Review

Current Status of Stress Echocardiography

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Summary: Stress echocardiography is a widely applied technique for the evaluation of individuals with known or suspected coronary artery disease. The technique combines echocardiographic imaging with exercise testing or pharmacologic stress. Advances in digital image acquisition and harmonic imaging have substantially improved the quality of echocardiographic images, and have therefore increased general applicability of stress echocardiography.

Key words: stress echocardiography, exercise echocardiography, dobutamine stress echocardiography

Introduction

Stress echocardiography has developed from a technique initially performed in a few tertiary care centers to a widely applied technique for evaluation of patients with known or suspected ischemic heart disease. Stress echocardiography includes imaging during or after exercise, pharmacologic stress, and atrial pacing. The purpose of this discussion is to provide an overview of the current status of stress echocardiography and to review the application of this evolving technique in specific patients subsets.

Exercise Echocardiography

Exercise echocardiography (ExEcho) relies on the ability to visualize segmental wall motion abnormalities due to exercise-induced myocardial ischemia. Several studies from different laboratories have provided a substantial body of data using stress echocardiography.^{1–10} Most studies have utilized treadmill exercise with immediate postexercise imaging, but bicycle ergometer offers the theoretical advantage of imaging during different levels of effort as well as at peak exercise. Although initial efforts at ExEcho yielded impressive results, interpretation of images from videotape proved tedious and therefore not widely applicable. The markedly increased acceptability and applicability of stress echocardiography has been in large part due to the development of digital image acquisition and the ability to provide side-by-side display of images acquired at baseline and during or after exercise. Several limitations to ExEcho still exist, including suboptimal image quality in certain patients, necessity for significant technical expertise required to obtain postexercise images, and reduced sensitivity in individuals with poor exercise tolerance.

Table I summarizes several larger trials assessing the diagnostic value of ExEcho. Sensitivity for detection of angiographic coronary stenosis ranges from 76 to 91%. Specificity in individuals without significant coronary stenosis ranges from 43 to 97%. Cohorts evaluated in these trials differ substantially with regard to gender, presence of previous myocardial infarction, mode of exercise, and overall prevalence of coronary artery disease.

Comparison of Exercise Echocardiography with Exercise Treadmill Testing and Exercise Single-Photon Emission Computed Tomography

Addition of echocardiographic imaging to exercise testing has resulted in improved accuracy of testing. In general, sensitivity of ExEcho exceeds that of exercise treadmill testing (ETT) alone. However, the advantage of ExEcho over ETT is in large part due to superior sensitivity for detection of single-vessel disease and greater overall specificity. The improved specificity appears to be particularly prominent in women and in individuals with abnormal baseline electrocardiogram

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TABLE I Selected studies using exercise echocardiography in patients with known or suspected coronary artery disease

First author (Ref. No.)	No. of patients	Sensitivity	Specificity
Limacher (1)	73	91/79 ^a	88
Armstrong (3)	95	88/79 ^a	87
Ryan (4)	64	78	100
Sawada (5)	57	86	86
Crouse (6)	228	97	64
Quinones (8)	289	74/85 ^b	88
Marwick (9)	179	84	86

^a Sensitivity in patients without resting wall motion abnormality.^b Sensitivity of coronary stenosis $\geq 70\%$.

(ECG), including patients with left ventricular hypertrophy or conduction abnormalities and those taking digoxin.^{5, 11}

Quinones *et al.* performed ExEcho and exercise single-photon emission computed tomography (SPECT) in 289 patients with known or suspected coronary artery disease.⁸ The two tests demonstrated agreement on wall motion analysis in 82%, with similar sensitivity and specificity. Of note, sensitivity for detection of multivessel disease (94% for both techniques) was considerably better than detection of single-vessel disease (58 and 61% for ExEcho and SPECT, respectively). A recent meta-analysis of 44 reported studies also demonstrated similar sensitivity of ExEcho and exercise SPECT (85 vs. 86%). Moreover, this analysis showed superior specificity of ExEcho compared with SPECT (77 vs. 64%), as well as greater incremental value of ExEcho over ECG alone.¹²

Prognostic Value of Exercise Echocardiography

Exercise echocardiography performed in patients following myocardial infarction has demonstrated efficacy for prediction of subsequent cardiac events and death.¹³ In a study of patients undergoing exercise testing after acute myocardial infarction, ExEcho demonstrated superior sensitivity and specificity compared with ETT for prediction of subsequent cardiac events.¹⁴ The value of ExEcho following myocardial infarction appears comparable with radionuclide imaging.¹⁵

Exercise Echocardiography in Women

Stress testing in women evaluated for ischemic heart disease has been particularly challenging for a variety of reasons. For example, stress ECG demonstrates poor sensitivity for detection of single-vessel disease, which appears to be more common in women with coronary artery disease. Overall specificity of ETT is reduced compared with men.^{16, 17} Addition of imaging modalities to exercise testing improves both sensitivity and specificity. Nonetheless, specificity of radionuclide imaging has been reportedly less than that observed in men;¹⁸ this is believed to be largely a consequence of soft tissue attenuation secondary to breast tissue.

Exercise echocardiography has demonstrated excellent sensitivity and specificity in women for detection of coronary artery disease. Sawada *et al.* performed ExEcho in women with chest pain and found sensitivity and specificity of 86% for detection of coronary disease;⁵ false negative studies were largely observed in women with a maximum heart rate of ≤ 125 beats/min. In this group, sensitivity of exercise ECG was only 29%, and specificity was 83%; exclusion of nondiagnostic ECGs yielded sensitivity of 47% and specificity of 78%. Exercise echocardiography was particularly useful in women with nondiagnostic ECGs. Marwick *et al.* similarly demonstrated enhanced specificity using echocardiographic imaging after exercise. Cost assessment analysis of several diagnostic strategies using coronary angiography, exercise ECG, and ExEcho suggested a cost-effective advantage using ExEcho as the initial approach.¹¹

Pharmacologic Stress Echocardiography

Exercise stress echocardiography is an important method for provoking myocardial ischemia and has the additional benefit of providing information on physiologic status as well as important prognostic information based on exercise capacity. However, certain patients are unable to exercise because of physical limitations, contraindications, or poor physical conditioning. In such patients, pharmacologic stress provides an important alternative. Several agents (including dobutamine, dipyridamole, adenosine, and arbutamine) have been used for induction of stress in patients unable to exercise. Comparative studies suggest that the use of agents such as dobutamine that result in an increase in myocardial oxygen consumption offers better overall sensitivity when combined with echocardiographic imaging. On the other hand, agents commonly used for radionuclide perfusion imaging, such as dipyridamole and adenosine, have often yielded inferior results with echocardiography. In a head-to-head comparison of dobutamine and adenosine with echocardiography and SPECT, Marwick *et al.* concluded that adenosine SPECT and dobutamine stress echocardiography (DSE) had comparable sensitivities for detection of coronary artery disease.¹⁹ Both modalities were superior to adenosine echocardiography. The prevalence of adverse effects is often greater with the currently used agents that affect myocardial perfusion. Nonetheless, extensive experience with adenosine and dipyridamole echocardiography²⁰ in assessment of patients with known or suspected coronary disease demonstrates that specificity of this diagnostic modality generally exceeds exercise and dobutamine echocardiography. Sensitivity of DSE appears comparable with ExEcho.^{10, 19, 21} Table II summarizes several larger studies using DSE for assessment of patients with known or suspected coronary artery disease.

Dobutamine stress echocardiography in women: Most studies assessing the utility of DSE have been comprised of predominantly male cohorts.^{22–27} Studies in women have yielded conflicting results. For example, Elhendy *et al.* suggested better specificity of DSE in women than in men,²⁸ while other investigators have reported lower sensitivity and

TABLE II Selected studies using dobutamine stress echocardiography in patients with known or suspected coronary artery disease

First author (Ref. No.)	No. of patients	Sensitivity	Specificity
Marcovitz (23)	141	96/87 ^a	66/91 ^a
Sawada (22)	103	89	85
Segar (24)	85	95	82
Marwick (19)	97	85	82
Beleslin (21)	136	82	77
Forster (25)	105	75	89

^a Sensitivity and specificity in 53 patients with normal resting wall motion.

inferior diagnostic accuracy of DSE in women.²⁹ Of importance is the fact that these studies have been influenced to varying degrees by patient selection and post-test referral bias. The Women's Ischemia Syndrome Evaluation (WISE) study prospectively enrolled women with suspected myocardial ischemia and clinical indication for cardiac catheterization.³⁰ In this cohort, DSE sensitivity for detection of multivessel disease was comparable with that observed in studies of male cohorts (81.8%), but sensitivity for detection of single-vessel disease was particularly poor; specificity in women without coronary stenosis was 80.6%.³⁰

Risk stratification following acute myocardial infarction: Dobutamine stress echocardiography is particularly suited to evaluation of patients following myocardial infarction, but may be associated with induction of arrhythmias. Findings by Smart *et al.* suggest that DSE can be safely performed in the first week following myocardial infarction. Findings during DSE also stratify patients at high risk for subsequent cardiac events, and therefore individuals who may benefit from early revascularization.³¹ These studies require further confirmation.

Detection of myocardial hibernation: Ventricular contractile dysfunction may occur in the presence of chronic coronary hypoperfusion and myocardial ischemia. This dysfunctional "hibernating myocardium" also demonstrates improved contractile function after revascularization. The important clinical distinction between hibernating and necrotic myocardium is evident from studies demonstrating improved functional capacity and survival following revascularization of patients with hibernating myocardium. Positron emission tomography (PET) appears to provide the most accurate test for detecting myocardial viability and has been shown to be highly accurate in predicting myocardial function after revascularization.³² However, the cost of PET is often prohibitive, and the equipment and expertise required are usually available only at larger medical centers. Dobutamine stress echocardiography offers the advantages of relatively low cost, avoidance of radiation exposure, brief performance time, and convenience for patients. Detection of hibernation by DSE is based on the premise that akinetic or severely hypokinetic segments due to chronic myocardial ischemia may be expected to show improved wall motion with inotropic stimulation.³³ Cigarroa

et al. performed DSE prior to coronary artery bypass surgery in patients with multivessel coronary artery disease and depressed left ventricular function.³³ Improvement in wall motion detected during DSE showed sensitivity of 82% for prediction of improved systolic function after revascularization. The absence of response to dobutamine infusion preoperatively was associated with a lack of improvement in wall motion postoperatively (specificity 86%). Other investigations have shown excellent correlation with PET in patients following myocardial infarction.³⁴

Limitations of dobutamine stress echocardiography: Dobutamine stress echocardiography is well tolerated in most patients,³⁵ but has several important limitations. The test is contraindicated in patients with decompensated congestive heart failure, unstable angina, atrial fibrillation or atrial flutter, known ventricular tachycardia, and uncontrolled systemic hypertension. In addition, sensitivity is reduced in patients with single-vessel coronary disease, and this appears particularly marked in women.³⁰ Concomitant use of beta adrenergic blocking agents is also associated with reduced sensitivity of DSE. Of note, submaximum studies have been shown to be associated with significant cardiac disease and subsequent cardiac events. The duration of study is considerable and drug infusion lasts ≥ 15 min in most patients. Side effects, although usually well tolerated, occurred in about 20% of patients.^{35,36} These included hypotension, tachyarrhythmias, tremors, nausea, and vomiting. More serious adverse including ventricular tachycardia or fibrillation and myocardial infarction are distinctly uncommon.

Atrial Pacing Echocardiography

Initial reports of atrial pacing during echocardiographic imaging for detection of ischemic heart disease also yielded promising results. However, the technique has not gained widespread use because of the semi-invasive nature and the poor tolerability in many patients. More recently, development of newer pacing catheters has improved patient acceptance. Lee *et al.* reported findings in 100 patients undergoing atrial pacing and dobutamine stress echocardiography and found pacing to be tolerated in most patients and echocardiographic findings to be comparable to DSE.³⁷ These findings suggest that pacing echocardiography may add to the diagnostic armamentarium of coronary artery disease, particularly in patients with contraindication to exercise or dobutamine infusion.

Contrast Agents in Stress Echocardiography

Contrast agents have been utilized in echocardiography almost since its inception, first to verify the identity of cardiac chambers and later to assist in diagnosis of valvular disease and cardiac shunts. Agitation of saline solution provides reliable opacification of right cardiac chambers and still serves as a sensitive indicator of right-to-left intracardiac shunts. Sonicated Renograffin has been used in the cardiac catheterization laboratory for assessment following catheter reperfusion techniques. These agents, however, have irregular and large bubble

sizes and are generally filtered by the pulmonary vasculature. Therefore, opacification of left cardiac structures is feasible only by direct injection into the aorta or coronary arteries. More recently, newer agents have been developed that permit opacification of the left cardiac chambers following peripheral venous injection.^{38,39} The only commercially available FDA-approved agent (Optison®) is indicated for enhancement of endocardial definition, but is being actively investigated for assessment of myocardial perfusion.⁴⁰

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