ARTICLES

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Does the Use of Atropine Provide Additional Ischemic Stimulus to Myocardium During Dobutamine Stress Echocardiography?

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The diagnostic value of dobutamine stress echocardiography has been widely reported, but the value of adding atropine to achieve a target heart rate has not been widely studied. The authors tested the hypothesis that atropine does not provide additional diagnostic accuracy to a dobutamine stress echocardiography test. The inotropic effect of dobutamine in large doses has been shown to induce ischemic changes in the myocardium. Because atropine mainly increases heart rate (chronotropic stimulus), there is controversy as to whether its effects produce an additional ischemic response during dobutamine stress echocardiography. The results of the present study suggest that the ischemic response during dobutamine stress echocardiography is related primarily to an inotropic stimulus and not a chronotropic stimulus, and therefore, the authors concluded it may not be necessary to add atropine routinely to dobutamine stress echocardiography tests.

Key words: atropine, dobutamine, stress echocardiography.

Coronary artery disease often is a silent disorder; most men and women aged more than 50 years in the United States have coronary atherosclerosis, and the majority have no signs or symptoms. In the United States, coronary artery disease accounts for more than 650,000 deaths per year.[1] More than 6 million people per year are reported to have a history of angina or have suffered a myocardial infarction.[1] A great deal of research has been dedicated to finding a diagnostic modality that would enable physicians to accurately detect coronary artery disease earlier in its course. Atherosclerosis is partly a result of lifestyle choices, and early detection might enable patients to decrease or modify risk factors (Table 1) that may ultimately lead them to a life-threatening myocardial infarction.

A precursor to myocardial infarction is myocardial ischemia,[2] Because myocardial ischemia often is induced by physical activity, exercise stress echocardiography (performed on a treadmill or stationary bike) has proven to be an effective noninvasive

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TABLE 1
Risk Factors of Atherosclerosis

Blood cholesterol levels
Smoking
Hypertension
Obesity
Stress
Physical inactivity
Diabetes
Heredity
Male sex
Increasing age

TABLE 3
Dobutamine Stress Echocardiography Protocol

Echocardiographic, and blood pressure monitoring every 3 minutes
Stepwise infusion every 3 minutes: 5, 10, 20, 30, 40, and 50 mcg/kg/min
Atropine infusion at last stage of dobutamine if heart rate <85% of predicted maximum
End points
Target heart rate achieved or intolerable symptoms occur or severe wall motion observed on echocardiograms

diagnostic tool in the detection of coronary artery disease. This modality, however, requires that patients are motivated to exercise and capable of stressing their cardiovascular system to a maximum. Patients who have musculoskeletal or neurologic conditions precluding exercise or a low tolerance to exercise may be poor candidates for this method of stress testing (Table 2). Exercise testing has been shown to have a lesser sensitivity with submaximal exercise. An increasingly popular alternative to exercise stress testing is the use of pharmacologic stressors used with echocardiography.

Several clinical trials have shown that the pharmacologic stressor dobutamine has proven to have a high sensitivity, specificity and, reproducibility in the detection of coronary artery disease.[3–5] Dobutamine mimics physical exercise in its ability to increase left ventricular contractility and wall stress.[6] Dobutamine primarily has an inotropic selectivity. However, it differs from exercise in that it does not increase heart rate or blood pressure in many patients. During exercise-increased inotropy, heart rate and blood pressure contribute to increased cardiac work. An increase in cardiac work requires an increased supply of oxygen to the heart. In the presence of significant coronary artery stenosis, the stressed myocardium is deprived of oxygen, causing the induction of ischemia.

Because the primary effect of dobutamine is to increase myocardial contractility and to a lesser extent heart rate, some of the patients in our study failed to achieve target heart rate with the last dosage of dobutamine. If these patients were asymptomatic during the last dosage of dobutamine, atropine was administered. Atropine is a vagolytic agent that works to block the parasympathetic nerve receptors that control or limit heart rate. With the suppression of the parasympathetic system, the heart rate rapidly increases. The aim of this study was to determine if the administration of atropine resulted in more frequent ischemic responses during dobutamine stress echocardiography tests.

TABLE 2
Factors That Limit Exercise

Pulmonary disease (chronic obstructive pulmonary disease)
Cerebrovascular disease (stroke)
Musculoskeletal abnormalities (arthritis or degenerative joint disease)
Poor condition or motivation
Limiting symptoms (fatigue, chest pain)

Methods

This retrospective study consisted of 137 patients who were referred for dobutamine stress echocardiography between January 1992 and August 1995. All patients had symptoms suggestive of coronary artery disease and were not able to exercise adequately. None of the stress tests in this study were considered uninterpretable. Therefore, all of the patients in our study were included. All of the patients in this study were stressed while on their current cardiac medications. The cardiac drugs included beta-blockers, calcium channel blockers, nitrates, and angiotensin-converting enzyme (ACE) inhibitors.

Informed consent was obtained before each study. Blood pressure, a 12-lead electrocardiogram (ECG), and echocardiograms were recorded at baseline and every 3 minutes thereafter until the patient's heart rate returned back to baseline. Target heart rate was calculated using [(220 - age) x 85%]. Dobutamine was infused intravenously using an infusion pump starting at doses of 5, 10, 20, 30, 40, and 50 mcg/kg/min in 3-minute stages (Table 3). If the patient's heart rate during the administration of the last dosage of dobutamine was below target heart rate, atropine was administered intravenously beginning at 0.25 mg and repeated up to 2 mg, if necessary.

All echocardiograms were performed using an Acuson 128 (Mountain View, CA) or a Hewlett Packard 1500 (Andover, MA) with a 2.5- or 3.5-MHz transducer. Standard parasternal, apical, and subcostal views were recorded on videotape. The infusion was stopped if the patient was having significant chest pain, sustained supraventricular tachycardia, hypotension (a systolic blood pressure < 20 mm Hg below control), dyspnea, nausea and vomiting, or severe wall motion abnormalities. The test also was discontinued if the patient failed to achieve target heart rate after the maximal dosage of atropine was given. If the patient had angina or prolongation of tachycardia associated with wall motion abnormalities, he or she received nitroglycerin or a short-acting intravenous beta-blocker at the discretion of the attending cardiologist.

Independently, two cardiologists, blinded to patient history and ECG data but with knowledge of the doses of dobutamine and atropine used, evaluated the echocardiograms for wall motion abnormalities. An ischemic response was defined as the presence of a new wall motion abnormality or the worsening of a resting wall motion abnormality. Wall motion abnormalities were considered to be a decrease in thickening or movement in a section of myocardium observed at any stage of the dobutamine–atropine infusion.

The left ventricle was assessed at baseline, peak dobutamine, and peak atropine. At each of these three stages, wall motion was assessed qualitatively and placed into one of three categories: 1) normal, 2) ischemic distribution in a single coronary artery vessel, or 3) ischemic distribution in multiple coronary artery vessels.

Continuous variables of the patient's gender, age, height, and weight were expressed as a mean ± standard deviation (SD). Target heart rate, baseline, peak dobutamine, and peak atropine heart rate also were expressed as mean ± SD. Analysis of systolic and diastolic blood pressures at each stage and changes in heart rate from baseline to peak dobutamine and from peak dobutamine to peak atropine were compared using the Student's paired t test. The double product (heart rate x systolic blood pressure) was used to estimate myocardial demand at baseline, peak dobutamine, and peak atropine. The required level of significance was $P < 0.05$.

Results

Dobutamine stress echocardiograms were performed on 137 patients (mean age, 55 years ± 10; range, 33–86). There were 49 men and 78 women. Of the 137 patients, 82 achieved 85% of their maximum predicted heart rate with dobutamine; 55 (40%) did not and received atropine. Clinical data for whom detailed pharmacologic histories were available showed 89 patients receiving beta-blocker therapy. Baseline echocardiograms showed left ventricular hypertrophy in 44 patients. During the stress test, there were 35 patients with more than 0.5 mm of ST segmental depression, 36 patients with arrhythmias, and 76 patients had other or nonspecific ST segmental ECG changes.

HEMODYNAMIC DATA

The baseline heart rate was 72 ± 9.7 beats per minute (bpm). At peak dobutamine, it was 113 ± 10 bpm ($P < 0.001$ *vs.* baseline), and it increased to 130 ± 9 bpm at peak atropine ($P < 0.001$ *vs.* peak dobutamine). The systolic blood pressure at baseline was 132 ± 20 mm Hg; it increased slightly at peak dobutamine to 142 ± 31 mm Hg ($P < 0.001$ *vs.* baseline), and it increased further at peak atropine to 148 ± 28 mm Hg ($P < 0.001$ *vs.* peak dobutamine). The diastolic blood pressure did not change significantly. It was 68 ± 14 mm Hg at baseline; it increased to 73 ± 13 mm Hg at peak dobutamine, and at peak atropine, it was 73 ± 15 mm Hg. The double product (heart rate x systolic blood pressure/10^3) at baseline was 9 ± 3; at peak dobutamine, it increased to 15 ± 5, and by peak atropine, the double product increased to 19 ± 5 (Table 4).

WALL MOTION ABNORMALITIES

Of the 55 patients who received atropine, wall motion abnormalities were present in 21, and the remaining 34 patients had normal results. Of the 21 patients with abnormal test results, 19 had inducible ischemia at peak dobutamine. These patients had no additional ischemic changes after atropine administration, although their target heart rate was achieved. Only two patients (3.6%) had new diagnostic information with the administration of atropine. These patients already had ischemic responses in a single coronary artery distribution at peak dobutamine. When atropine was administered, both patients demonstrated the presence of multiple vessel disease (P = not significant *vs.* peak dobutamine).

Discussion

The results of this study show that of the 21 patients who required atropine and were consid-

TABLE 4
Hemodynamic Changes

Changes in Heart Rate		
Baseline	73 ± 15 beats per minute	
Peak dobutamine	112 ± 27 beats per minute	($P < 0.001$ *vs.* baseline)
Peak atropine	130 ± 20 beats per minute	($P < 0.001$ *vs.* dobutamine)
Changes in Systolic Blood Pressure		
Baseline	132 ± 20 mm Hg	
Peak dobutamine	142 ± 31 mm Hg	($P < 0.001$ *vs.* baseline)
Peak atropine	148 ± 28 mm Hg	($P < 0.001$ *vs.* dobutamine)
Changes in Diastolic Blood Pressure		
Baseline	68 ± 14 mm Hg	
Peak dobutamine	73 ± 13 mm Hg	($P < 0.001$ *vs.* baseline)
Peak atropine	73 ± 15 mm Hg	($P < 0.001$ *vs.* dobutamine)
Changes in Oxygen Consumption—Rate Pressure Product (Heart rate × systolic blood pressure × 0.001)		
Baseline	9 ± 3	
Peak dobutamine	15 ± 3	
Peak atropine	19 ± 5	

ered to have an abnormal stress test, 19 had inducible wall motion abnormalities before the administration of atropine. Only two patients had additional ischemic changes with atropine. Both of these patients had preexisting abnormalities at baseline with deteriorating wall motion throughout the entire study. Our data suggests that although the infusion of atropine allowed the patients in our study to achieve target heart rate, it was the inotropic effects of dobutamine that appeared to be the more important factor in producing ischemic changes and not the chronotropic effects of atropine.

CLINICAL IMPLICATIONS

We believe that in a routine hospital or clinical setting for the identification of coronary artery disease, exercise stress testing is preferred for patients who are able to exercise. However, for patients who are unable to walk on a treadmill or ride a bike, dobutamine stress echocardiography should be strongly considered. Pharmacologic stress testing has proven to be a highly reliable and effective tool in the assessment of coronary artery disease. Dobutamine is easy to administer, and it enables the generation of incremental stress, which is analogous to the stages of exercise. It also allows for continuous echocardiographic monitoring with technically easier image acquisition because patients are at rest and optimally positioned.

The safety of pharmacologic stress testing is a concern to physician and patient. Dobutamine stress echocardiography involves no radiation exposure. It is quicker and more cost-effective than nuclear medicine stress testing. In two separate studies, one by McNeill et al[2] and one by Polderman et al,[7] both concluded that there were no severe side effects associated with a dobutamine stress echocardiography test. Poldermans' group indicated that the majority of side effects associated with their stress tests were hypotension and arrhythmias. Poldermans' group further concluded that dobutamine stress echocardiography tests were safe and feasible but that caution should be used in patients with a history of ventricular arrhythmias or poor left ventricular function at rest.

To date, there has not been any data to suggest that the use of atropine during a dobutamine stress echocardiography test has caused adverse outcomes. However, one of the primary considerations for doing the present study was to determine if the addition of atropine yielded additional diagnostic accuracy. We found that although atropine allowed patients to achieve their target heart rate, it did not appear to provide additional ischemic stimulus to the myocardium during the stress test. In all of the atropine patients studied, only two displayed increasing wall motion abnormalities with atropine. We therefore concluded that achieving 85% of the maximum predicted heart rate with atropine may not be necessary in the advent of myocardial ischemic events.

LIMITATIONS OF THE STUDY

Attempts were made to limit any potential sources of bias in this retrospective analysis by analyzing and interpreting all data in blinded fashion. Although no echocardiograms were believed to be uninterpretable, some were of marginal quality (technically difficult).

Many patients in our study did not necessarily achieve target heart rate. Some of the studies were stopped when the patient's heart rate was within 10–15 beats of target despite receiving atropine. Cohen et al[5] did a comparative analysis to determine the sensitivity and specificity of detecting coronary artery disease using 85% of the patient's maximal age predicted heart rate as an endpoint for terminating a pharmacologic stress test. They found that dobutamine-induced ischemia was produced at an average of 58% of the maximal predicted heart rate. Their study concluded that 85% as a cut-off point may be excessively high and that achieving 85% of target rate did not necessarily yield new diagnostic information. They also calculated and compared the myocardial oxygen demand in healthy and diseased myocardium in the presence of increased pharmacologic stress and found that the workload on the heart did not appear to greatly increase with atropine administration (dobutamine *vs.* atropine = $P > 0.001$). The results of our study showed similar results.

Some patients in our study were stressed while on their current cardiac medications, and as a result, a large percentage of did not achieve target heart rate with dobutamine administration. A study by Sawada et al[6] looked at the overall sensitivity and specificity of beta-blockers on stressed myocardium and concluded that the doses of dobutamine administered to patients receiving beta-blockers were not increased significantly above the doses given to those who were not. Additionally, their data showed that 15 of 17 patients who had normal baseline echocardiograms and were taking beta-blockers had stress-induced wall motion abnormalities with dobutamine administration. They concluded that beta-blockers had a minimal effect on the induction of ischemia in the presence of coronary artery disease when the heart was being stressed with dobutamine.

Conclusion

Coronary artery disease remains one of the leading causes of death in the United States. Americans who smoke, have high blood pressure, are overweight, and do not exercise are at a particularly high risk for developing the fibrous fatty plaque that is responsible for causing a decrease in blood supply to the myocardium.

A myocardial infarction often results with increased physical activity. The heart is forced to work harder requiring more oxygen. In the presence of vessel disease, blood flow is cut off to the surrounding myocardium, causing tissue starvation and ultimately tissue death. Myocardial ischemia is a good marker of an impending myocardial infarction. Many studies have indicated that if ischemic events can be reproduced during exercise or during a pharmacologic stress test, a myocardial infarction may be prevented. Early detection is the key to improving the patient's quality of life. If the stage of the disease is early enough in its course, patients might be able to reduce their risk factors, decreasing the risk of mortality associated with a myocardial infarction.

For patients who are unable to exercise, dobutamine stress echocardiography has been widely proven to be an accurate, safe, and practical tool in the detection of coronary artery disease. Dobutamine's inotropic properties reproduce the effects of physical exercise on the heart. It would appear that the inotropic stimulus of dobutamine is the major factor that causes the reproduction of ischemic events in the myocardium during a dobutamine stress echocardiography test. Although the chronotropic stimulus of atropine allowed patients to achieve their target heart rate, it did not produce a significant amount of stimulus needed for myocardial ischemic events. As a result, we concluded that the chronotropic effects of atropine may not be necessary in a dobutamine stress echocardiography test.

Additional investigation should be done to reassess what the best criteria for an endpoint to dobutamine stress echocardiography should be. The endpoint should yield the highest diagnostic accuracy and not subject the patients to additional stress, discomfort, or increased risk.

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References

1. Porth C: *Pathophysiology Concepts in Altered Health States*. Philadelphia, JB Lippincott Company, 1994.
2. McNeill J, Paolo M, Fioretti, et al: Enhanced sensitivity for detection of coronary artery disease by atropine to dobutamine stress echocardiography. *Am J Cardiol* 1992; 70:41–46.
3. Mazeika P, Nadazdin A., et al: Dobutamine stress echocardiography for detection and assessment of coronary artery disease. *J Am Coll Cardiol* 1992;19:1203–1214.

4. Cohen J, Ottenweller J, Achenkunju K, Duvvuri S: Comparison of dobutamine and exercise echocardiography for detecting coronary artery disease. *J Am Coll Cardiol* 1993; 72:1226–1231.
5. Sawada S, Segar S, Ryan T, et al: Echocardiographic detection of coronary artery disease during dobutamine infusion. *Circ Res* 1991;83:1605–1614.
6. Tuttle R, Mills J: Development of a new catecholamine to selectively increase cardiac contractility. *Circ Res* 1975; 36:185–196.
7. Poldermans D, Fioretti PM, Forster T, et al: Dobutamine stress echocardiography for assessment of perioperative cardiac risk in patients taking beta blockers. *Eur Heart J* 1994;15:355–360.