress is subjective and can be difficult enough to warrant other methods (e.g., nuclear imaging or angiography) to be able to exclude concomitant coronary artery disease confidently. For example, a nonischemic cardiomyopathy may echocardiographically image as global dysfunction with some heterologous wall motion responses that may be difficult to discern from regional ischemia. A similar problem can occur with multiple preexisting infarct regions that may make any changes in function with DSE very difficult to determine. If it is clinically necessary to measure the degree of ischemia (not necessarily viability), nuclear perfusion imaging may be preferable.

Contrast Agents and Dobutamine Stress Echocardiography

Stress echocardiography is limited in significant numbers of patients by inadequate endocardial border visualization. Transpulmonary contrast agents improve endocardial definition and many laboratories commonly use them during stress echocardiography. One study of 30 patients with multiple ventricular wall segments that were suboptimally imaged reported that 77% become adequately interpretable after intravenous Albunex⁶² (5% human sonicated albumin). Unfortunately, rapid microbubble air loss results in rapidly decreasing echogenicity. This has led to the development of numerous second-generation agents with improved microbubble capsules that are beginning to have widespread application, including stress testing.^{63,64} Myocardial contrast echocardiography is a different application of these agents wherein myocardial perfusion is detected after intravenous or intracoronary injection. This allows determination of viability by a different mechanism. There have been some direct comparisons with DSE. One study using Renografin-76 (inert perfluorocarbon microbubbles) found similar sensitivity between the methods, but that DSE had better specificity.⁶⁵ The main difference was in akinetic segments where detecting contractile reserve by DSE was a better predictor of functional recovery after revascularization than was perfusion by myocardial contrast echo. Likewise, the use of intracoronary Albunex compared with DSE and DNS in patients with ischemia prior to coronary revascularization showed similar sensitivities, but a biphasic response with DSE did have superior specificity.⁶⁶ An excellent predictive value has been reported with the combination of DSE and myocardial contrast echo.⁶⁷

Cost Effectiveness

Supervision of DSE by a specially trained registered nurse is a potential venue for cost reduction while maintaining safety. A group at the Mayo Clinic has reported on 1,035 consecutive outpatient DSEs, half monitored by a cardiologist (or fellow) and half by a registered nurse sonographer. There was one significant tachyarrhythmia in each group.⁶⁸ Financially, a recent meta-analysis found stress echocardiography cost effective in terms of quality-adjusted life-years gained relative to nuclear perfusion [planar thallium or single-photon emission computed tomography (SPECT) or positron emission tomography (PET)].⁶⁹

Future Directions

The technical accuracy of DSE is continually improving with advances in echocardiographic imaging technology such as the use of second harmonic detection, acoustic quantification, color kinesis, tissue velocity index, and improved software to manipulate data. Second harmonic imaging, where ultrasound is transmitted at one frequency and received at twice the transmitted frequency, improves endocardial border visualization as well as detection of microbubbles in contrast agents in the majority of cases.⁷⁰ A recent prospective, randomized trial assessing harmonic versus fundamental (routine) stress echocardiography imaging showed clinically improved endocardial visualization in the harmonic cohort.⁷¹ Other new technology utilizing color tissue Doppler imaging M-mode is based on segmental wall velocity differences between rest and after low-dose dobutamine. This has been reported to have a sensitivity of 89% for predicting reversible myocardial dysfunction an average of 3 days after infarction versus 75% for conventional DSE.⁷² A similar approach involves using a "bull's-eye" type display of tissue Doppler velocity distribution during rest and stress to attempt to quantitate and simplify DSE interpretation.⁷³ In the heart transplantation field, a recent report found serial DSEs to have a sensitivity of 72% in detecting cardiac allograft vasculopathy (compared with coronary angiography).⁷⁴ Low-dose DSE has also been reported to help identify reversible brain death-induced myocardial dysfunction in potential heart transplant donors.⁷⁵ The ultimate clinical roles for these promising applications awaits the results of ongoing investigations.

Conclusions

Dobutamine stress echocardiography is a cost-effective, reliable, and safe procedure comparable with nuclear perfusion stress testing for the evaluation of myocardial ischemia in the large majority of patients. Long-term studies are now available firmly establishing the prognostic positive and negative predictive power of DSE in coronary artery disease and the determination of myocardial viability. Refinements in application allow the common use of DSE preoperatively, in

the emergency department, in female patients, and in valvular disease. Limitations of DSE are now better understood with the promise of constantly improving technology, such as myocardial contrast agents, giving the field of "opportunity for more to do."

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