Effects of Prolonging Peak Dobutamine Dose During Stress Echocardiography

NEIL J. WEISSMAN, MD, FACC, GEOFFREY A. ROSE, MD,* GARY P. FOSTER, MD,* MICHAEL H. PICARD, MD, FACC*
Washington, D.C. and Boston, Massachusetts

Objectives. This study sought to test whether the physiologic advantage of a prolonged dobutamine stage during stress echocardiography can be effectively combined with a clinically practical infusion protocol.

Background. Dobutamine has a half-life of 2 min and requires up to 10 min to achieve steady state. Despite these known pharmacodynamics, dobutamine stress echocardiography is routinely performed by advancing doses at 3-min intervals. Canine studies have shown that dobutamine stress echocardiography end points will occur at a lower dose if each stage is prolonged, but these findings have yet to be used in the clinical setting.

Methods. The standard 3-min dobutamine dose stage during stress echocardiography was modified by extending the peak dose (40 μg/kg body weight per min) for an additional 2 min. Consecutive patients underwent this modified protocol to test whether the requirement for atropine could be reduced. According to this modified protocol, if a dobutamine stress echocardiographic end point (85% of maximal predicted heart rate, new wall motion abnormalities, hypotension, arrhythmia or intolerable symptoms) was not reached at 3 min of the peak dose, this dose was prolonged for an additional 2 min. If a dobutamine stress echocardiographic end point was still not attained, atropine (up to 1.0 mg intravenously) was administered.

Results. The study included 84 patients, 22 of whom (26.2%) achieved a dobutamine stress echocardiographic end point using the standard 3-min stage. Of the 62 patients who did not reach an end point in the initial 3 min of peak dobutamine dose, the additional 2 min of dobutamine increased heart rate (from 99.6 ± 23.8 to 107.2 ± 23.2 beats/min, p<0.01) and allowed 20 patients (32.3%, p<0.01) to attain an end point. Of the remaining 42 patients, 23 never achieved a stress echocardiographic end point, despite 1.0 mg of atropine. One patient developed supraventricular tachycardia during the additional 2 min of dobutamine, and one developed nonsustained ventricular tachycardia after receiving atropine.

Conclusions. These data demonstrate that a significant number of patients (32%) who do not reach a dobutamine stress echocardiographic end point with the standard protocol can safely attain an end point solely by extending the duration of the peak dose. Adoption of this strategy may reduce the need for supplemental atropine and its potential adverse effects.

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Despite the wide acceptance of dobutamine stress echocardiography as a noninvasive method for detecting myocardial ischemia, a lack of protocol standardization persists. In the United States, dobutamine protocols most commonly use 3-min stages of increasing dobutamine doses. However, dobutamine stage duration was adopted from the standard Bruce protocol used in exercise treadmill tests without consideration of dobutamine pharmacokinetics (1,2). The pharmacologic half-life of dobutamine is 2 min, with steady state not obtained for up to 10 min (3,4). Thus, 3-min dobutamine stage results in advancing the dose before achieving steady state.

Using a canine model, we previously showed (5) that prolonging the duration of infusion of each dobutamine dose stage will result in a greater hemodynamic effect at lower doses, which may improve test accuracy without requiring additional pharmacologic agents or higher dobutamine doses. In addition, dobutamine stress echocardiographic end points were achieved at a lower dobutamine dose with prolonged stages (5). The limitation of 3-min stages has been recognized clinically in the assessment of myocardial viability, where low dose dobutamine is typically extended for at least 5 min (6–8). Although a logical approach to dobutamine stress testing based on dobutamine pharmacodynamics would be to extend the duration of each dobutamine stage to 10 min, such a long test is not practical in the clinical setting. In an attempt to balance drug effect with a test design of practical duration, we hypothesized that the beneficial effects of a prolonged stage could be attained by extending the peak dobutamine dose.
therefore chose to test whether modifying the 40-μg/kg body weight per min dobutamine dose by extending it an additional 2 min would result in a greater proportion of patients reaching an end point while reducing the need for atropine.

**Methods**

**Patient selection.** Eighty-four consecutive patients presenting for diagnostic dobutamine stress echocardiography to the echocardiography laboratories at the Massachusetts General Hospital (n = 54) and Georgetown University Hospital (n = 30) without exclusion criteria were enrolled in the study. Exclusion criteria included a myocardial infarction within 3 days, unstable rest angina requiring intravenous nitroglycerin, recent ventricular tachycardia, uncontrolled atrial fibrillation, Wolff-Parkinson-White syndrome or contraindication to atropine. Concurrent medications were continued at the discretion of the referring physician. Whenever possible, beta-adrenergic antagonists were held for at least 24 h before stress echocardiography. All patients gave written informed consent to participate in the stress echocardiographic protocol.

**Modified dobutamine protocol.** All dobutamine stress tests were performed under continuous 12-lead electrocardiographic (ECG) and noninvasive blood pressure monitoring. After obtaining rest heart rate, blood pressure and left ventricular two-dimensional echocardiographic images, the dobutamine infusion was initiated. Dobutamine was infused in 3-min stages with increasing doses of 5, 10, 20, 30 and 40 μg/kg per min. At the end of each dose, standard two-dimensional echocardiographic images of the left ventricle, a 12-lead ECG and blood pressure were obtained. End points for termination of the dobutamine infusion included new wall motion abnormalities, 85% of maximal predicted heart rate, sustained arrhythmias, intolerable symptoms or hypotension (decrease in systolic blood pressure >20 mm Hg). Echocardiographic images were recorded onto 0.5-in. VHS videotape for subsequent analysis. In addition, individual cardiac cycles of four left ventricular views (parasternal long and short axis and apical four and two chamber) at baseline, low dose and peak stress were digitized in a standard quad screen format that allowed on-line side by side comparison. The on-line assessment of wall motion and hemodynamic response to dobutamine was made independently by experienced echocardiographers (N.J.W., M.H.P.).

If an end point was not obtained at the end of the 3-min stage at 40 μg/kg per min of dobutamine, then the ECG, hemodynamic and echocardiographic images were recorded, and the dobutamine infusion was continued for an additional 2 min. Hemodynamic, ECG and left ventricular echocardiographic images were recorded again, and if the patient still did not reach a dobutamine stress echocardiographic end point, atropine (up to 1.0 mg) was administered intravenously. No further pharmacologic stress beyond dobutamine (40 μg/kg per min for a total cumulative dose of 395 μg/kg) and atropine (1.0 mg total) was administered.

**Table 1. Hemodynamic Variables at Peak Dobutamine Stages**

<table>
<thead>
<tr>
<th>Dobutamine (40 μg/kg per min)</th>
<th>3-min Duration (n = 73)</th>
<th>5-min Duration (n = 62)</th>
<th>Atropine* (n = 42)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR (beats/min)</td>
<td>100 ± 24</td>
<td>107 ± 23†</td>
<td>129 ± 19†</td>
</tr>
<tr>
<td>SBP (mm Hg)</td>
<td>154 ± 33</td>
<td>149 ± 33</td>
<td>163 ± 37</td>
</tr>
</tbody>
</table>

*After administration of atropine up to a maximum of 1.0 mg if no end point was obtained with a lower dose. †p < 0.01 versus heart rate (HR) at 3-min duration. §p < 0.001 versus heart rate at 5-min duration. Data presented are mean value ± SD. SBP = systolic blood pressure.

**Statistical analysis.** Results are expressed as mean value ± SD. A paired, two-tailed Student t test was used to compare the hemodynamic responses with the 3- and 5-min dobutamine infusion protocols at 40 μg/kg per min. The proportion of patients attaining a dobutamine stress echocardiographic end point, thus avoiding the need for atropine because of the prolonged infusion protocol, was assessed with a Fisher exact test. Only p values ≤0.05 were considered significant.

**Results**

**Patients.** Eighty-four patients (55 men, 29 women; mean age 61.3 ± 14.4 years, range 21 to 83) were enrolled in the study. Before the stress test, rest heart rate was 74 ± 13 beats/min and systolic blood pressure 142 ± 26 mm Hg. Sixteen (19%) of 84 patients were taking beta-adrenergic blocking medication, which was present for 12 to 24 h in 19 patients (23%).

Of the 84 patients enrolled, 11 (13%) reached a dobutamine stress echocardiographic end point before the 40 μg/kg per min dose (n = 3 at 20 μg/kg per min; n = 8 at 30 μg/kg per min). Sixty-two of the 73 patients who reached 40 μg/kg per min underwent a prolonged infusion because they failed to reach an end point with the standard 3-min stage. As displayed in Table 1, heart rate increased from 100 ± 24 to 107 ± 23 beats/min (p < 0.01) with the longer peak dose stage, but blood pressure did not change (154 ± 33 vs. 149 ± 33 beats/min, p = NS). The additional 2 min of dobutamine allowed 20 (32.3%) of the 62 patients to reach an end point and thus avoid atropine (p < 0.01). The end points reached included 85% of maximal predicted heart rate (n = 9), new wall motion abnormalities (n = 6), hypotension (n = 2), intractable symptoms (palpitations [n = 1], “nervousness” [n = 1]) and development of supraventricular tachycardia (n = 1).

Among the 42 patients who did not reach an end point with the prolonged peak dobutamine dose, all received atropine (0.74 ± 0.29 mg), with a resulting heart rate increase of 27.7 ± 19.9 beats/min (p < 0.001). Of these patients, 16 (38.1%) achieved target heart rate, 1 developed a new wall motion abnormality, 1 complained of intolerable palpitations, and 1 developed nonsustained ventricular tachycardia with atropine. Therefore, a total of 19 (45.2%) of 42 patients who did not reach a test end point with the prolonged dobutamine infusion did obtain an end point with atropine. Among the 42 patients

![Image](image-url)
who required atropine, 54.8% (23 of 42) never achieved a test end point despite administration of the maximal atropine dose (1.0 mg). As displayed in Table 2, the end points responsible for test termination at each of the peak stages were similar for standard duration dobutamine, prolonged peak dobutamine or atropine. Of the nine patients whose test was positive due to a new wall motion abnormality, eight (89%) developed this end point without the need for atropine. Figure 1 is a flow diagram that summarizes the response of all patients enrolled in the study and the dose at which an end point was achieved.

For those patients who did not reach an end point at 3 min of 40 μg/kg per min, rest heart rate, age and gender were not predictive (p = NS) of prolonged infusion effectiveness or atropine effectiveness. Similarly, concurrent beta-adrenergic blocking medication was not associated with the final dobutamine dose, ability of a prolonged infusion to reach an end point, or ability of atropine to reach an end point. This may be due to the small number of patients taking concurrent beta-blocker therapy (n = 16). Higher heart rate at the end of 3 min of the peak dobutamine dose was the only variable predictive of a prolonged infusion success (108 ± 12 vs. 87 ± 19 beats/min, p < 0.001).

**Discussion**

Dobutamine pharmacodynamics requires up to 10 min to reach steady state and exert its full hemodynamic effect (3,4). Therefore, stress echocardiography performed with 3-min stages reach peak physiologic stimulation through a series of transient escalating doses of dobutamine that summate without ever reaching steady state, and the full effect of any one dose of dobutamine is not attained before the elevation of the dobutamine dose to the next level. Thus, prolonging the stage duration, even by a few minutes, would allow the dobutamine dose to approach its potential physiologic effect. This effect has been previously confirmed in a canine model (5) in which a 5-min dobutamine stage allowed dobutamine stress echocardiographic end points to be attained at a lower dobutamine dose than 3-min stages (5). In the purist sense, dobutamine stress echocardiographic protocols would use 10-min stages so that the full potential of each dobutamine dose could be realized before advancing to the next dose, but the duration of such a test must be balanced with clinical practicality. The approach in this study, as an initial step, was to extend the 40 μg/kg per min dobutamine dose to gain more of the physiologic effects of the peak dose without excessively prolonging the protocol. This simple modification resulted in an additional 32% of the patients reaching a dobutamine stress echocardiographic end point, thus avoiding the need for atropine.

**Value and limitation of dobutamine stress testing.** Pharmacologic stress testing has become a routine diagnostic tool in clinical practice because of the high proportion of patients with suspected coronary disease who are unable to adequately exercise. Because of the low sensitivity of ECG changes with pharmacologic stress (9,10), imaging is required. Echocardiography in conjunction with dobutamine has a high sensitivity and specificity for the diagnosis of occlusive coronary disease, application in a wide range of patients, easy integration into current echocardiography laboratories and comparable safety to other forms of stress testing (1,11,12). However, the rapid
deployment of dobutamine stress echocardiography has resulted in the widespread use of an infusion protocol that is based on exercise physiology rather than dobutamine pharmacodynamics. Consequently, dobutamine stress protocols require more time than most exercise protocols, may not reach a predetermined heart rate without the addition of a supplemental pharmacologic agent, require a prolonged period of recovery and might not be as effective in the presence of concomitant beta-adrenergic antagonists (13,14).

**Advantages of modified dobutamine protocol.** The positive inotropic and chronotropic stimulation from dobutamine, which increases myocardial oxygen demand, is coupled through the same beta_2-adrenergic receptor (15,16). Because the physiologic response to dobutamine is linearly related to plasma dobutamine levels (17), prolonging dobutamine infusions results in a greater myocardial oxygen demand by increasing the dobutamine plasma level. This finding has been confirmed by Poldermans et al. (18) in an initial study measuring the catecholamine response to a prolonged low dose dobutamine infusion that demonstrated a progressive increase in heart rate during the first 9 min. Likewise, the increase in heart rate seen in our study is probably due to an increased plasma dobutamine level stimulating a greater proportion of the adrenoreceptors. When the adrenoreceptors are occupied by adrenergic antagonists, the response to dobutamine will be dependent on the level of beta-blockade, dobutamine plasma levels and the underlying catecholamine state/left ventricular function of the patient (19,20). This represents another clinical setting in which prolonging the dobutamine infusion would provide higher plasma levels of dobutamine to potentially overcome the beta-blockade. Only a minority of patients in this study were receiving beta-blockade therapy, and they constitute a heterogeneous group with varying levels of beta-blockade and underlying catecholamine stimulation. A controlled study measuring beta-receptor activity before dobutamine infusion would further elucidate the value of prolonging peak stage duration in these patients.

Extending the final dobutamine dose is a practical alternative to the standard 3-min stage. This modified protocol allows dobutamine stress echocardiography to start at conventional low doses and step up at a rapid rate to peak dose while providing a means to avoid atropine in some patients. During the present protocol, three patients were not entered into the study because they were not candidates for atropine due to preexisting medical conditions. In all three patients, target heart rate was achieved by extending the 40-mg/kg per min dose: But is the avoidance of atropine necessary or even beneficial? Dobutamine–atropine stress testing is widely used, with a low incidence of severe adverse effects (1). Atropine reliably increases heart rate and improves the sensitivity of dobutamine stress echocardiography, especially in patients receiving beta-blockade therapy (13). The goal of stress echocardiography is to detect inducible ischemia by increasing myocardial oxygen demand. Atropine increases oxygen demand by increasing heart rate but has a minimal effect on the other determinants of myocardial oxygen, such as left ventricular contractility and wall tension (21). It is therefore not surprising that the recent study by Ling et al. (22), investigating the incremental value of atropine during dobutamine stress echocardiography, demonstrated only a modest influence of atropine on overall diagnostic sensitivity. Because dobutamine provides both inotropic and chronotropic stimulation, a greater increase in myocardial oxygen demand is expected for a given increase in heart rate produced by dobutamine than by atropine. This increased oxygen demand could improve sensitivity by inducing ischemia in the setting of a mild obstruction to flow, which may have otherwise gone undetected, or produce ischemia at an earlier stage for an equivalent stenosis. Prolonged dobutamine stages may therefore improve sensitivity over the standard dobutamine–atropine protocol. This improved sensitivity is supported by the finding that six (67%) of nine patients with inducible wall motion abnormalities were detected by the prolonged dobutamine arm. In fact, atropine only induced a new regional wall motion in 1 (2%) of 42 patients who did not respond to the prolonged dobutamine infusion. In concordance with previous studies, the majority of patients with obstructive coronary stenoses are detected before the addition of atropine (22). Atropine after a prolonged dobutamine stage may solely increase heart rate to the target rate (in 16 of 42 patients), with a marginal contribution to the primary purpose of dobutamine stress echocardiography—detection of significant coronary stenosis. Further investigation will be necessary to determine the risk/benefit ratio of prolonging the peak dobutamine stage.

**Application of modified dobutamine protocol.** Clinical identification of patients who would benefit from the prolonged peak dobutamine infusion may be difficult. Clearly, patients who do not reach an adequate heart rate with the current dobutamine stress echocardiographic protocol and are not candidates for atropine (because of narrow-angle glaucoma, myasthenia gravis, obstructive uropathy or obstructive gastrointestinal disorder) would benefit from the prolonged dobutamine infusion. Fortunately, patients who fall into this category are rare. It would be ideal to prospectively identify patients in which prolonged dobutamine infusion will be successful. Other preliminary reports (23) suggest that heart rate at the 20 mg/kg per min stage may be predictive of chronotropic incompetence at the peak dobutamine stage. In our study, only heart rate at the end of 3 min at 40 mg/kg per min was predictive of attaining target heart rate with the prolonged infusion. A reasonable approach would therefore be to select those patients who are close to, but not at, target heart rate at the end of the current dobutamine stress echocardiographic protocol for additional dobutamine rather than atropine. Because there were no pretest characteristics that were able to predict who would respond to the prolonged infusion, a larger study investigating the utility of prolonged dobutamine infusions in selected patient groups is necessary to clarify its clinical role.

**Limitations of the study.** The small sample size of the present study precludes adequate analysis of clinically relevant subgroups, such as those receiving concomitant beta-blocker...
therapy. Beta-antagonists attenuate and delay the dobutamine response (14). Prolonged dobutamine infusion provides a higher serum level of beta-agonists that should overcome the beta-blockade and counteract the attenuated response. Thus, patients taking beta-blockers should especially benefit from the modified protocol; however, the small number of patients (n = 16) receiving varying levels of beta-blocker therapy in this study precludes adequate analysis.

The results of any investigation of a diagnostic test depend on the patients studied. In our study, the majority of patients were men between 50 and 70 years old, with a moderate pretest likelihood of coronary disease. Our results would apply to this patient cohort but need to be further assessed before application in patients with a different pretest likelihood of disease.

The present study was designed to test the feasibility of a modified dobutamine infusion protocol that used an extended peak dose, but it does not provide a head to head comparison of different protocols (24). Thus, future studies are necessary to determine how the extended peak infusion protocol compares with standard dobutamine and dobutamine-atropine protocols.

Conclusions. We showed that a simple modification of the dobutamine stress infusion protocol is feasible and can increase test sensitivity and decrease the need for atropine. Further evaluation of extended dobutamine infusions will be necessary to determine the optimal protocol for stress echocardiography.

References
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