Clinical value of hyperemic left ventricular systolic function in vasodilator stress testing

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Exercise results in increased left ventricular contractility in normal individuals. Similar changes can also be seen with vasodilator stress. This article discusses the physiologic basis of these changes as well as reviews the clinical data supporting the use of these parameters for diagnostic and prognostic evaluation. Methodologic limitations as well as other concomitant pathologic processes which may confound interpretation of stress-induced changes in LVEF are also reviewed.

Key Words: Vasodilator stress • ejection fraction • A2A adenosine receptor agonists • adenosine • dipyridamole

INTRODUCTION

The concept of an ischemic cascade has been well refined and validated in the medical literature (Figure 1). In this model, abnormalities of myocardial perfusion trigger a series of downstream changes, both adaptive and maladaptive. Metabolic changes such as a shift towards glycolysis, lactate production, and increased adenosine are followed by relaxation abnormalities and subsequently systolic dysfunction.[1,2] Electrocardiographic changes, symptoms, and tissue infarction generally occur later in the cascade.

Supporting this model, exercise-induced deterioration of global left ventricular function was documented during the 1970s in patients with coronary artery disease (CAD) using contrast ventriculography.[3,4] Within a few years, these results were replicated non-invasively with radionuclide cineangiography.[5] The diagnostic[6,7] and prognostic[8] value of this finding was validated in the early 1980s.

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MECHANISMS FOR INCREASED GLOBAL SYSTOLIC FUNCTION WITH STRESS

Exercise increases demand for oxygen and nutrients in skeletal muscle, through a variety of mechanisms including increased sympathetic tone, vagal withdrawal, and nitric oxide- and metabolite-mediated pathways.[9] These collectively cause coronary vasodilation as well as positive chronotropy and inotropy, all resulting in increased cardiac output due predominantly to increased heart rate but also by increased ejection fraction. Dobutamine, a sympathomimetic agent, recapitulates many of these effects, although perhaps less completely than exercise.[10]

All three currently used vasodilators (*i.e.,* dipyridamole, adenosine, and regadenoson) also increase ejection fraction with stress in individuals without coronary artery disease.[11–15] There are several possible mechanisms for this. First, adenosine results increased venous return (i.e., preload) causing increased contractility via the Frank-Starling mechanism.[12] Second, increased coronary perfusion itself increases myocardial contractility[16] *via* the Gregg mechanism.[17] Third, regadenoson, and presumably the other agents, increases heart rate in a manner which can be abrogated by hexamethonium ganglionic blockade in rats despite decreased blood pressure, indicating sympathetic activation beyond simple baroreflex response.[18] Further, regadenoson administration nearly doubled plasma

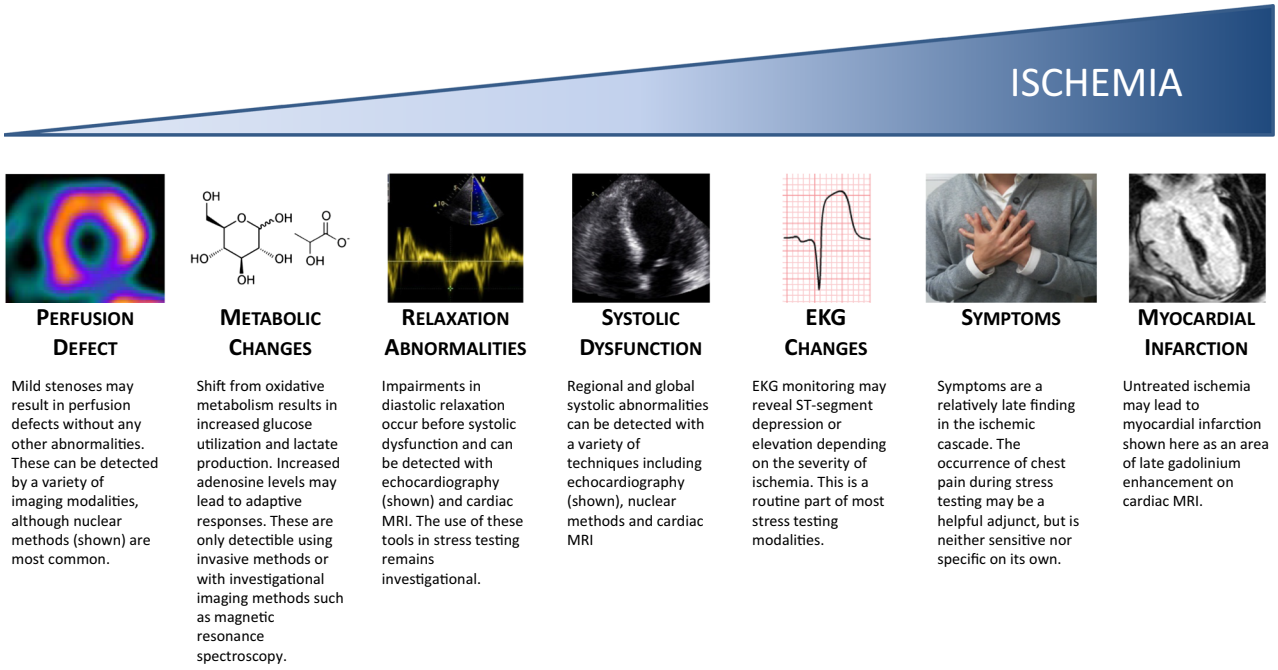

Figure 1. Illustration of ischemic cascade model in which increasing severity and duration of ischemia arising from abnormalities of myocardial perfusion lead in turn to disturbances in myocardial metabolism, altered myocardial relaxation, decreased myocardial contractility, electrocardiographic repolarization abnormalities, clinical symptoms, and eventually myocardial infarction. Adapted from Farhad and Murthy.[10]

norepinephrine levels. This sympathetic activation is likely to also contribute to increased contractility. Failure to augment left ventricular ejection fraction (LVEF) in response to the inotropic effects of sympathetic drive during acute vasodilator stress may reflect advanced coronary disease and/or other serious abnormalities.

GLOBAL SYSTOLIC FUNCTION IN NON-NUCLEAR STRESS TESTING

Although the initial application of peak stress systolic function was performed using nuclear techniques in the 1970s, evaluation of regional and global systolic function in response to exercise now forms the basis of stress echocardiography Evaluation of contractile response using echocardiographic imaging in response to dipyridamole stress has been well validated, with numerous diagnostic and prognostic studies.[19,20] Importantly, the higher specificity of vasodilator stress echocardiography compared to dobutamine may reflect a higher threshold in the extent and/or severity of coronary disease required to induce contractile abnormalities in response to vasodilators.[19]

In clinical practice, stress cardiac magnetic resonance imaging is generally performed by evaluating first-pass contrast enhancement of the myocardium under vasodilator stress. However, contractile function increases acutely with vasodilator administration[13] and failure to increase global and regional function has diagnostic and prognostic value.[21–23]

SYSTOLIC FUNCTION DURING STRESS IN CARDIAC PET

Interest in stress-induced changes in LVEF among the nuclear cardiology community was renewed after it was observed in an analysis of 510 patients referred for ^{82}Rb rest/stress PET and coronary angiography that LVEF reserve in response to adenosine or dipyridamole was a strong independent predictor of left main or 3-vessel CAD.[24] An LVEF reserve of >5% had a negative predictive value of 97% for severe left main or 3-vessel CAD. Conversely, an LVEF <−5% had a positive predictive value of 77%. Similarly, regadenoson stress LVEF reserve was significantly greater in individuals with normal compared to mild, or moderately to severely abnormal myocardial perfusion imaging.[14] A follow-up analysis of 1432 patients undergoing vasodilator rest/stress 82Rb PET demonstrated that LVEF reserve <0 compared to ≥0 was associated with a much higher rate of cardiac events (5.3%/year vs

2.1%/year, $P < .001$) and all-cause mortality (9.2%/year vs 4.3%/year, $P < .001$). Even after adjusting for clinical, rest LVEF, and rest and stress perfusion findings, LVEF was an independent predictor of cardiac events (hazard ratio 0.79/5% increase, $P = .03$).

EARLY POST-STRESS SYSTOLIC FUNCTION WITH SPECT

An international multi-center trial has established that early post-stress imaging at 15 minutes post-exercise leads to equivalent image quality compared to delayed imaging at 60 minutes with greater detection of post-ischemic stunning as manifested by decreased post-stress LVEF.[25] Although early post-stress imaging with vasodilator SPECT is feasible,[26] it is not commonly done in practice. Further, only a few studies have evaluated the clinical utility of post-stress LVEF with SPECT, but have generally found that post-stress stunning in the form of decreased LVEF is an important predictor of events.[27–29] However, when stress imaging is done late after vasodilator administration, after the effects are likely to have worn off, the diagnostic and prognostic value are likely to be attenuated.[30]

IMPORTANT LIMITATIONS AND CAVEATS

Importantly, stress echocardiography has enabled the evaluation of the time course of stress-induced wall motion abnormalities.[31] Although these are generally relatively transient, they may persist for as long as 25 minutes after termination of dobutamine stress in patients with three-vessel coronary disease. However, using cardiac MRI global increases in LVEF in response to adenosine generally resolved within 3-4 minutes after adenosine infusion.[32] This underscores the greater importance of imaging during or immediately after stress in order to capture vasodilator-induced contractile abnormalities. Unfortunately, most vasodilator SPECT images are obtained at approximately 40-60 minutes post stress, when ischemia-induced changes in global and regional function should almost certainly have resolved.[30] While the value of early SPECT imaging has been established for patients undergoing exercise stress testing,[25] early imaging is not widely used with vasodilator stress but is potentially feasible.[26] Further, because many laboratories collect images over longer periods of up to 20 minutes or longer when using ^{13}N-ammonia, underestimation of LVEF reserve compared to protocols reconstructing gated images from the first 3-5 minutes of imaging is likely.

Arrhythmias may also have a significant impact on observed contractile reserve. Generally, vasodilators result in increased heart rate, although response is somewhat variable and is itself maybe related to prognosis.[33] Either resolution of arrhythmia, as might occur in some patients with resting premature ventricular contractions, or induced arrhythmias during stress could change average global LVEF without directly reflecting underlying ischemia. Along these lines, errors in gating due to incorrect placement of R-R acceptance window or inappropriate triggering based on T-waves or artifacts need to be excluded as part of routine quality control.

Although the implications for vasodilator stress are not known, changes in LVEF with exercise may not be specific for obstructive CAD. Increased afterload, aging, or valve disease may attenuate LVEF responses to exercise. Mental stress induced a decline in LVEF via an increase in afterload, in middle-aged men and women without evidence of coronary artery disease.[34] Increasing age may attenuate the changes in LVEF with exercise. In a study of 77 asymptomatic volunteers (ages 20-95 years), the change in LVEF from rest to upright bicycle exercise was inversely related to age ($R = -.71$, $P < .001$).[35] Chronic regurgitation of the mitral or aortic valves may also decrease LVEF with exercise and portends adverse prognosis.[36]

Finally, the implications of failure to augment LVEF or even modest decreases in LVEF in small ventricles remain unclear. Given spatial resolution limitations of nuclear methodologies, it is unlikely that a decline in LVEF from 70% to 65% in a small ventricle, as is common in smaller women, is as concerning as a drop from 55% to 45% in a normal-sized ventricle.

CONCLUSIONS

The concept of vasodilator-induced changes in LVEF is well grounded in theoretical, animal, and human data including clinical validation for diagnostic and prognostic assessment. However, reproduction of clinical validation in larger cohorts in multiple centers would be an important future direction.

Disclosures

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