Atropine as an adjunct to supine bicycle stress echocardiography: an alternative strategy to achieve target heart rate or rate pressure product

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Aims
To investigate the use of atropine to achieve target heart rate (THR) and rate pressure product (RPP) during supine bicycle exercise stress echocardiography (SBESE) to increase the number of diagnostic stress tests.

Methods and results
Forty-four patients that were unable to achieve THR or RPP during SBESE performed to evaluate ischaemia were given 0.4–1.2 mg of atropine to augment THR and RPP. After atropine (0.7 ± 0.3 mg) the maximum heart rate (HR) achieved was 133 (± 16) bpm, mean THR was 82% (±8%), and average RPP was 22 716 (± 4915) b/min × mmHg. Of the patients with a non-diagnostic SBESE, with the use of atropine 80% of those patients achieved a diagnostic test. There were no major adverse affects from the administration of atropine.

Conclusion
The use of atropine to augment the HR or RPP during SBESE (i) is safe; (ii) enables the assessment of ischaemia at peak effort; and (iii) allows assessment of exercise haemodynamics in patients with sub-maximal exercise capacity and chronotropic incompetence.

Keywords
Atropine • Stress echocardiography • Exercise echo

Introduction
Exercise as well as pharmacologic stress testing is used for the non-invasive detection of obstructive coronary artery disease (CAD) based on the presence of stress-induced myocardial ischaemia.1 Compared with pharmacological stress testing, exercise stress testing has a higher sensitivity and specificity in detecting CAD in subjects who have an adequate chronotropic response to exercise.2–4 In order to assess for inducible ischaemia, patients must be able to exercise to achieve at least 85% of their maximum age-predicted heart rate (MPHR).2–4 However, a significant number of subjects (23–39%) do not reach their target heart rate (THR), either due to chronotropic incompetence or due to sub-maximal exercise capacity.5–9 Pharmacological stress testing with dobutamine is used to induce ischaemia by triggering an increase in myocardial oxygen demand through an increase in the heart rate (HR) and rate pressure product (RPP).10,11 Atropine is an anticholinergic drug that also causes a rapid increase in the HR, and has been commonly used in pharmacological stress test protocols.11–14 The safety of intravenous atropine in doses ranging from 0.5 to 2 mg and its use with dobutamine as an adjunct to augment HR have been studied and validated.14–17 Supine bicycle exercise stress echocardiography (SBSE) has the advantage of allowing echo assessment of sequential wall motion during exercise and at peak exercise, and avoids a drop in the HR during peak exercise and imaging as occurs with treadmill stress echo. Unfortunately, compared with treadmill stress testing, an inadequate or blunted HR response is more common
during SBESE. While atropine administration during treadmill stress and single photon emission computed tomography testing (SPECT) has been reported, there are no prior studies on the utility of intravenous atropine in SBESE. In our stress echo laboratory, we have found that a significant number of our patients have had sub-optimal or non-diagnostic SBESE studies due to an inadequate THR or RPP. Because of this, we recently (April 2009) started administering atropine as part of the clinical stress echo test when the THR (≥85% MPHR) or a RPP ≥20 000 was not achieved in order to augment the HR and blood pressure response to supine exercise. This study was done to evaluate the utility of intravenous atropine to augment HR or RPP during SBESE in patients who failed to achieve their target HR or RPP.

Methods

Study population
We reviewed consecutive stress echocardiograms from August of 2008 to March of 2009 (a time period prior to our use of atropine) to determine the prevalence of inadequate studies due to a failure to reach THR or a RPP ≥20 000 during SBESE. Then, from 21 December 2009 to 14 February 2011 we identified 44 patients (26 women, mean age 55 ± 13 years) being evaluated for CAD that were given atropine to augment THR and/or RPP after failing to achieve 85% of MPHR or RPP ≥20 000 during SBESE.

Exercise protocol and monitoring
All patients underwent SBESE with a variable load (25–200 W) as dictated by the echocardiologist’s perceived fitness of the patient. Supine bicycle ergometer (Medical Positioning Kansas city, MO, USA) was used with a head tilt of up to 20° to obtain optimal echocardiographic images. The twelve-lead electrocardiogram (ECG) was continuously monitored and blood pressure determined at a minimum of 2-min intervals during exercise, at peak stress, and at recovery. Maximal and per cent of MPHR achieved, systolic blood pressure, diastolic blood pressure, baseline and peak RPP, number of metabolic equivalents (METS) achieved, resistance on the bicycle, test duration, and total dose of atropine administered was recorded. The stress test was terminated in accordance with recommendations for stress testing if there were ST-segment shifts for ischaemia ≥2 mm, extreme fatigue, excessive blood pressure rise (systolic blood pressure ≥240 mmHg, diastolic blood pressure ≥120 mmHg), achievement of target HR (≥85% of MPHR (MPHR is defined as 220 bpm—age)), achievement of RPP ≥20 000 (RPP as product of HR and systolic blood pressure), maximum dose of atropine 1.2 mg, sustained arrhythmia, severe angina, or intolerable side effects. Resistance was decreased when patients could no longer cycle at 60 rpm consistently.

Supine bicycle exercise stress echocardiography protocol
After obtaining the rest images from the standard parasternal and apical views, patients pedalled at constant speed (60 rpm) beginning at a workload of 25–50 W and increasing by 25 W every 1–2 min. Parasternal long-axis, short-axis, apical two-, three-, and four-chamber views were acquired in the supine position at rest and peak exercise with the following ultrasound systems—Sequoia ultrasound (Simens/Acuson, Mountain View, CA, USA), Logiq E9 (General Electric, Watertown, WI, USA) and Philips iE33 (Phillips Medical Systems, Andover, MA, USA). Imaging was facilitated with lateral tilting of the bicycle up to 25° during acquisition. Digitized echocardiographic images at baseline and peak exercise were recorded in a continuous loop format and selected loops were displayed side by side in a quad screen format according to a standard protocol. All tests were interpreted by an experienced echocardiologist at the Cedars-Sinai Center Noninvasive Laboratory. Segmental left ventricular wall motion was evaluated according to the recommendations of the American Society of Echocardiography using a 16-segment left ventricular model. Wall motion scoring was as follows: normal or hyper dynamic, hypokinesis, akinesis, and dyskinesis. A normal response was defined as a normal or hyperdynamic function during exercise; ischaemia as the development of new wall motion abnormality or worsening of resting hypokinesia, whereas a fixed abnormality was defined as a wall motion abnormality that did not change during stress. The SBESE images were also analysed by a different reader who was blinded to the study to avoid intra-observer bias. The ejection fraction was calculated using biplane Simpson’s method.

Atropine protocol
In these 44 patients who were unable to reach target HR, atropine was given intravenously in doses of 0.4 mg each 1 min apart, up to a maximum of 1.2 mg with continuous ECG monitoring. Any adverse events associated with atropine administration were recorded.

Recovery
All patients were monitored for symptoms and adverse events until the HR and blood pressure reached the baseline.

Results

Of the 274 SBESE studies reviewed from August of 2008 to March of 2009 before the use of atropine, there were 24 patients (9%) who did not reach THR. The mean THR achieved in the suboptimal study group was 76 ± 6% of MPHR. From 21 December 2009 to 14 February 2011, 615 patients underwent SBESE, of which 44 (7%) patients were not able to achieve RPP ≥20 000 or 85% of MPHR. Consequently, these patients were given intravenous atropine. The average age was 57 ± 12 years (18 males and 26 females). All patients were referred for evaluation of CAD or ischaemia.

Exercise haemodynamics
Table 1 summarizes the haemodynamic changes during SBESE at baseline and peak stress.

ECG, heart rate, and rate pressure product response
All patients had non-ischaemic baseline ECG characteristics (normal or non-specific ST-T changes). The HR at baseline was 69 ± 11 and 133 ± 16 bpm at peak stress. The mean intravenous atropine dosage administered was 0.7 ± 0.3 mg (range 0.4–1.2 mg). At the time when atropine was given, the HR was 114 ± 11 bpm (69% ± 7% of MPHR). Target HR achieved at peak stress was 82 ± 8%. Mean RPP at rest was 9362 ± 2381 and 22 716 ± 4615 mmHg × bpm at peak stress (Table 1). After administration of intravenous atropine, 21 (48%) patients achieved...
85% of MPHR but failed to achieve RPP of ≥ 20,000. Of the nine patients who did not achieve both 85% of MPHR and RPP ≥ 20,000; one (2%) patient achieved 85% of MPHR but failed to achieve RPP of ≥ 20,000. Two (4.5%) patients had symptoms of angina and also new wall motion abnormalities during stress and, thus, the SBESEs were terminated before achieving THR or target RPP. Of 20 patients who did not achieve 85% of MPHR, 11 patients achieved target RPP ≥ 20,000. The percentage of MPHR achieved by these 11 patients was 74–84%.

Thus, the test became diagnostic with atropine in patients who otherwise would have had a non-diagnostic SBSE, with the use of atropine, 80% achieved a diagnostic stress test by either achieving an adequate MPHR (≥ 85%) or RPP (≥ 20,000), or with evidence of ischaemia on echo or with the onset of chest pain.

Exercise performance during stress testing is a strong predictor of future cardiac events. Referral for cardiac catheterization in stable patients is determined by an ischaemic response to stress testing. Cardiac stress tests that are non-diagnostic frequently lead to additional stress testing, which entails added cost and possible morbidity.25 Non-diagnostic stress testing can also lead to inappropriate clinical management as patients with an inadequate HR response to exercise may have a false-negative test. In our laboratory, we found that between 7 and 9% of patients have a suboptimal response to the maximum dose of atropine. The mean exercise duration was 8.5 ± 4 min. At peak stress the maximum workload achieved was 123 ± 52 W and 7 ± 2 METS.

## Echocardiography

Most patients (43/44, 98%) had normal wall motion at rest. The calculated left ventricular ejection fraction at baseline was 63 ± 5 and 74 ± 6% at stress. Six (14%) patients had wall motion abnormalities consistent with ischaemia in response to atropine, two of whom had abnormalities before reaching peak stress for which the test was stopped. The estimated pulmonary artery systolic pressures were normal at baseline and during stress in all patients. In total, six patients developed new segmental wall motion abnormalities during the exercise–atropine stress echo. One patient with baseline apical hypokinesis had worsening of the apical wall motion at peak stress consistent with ischaemia; this patient was also found to have evidence of inducible ischaemia in the apical area by myocardial perfusion scan. The other five patients had normal wall motion at baseline but developed segmental regional wall hypokinesis at peak stress.

## Complications

There were no arrhythmias, hypertensive or hypotensive responses, or other complications during the stress test or recovery. Blood pressure and HR reached baseline in all patients during recovery. The most common complaints among patients were leg cramps and fatigue. There were no major side effects associated with intravenous atropine in any patient.

## Discussion

This is the first study to evaluate the utility of atropine for augmentation of the HR or RPP during SBESE testing. This study demonstrates that atropine is efficacious in augmenting the HR and RPP response to exercise in patients undergoing SBESE. Of the patients who otherwise would have had a non-diagnostic SBSE, with the use of atropine, 80% achieved a diagnostic stress test by either achieving an adequate MPHR (≥ 85%) or RPP (≥ 20,000), or with evidence of ischaemia on echo or with the onset of chest pain.

### Table 1 Haemodynamic parameters at baseline and peak stress

<table>
<thead>
<tr>
<th>n = 44</th>
<th>Baseline</th>
<th>Peak stress</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate, bpm</td>
<td>69 ± 11</td>
<td>133 ± 16*</td>
</tr>
<tr>
<td>% Target HR</td>
<td>NA</td>
<td>82 ± 8*</td>
</tr>
<tr>
<td>Systolic blood pressure, mmHg</td>
<td>134 ± 16</td>
<td>174 ± 22</td>
</tr>
<tr>
<td>Diastolic blood pressure, mmHg</td>
<td>80 ± 14</td>
<td>86 ± 16</td>
</tr>
<tr>
<td>Rate pressure product (RPP), mmHg x bpm</td>
<td>9362 ± 2381</td>
<td>22 716 ± 4615</td>
</tr>
<tr>
<td>% Reaching MPHR ≥ 85% and RPP ≥ 20,000</td>
<td>N/A</td>
<td>48 (n = 21)</td>
</tr>
<tr>
<td>% Reaching MPHR ≥ 85% only</td>
<td>N/A</td>
<td>2 (n = 1)</td>
</tr>
<tr>
<td>% Reaching RPP ≥ 20,000 only</td>
<td>N/A</td>
<td>25 (n = 11)</td>
</tr>
<tr>
<td>% Stopped due to angina</td>
<td>N/A</td>
<td>4.5 (n = 2)</td>
</tr>
<tr>
<td>% Not reaching MPHR ≥ 85% or RPP ≥ 20,000</td>
<td>N/A</td>
<td>20 (n = 9)</td>
</tr>
</tbody>
</table>

HR, heart rate; bpm, beats per minute; MPHR, maximum predicted heart rate; NA, not applicable.

*The heart rate at time of atropine was 114 ± 11 bpm and 69 ± 7% of MPHR.

### Figure 1 Supine bicycle stress echocardiography results. THR, target heart rate; RPP, rate pressure product.
The physiological mechanism of chronotropic incompetence is often not clear, and in some patients this may represent a form of sick sinus syndrome.\textsuperscript{5–7} Atropine results in a prompt increase in HR through parasympathetic blockade.\textsuperscript{26} When administered intravenously, atropine decreases sinus node recovery time and improves conduction through the atrioventricular node, resulting in a rapid increase in the HR.\textsuperscript{26} Intravenous atropine has also been studied during exercise myocardial perfusion SPECT, and has been shown to be useful for augmenting the HR in patients with a blunted HR response to exercise.\textsuperscript{10–22} Its safety and feasibility in exercise SPECT and with dobutamine in pharmacological stress echocardiography has also been reported.\textsuperscript{14–17,20,22} There are extensive data on pharmacological stress testing, particularly the use of dobutamine, and its sensitivity in diagnosing ischaemia in patients in whom exercise stress testing cannot be performed.\textsuperscript{10,11} However, dobutamine infusion has a 15–28\% rate of hypotension in older patients.\textsuperscript{3,27,28} The use of intravenous atropine, along with dobutamine, improves the sensitivity of the test without losing the specificity.\textsuperscript{13,14} Intravenous atropine (0.4–2 mg), in the absence of contraindications, is well tolerated and without major side effects.\textsuperscript{19–22}

The ability to assess exercise capacity and measure the RPP at peak exercise allows a more accurate assessment of ischaemia. RPP correlates well with oxygen consumption during exercise and is a better prognostic predictor of CAD than the maximal HR and blood pressure alone.\textsuperscript{29} With exercise–atropine SBESE, the patient’s exercise capacity can be assessed, followed by the administration of atropine to augment HR or RPP which allows the physician to assess the ischaemic response and permits a detailed assessment of exercise haemodynamics. In our study, we were able to increase the diagnostic yield of the test after administering atropine to our patients, and there were no significant side effects from the atropine.

**Study limitations**

The small sample size (n = 44) and the retrospective nature of our study are the major limitations. Also, given the safety profile of atropine, in the future we would recommend a maximum dose of 2 mg iv, which may reduce the number of inadequate tests. In centres where patients do not routinely have an intravenous inserted for stress testing, the stress test would need to be terminated in order for the patient to have an intravenous placed and the patient would need to resume exercise and have atropine administered if THR is not achieved. We recognize this is somewhat of a disadvantage if patients do not receive an intravenous prior to exercise testing. Nonetheless this approach may still be better than referring the patient for another form of stress testing. However, in our laboratory, we routinely insert an intravenous in all patients undergoing stress echocardiography so that we have intravenous access should we need to administer LV contrast for optimal image quality and assessment of segmental wall motion, or need to give atropine to help achieve THR.

**Conclusion**

In this study of patients undergoing SBESE who were not able to achieve the target HR, or RPP, the use of atropine converted 80% of non-diagnostic studies into diagnostic stress echocardiograms by increasing the patients THR and/or RPP response during exercise. SBESE with atropine appears to provide an easy and feasible alternative to pharmacological stress in patients with a blunted HR response to exercise.

**Conflict of interest:** none declared.

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