CME CREDIT

Stress echocardiography: its emerging role in identifying viable myocardium

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SUMMARY Stress echocardiography is an emerging technique for identifying viable myocardium in patients with left ventricular systolic dysfunction or myocardial infarction.

KEY POINTS An enhancement in systolic wall thickening when low doses of dobutamine are infused indicates the myocardial segment is viable. Dobutamine echocardiography is safe and readily portable and produces images immediately available for interpretation and clinical decision-making. Dobutamine echocardiography will likely play a larger role in guiding coronary revascularization; however, larger studies are needed to fully define its role.

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WHEN a patient presents with an abrupt coronary occlusion, urgent intervention with thrombolysis or angioplasty is indicated to restore perfusion and prevent infarction. However, once the myocardium is already damaged, the therapeutic decision is less clear-cut. In a patient with chronic ischemia and systolic dysfunction, or in a patient who still has poor perfusion after undergoing thrombolysis for a myocardial infarction, one would like to know whether damaged myocardium is still viable, and whether, therefore, the patient would actually benefit from revascularization. There is now emerging evidence that stress echocardiography with dobutamine might supply this information. However, further study is needed to define the role of this test in these situations. This paper will review information to date.

BACKGROUND

Noninvasive cardiac testing is playing a prominent and emerging role in diagnosing ischemic heart disease and in guiding its management. The goal of testing is to as-

sess myocardial blood flow by directly observing myocardial function during stress. This is readily accomplished by coupling echocardiography with exercise. Alternatively, it can be accomplished by infusing dobutamine, dipyridamole, or adenosine, a method now used clinically to detect inducible regional myocardial dysfunction. Abnormal test results suggest the presence of a hemodynamically significant epicardial coronary artery obstruction.

Coronary artery disease and subsequent myocardial ischemia and infarction are regional processes. Further, during an acute myocardial infarction, the left ventricular ejection fraction is often unaffected and is therefore misleading, given the compensatory hyperkinesis of the noninfarcted regions. Thus, left ventricular systolic dysfunction is most accurately reflected in regions or territories, generally ascribed to one of the three major epicardial coronary arteries. Since myocardial ischemia and infarction result in reduced myocardial systolic wall thickening, echocardiography is well suited to visually assess these conditions.

VIABILITY AFTER MYOCARDIAL INFARCTION

Myocardial "stunning" (reversible systolic dysfunction following ischemia of the left ventricle) is a separate entity that stress echocardiography can help identify. Stunning represents a sublethal injury resulting from transient interruption of myocardial blood flow,[1] as seen in patients with successful reperfusion after thrombolysis. (Myocardial "hibernation," in contrast, reflects chronic ischemia.) The myocardial dysfunction is generally regional, corresponding to the myocardial territory perfused by the involved coronary artery. During the acute phase, reversible and irreversible myocardial injury appear similar on echocardiography, with reduced systolic thickening at rest, near-normal resting diastolic wall thickness, and no evidence of the myocardial thinning and scarring typically seen with chronic infarction.

However, the time course of myocardial scar development as seen on echocardiography is unclear. In dogs, coronary occlusion lasting less than 20 minutes does not result in myocardial necrosis, but it does produce prolonged (but reversible) dysfunction in the segment supplied by that artery.[2–4] After thrombolysis, it is important to identify viable stunned myocardium and to differentiate it from irreversibly infarcted myocardial tissue; doing so helps clarify if a patient may need urgent revascularization. When appropriately applied, urgent revascularization attenuates ongoing ischemia and therefore reduces the severity of postischemic dysfunction.

Myocardial stunning is also frequently observed during exercise echocardiography. However, when a patient exhibits regional, stress-induced, systolic myocardial dysfunction, the abnormality often persists well into the recovery phase of testing. This represents inadequate oxygen delivery during a period of elevated oxygen requirements, suggesting ongoing myocardial ischemia vs myocardial stunning.

Mechanisms of stunning

Many mechanisms have been proposed for myocardial stunning, including the generation of oxygen-derived free radicals during ischemia, excitation-contraction uncoupling due to dysfunction of the sarcoplasmic reticulum, and calcium overload.[5] Myocardial stunning is probably multifactorial and involves each of these mechanisms to some degree.

Bolli et al[6] have proposed that postischemic left ventricular dysfunction may be the result of the myocardium's inability to generate enough high-energy phosphates to sustain contractile function. However, improved contractile function, as observed during inotrope infusion, suggests the myocardium can still generate adenosine triphosphate (ATP) and is viable. Several studies[7–11] have addressed the inotropic reserve of postischemic myocardium after both single and multiple short-term coronary occlusions and a period of reperfusion. Each study has documented a significant increase in systolic wall thickening during inotrope infusion. Thus, experimentally stunned myocardium possesses considerable functional reserve, and therefore, inability to generate ATP is not a likely cause of ischemic dysfunction.

Detecting viable but stunned myocardium

In a myocardial segment abnormal at rest, regional improvement in wall thickening during inotrope infusion indicates viability. Ellis and colleagues[12] administered dopamine to mongrel dogs after 2 hours of coronary artery ligation. Myocardium subjected to ischemia followed by reperfusion contracted poorly. However, it responded to inotropic stimulation by dopamine at both 1 and 24 hours after reperfusion. The investigators concluded that dopamine stimulates the reperfusion-salvaged

(but noncontracting) myocardium to contract as early as 1 hour after reperfusion.

Pierard and colleagues[13] compared the results of dobutamine echocardiography and positron emission tomography (PET) in identifying viable myocardium in 17 patients after myocardial infarction and thrombolytic therapy. Regional glucose uptake and perfusion (as determined by PET) and regional systolic thickening at rest and during intravenous dobutamine infusion (as assessed by echocardiography) were compared in corresponding left ventricular segments. Of the 11 patients in whom PET demonstrated the presence of viable myocardium, 10 also exhibited viable tissue on echocardiography during infusion of dobutamine. During the acute phase of myocardial infarction, myocardial segments that remained akinetic or dyskinetic during dobutamine infusion demonstrated no return of contractile function on follow-up. On the other hand, myocardial segments in which systolic wall thickening improved during dobutamine infusion were likely to have returned to normal when assessed several months later.

Subsequently, Barilla et al[14] investigated the sensitivity of low-dose (5 to 10 μg/kg/minute) dobutamine echocardiography 4 ± 2 days after the onset of symptoms of an acute anterior myocardial infarction. All 21 patients had residual high-grade stenosis of the left anterior descending (LAD) artery. Myocardial segments that were dyskinetic, akinetic, or severely hypokinetic were assessed echocardiographically for improvement in myocardial wall thickening. Twenty patients demonstrated transient segmental improvement in myocardial wall thickening with dobutamine. In patients who underwent revascularization, function had recovered at 5 ± 3 days after revascularization almost to the level seen with dobutamine infusion before revascularization; at 40 ± 15 days, this group had significantly better function than the group that underwent medical treatment only. Patients with non-Q-wave infarctions had greater improvement in regional myocardial function than did patients with Q-wave infarctions, leading the authors to conclude that patients with non-Q-wave myocardial infarction and patients who have undergone thrombolytic therapy have areas of noncontractile but viable myocardium that can be identified by low-dose dobutamine infusion.

Smart et al[15] performed multistage dobutamine stress echocardiography within 7 days of thrombolytic therapy to determine whether dobutamine-responsive wall motion accurately detects reversible postischemic dysfunction irrespective of infarct location. Four weeks after myocardial infarction, resting echocardiography was repeated: improved wall motion within the infarct zone was identified as reversible dysfunction. Independent indicators of reversible ischemic dysfunction were non-Q-wave myocardial infarction and infarct-zone wall motion that responded to low-dose dobutamine infusion. Dobutamine-responsive wall motion during any stage of dobutamine echocardiography was very specific for reversible dysfunction but was sensitive only at low doses. Non-Q-wave myocardial infarction and a low peak creatine phosphokinase (CPK) concentration were also specific but less sensitive. Of the patients who underwent revascularization, 77% demonstrated dobutamine-responsive wall motion preoperatively, which predicted the extent of recovery. In the patients who did not undergo revascularization, dobutamine-responsive wall motion predicted the extent of recovery with 97% accuracy.

VIABILITY IN CHRONIC CORONARY ARTERY DISEASE

An equally important and more challenging clinical problem is encountered when attempting to establish myocardial viability in the setting of depressed myocardial function. Frequently, this occurs after myocardial infarction, in particular, after thrombolytic agents have been administered. This raises the specter of "incomplete infarction," which may be manifested by areas of viable myocardium in the infarct-related artery territory that may or may not contract. Thus, we need a test that will reliably distinguish irreversible myocardial dysfunction (ie, myocardial scar) from depressed but reversible postischemic dysfunction, thereby assisting in patient selection for myocardial revascularization.

Early studies demonstrated that reversal of wall-motion abnormalities with inotropic stimulation or nitroglycerin predicts recovery of left ventricular function after revascularization.[16–19] It was formerly believed that persistent left ventricular systolic dysfunction at rest was caused by irreversible myocardial necrosis. However, the concept of myocardial hibernation, proposed by Rahimtoola,[20] suggests that resting left ventricular systolic dysfunction is a normal response of the heart to a chronic low-blood-flow state, in essence redefining and normal-

izing the balance of myocardial oxygen supply and demand.

Hibernating myocardium has since been repeatedly demonstrated clinically, eg, in patients with left ventricular dysfunction at rest and diffuse coronary artery disease who undergo successful surgical revascularization and experience improvement in left ventricular systolic function. As another example, a patient with regional myocardial dysfunction due to an advanced but localized epicardial coronary artery stenosis may improve after percutaneous transluminal coronary angioplasty. These are common, everyday occurrences. However, a reliable test is needed to detect myocardial hibernation. Such a test could be performed before angioplasty or revascularization to predict which patients would benefit from these procedures.

Cigarroa et al[21] performed dobutamine echocardiography in 49 consecutive patients with multivessel coronary artery disease and depressed left ventricular function. Twenty-five of these patients underwent successful myocardial revascularization. Nine of 11 patients in whom contractility improved during dobutamine infusion before revascularization demonstrated improved systolic wall thickening afterward. In contrast, 12 of 14 patients in whom contractility did not improve during dobutamine infusion before revascularization did not improve afterward. From these results, it was concluded that dobutamine stress echocardiography identifies hibernating myocardium and predicts the recovery of segmental left ventricular function after coronary revascularization. However, after longer periods of coronary occlusion, when myocardial necrosis was documented, Mercier and colleagues[22] found no improvement in systolic wall thickening after reperfusion either spontaneously or in response to inotropic infusion.

Most recently, La Canna et al[23] performed low-dose dobutamine echocardiography in 33 patients with angiographically proven coronary artery disease and persistent left ventricular systolic dysfunction before they underwent coronary artery bypass surgery, immediately after surgery, 2 weeks later, and 3 months later. Preoperative dobutamine echocardiography correctly predicted improvement in 178 of the 205 segments that eventually recovered function after revascularization. Additionally, it correctly identified 89 of the 109 segments that did not recover postoperatively. The authors concluded that preoperative dobutamine echocardiography predicts early improvement in wall motion after surgical revascularization in patients with known coronary artery disease and chronic left ventricular dysfunction.

CONCLUSION

To date, no large studies in patients have been performed using stress echocardiography to detect viable myocardium. However, the current accumulated evidence suggests that echocardiography performed during low-dose dobutamine infusion successfully demonstrates stunned and perhaps hibernating myocardium. Larger studies are needed to address these issues in patients with chronically depressed left ventricular function or myocardial infarction.

Experience has proven dobutamine echocardiography safe in these patient groups: it precipitates nonsustained arrhythmia and angina only rarely. It possesses other advantages beyond safety: it is portable and relatively inexpensive, does not entail radiation exposure, and provides immediate results for interpretation and clinical decision-making. Future issues to be addressed include establishing the optimal dobutamine dose and developing a quantitative system of assessing systolic myocardial wall thickening. In addition, studies in larger patient groups need to be done to compare the utility of stress echocardiography with other technologies such as PET and thallium imaging in identifying viable myocardium.

REFERENCES

1. **Bolli R.** Mechanism of myocardial stunning. Circulation 1990; **82:**723–738.
2. **Hess ML, Barnhart GR, Crute S, Komtawana P, Krause S, Greenfield LJ.** Mechanical and biochemical effects of transient myocardial ischemia. J Surg Res 1979; **26:**175–184.
3. **Heyndrickx GR, Baig H, Nellers P, Levsen L, Fishbein MC, Vatner SF.** Depression of regional blood flow and wall thickening after brief coronary occlusions. Am J Physiol 1978; **234:**H653–H659.
4. **Puri PS.** Contractile and biochemical effects of coronary reperfusion after extended periods of coronary occlusion. Am J Cardiol 1975; **36:**244–251.
5. **Bolli R.** Mechanism of myocardial stunning. Circulation 1990; **82:**723–738.
6. **Bolli R, Wei-xi Z, Myers M, Hartley C, Roberts R.** Beta-adrenergic stimulation reverses postischemic myocardial dysfunction without producing subsequent functional deterioration. Am J Cardiol 1985; **56:**964–968.
7. **Jennings RB, Reimer KA.** Factors involved in salvaging ischemic myocardium: effects of reperfusion of arterial blood. Circulation 1983; **68(Suppl I):**I-25–I-36.

8. **Kloner RA, Ellis SG, Lange R, Braunwald E.** Studies of experimental coronary artery reperfusion: effects on infarct size, myocardial function, biochemistry, ultrastructure and microvascular damage. Circulation 1983; **68(Suppl I):**I-8–I-15.
9. **Heyndrickx GR, Millard RW, McRitchie RJ, Maroko PR, Vatner SF.** Regional myocardial functional and electrophysiological alterations after brief coronary artery occlusion in conscious dogs. J Clin Invest 1975; **56:**978–985.
10. **Weiner JM, Apstein CS, Arthur JH, Pirzada FA, Hood WB Jr.** Persistence of myocardial injury following brief periods of coronary occlusion. Cardiovasc Res 1976; **10:**678–686.
11. **Heyndrickx GR, Baig H, Nellens P, Leusen I, Fishbein MC, Vatner SF.** Depression of regional blood flow and wall thickening after brief coronary occlusions. Am J Physiol 1978; **234:**H653–H659.
12. **Ellis SE, Wynne J, Braunwald E, Henschke CI, Sander T, Kloner RA.** Response of reperfusion-salvaged, stunned myocardium to inotropic stimulation. Am Heart J 1984; **107:**13–19.
13. **Pierard LA, DeLandsheere CM, Berthe C, Rigo P, Klubertus HE.** Identification of viable myocardium by echocardiography during dobutamine infusion in patients with myocardial infarction after thrombolytic therapy: comparison with positron emission tomography. J Am Coll Cardiol 1990; **15:**1021–1031.
14. **Barilla F, Gheorghiade M, Alam J, Khaja F, Goldstein S.** Low-dose dobutamine in patients with acute myocardial infarction identifies viable but not contractile myocardium and predicts the magnitude of improvement in wall motion abnormalities in response to coronary revascularization. Am Heart J 1991; **122:**1522–1531.
15. **Smart SC, Sawada S, Ryan T, et al.** Low-dose dobutamine echocardiography detects reversible dysfunction after thrombolytic therapy of acute myocardial infarction. Circulation 1993; **88:**405–415.
16. **Nesto RW, Cohn LH, Collins JJ, Wynne J, Holman L, Cohn PF.** Inotropic contractile reserve: a useful predictor of increased 5-year survival and improved postoperative left ventricular function in patients with coronary artery disease and reduced ejection fraction. Am J Cardiol 1982; **50:**39–44.
17. **Popio KA, Gorlin R, Bechtel D, Levine JA.** Postextrasystolic potentiation as a predictor of potential myocardial viability: preoperative analyses compared with other studies after coronary artery bypass surgery. Am J Cardiol 1977:39:944–951.
18. **Helfant RH, Pine R, Meister SG, Feldman MS, Trout RG, Banks VS.** Nitroglycerin to unmask reversible asynergy: correlation with post coronary bypass ventriculography. Circulation 1974; **50:**108–113.
19. **Horn HR, Teicholz LE, Cohn PF, Herman MV, Gorlin R.** Augmentation of left ventricular contraction pattern in coronary artery disease by an inotropic catecholamine: the epinephrine ventriculogram. Circulation 1974; **49:**1063–1071.
20. **Rahimtoola SH.** The hibernating myocardium. Am Heart J 1989:117:211–221.
21. **Cigarroa CG, deFilippi CR, Brickner E, et al.** Dobutamine stress echocardiography identifies hibernating myocardium and predicts recovery of left ventricular function after coronary revascularization. Circulation 1993; **88:**430–436.
22. **Mercier J, Lando U, Kanmatsue K, et al.** Divergent effects of inotropic stimulation on the ischemic severely depressed reperfused myocardium. Circulation 1982; **66:**397–400.
23. **La Canna G, Alfieri O, Giubbini R, Gargano M, Ferrari R, Visioli O.** Echocardiography during infusion of dobutamine for identification of reversible dysfunction in patients with chronic coronary artery disease. J Am Coll Cardiol 1994; **23:**617–626.