The Diagnostic Value of Adenosine Stress-Contrast Echocardiography for Diagnosis of Coronary Artery Disease in Hypertensive Patients: Comparison to TI-201 Single-Photon Emission Computed Tomography

Constadina Aggeli, Euaggelia Christoforatou, Georgios Giannopoulos, Georgios Roussakis, Christos Kokkinakis, John Barbetseas, Charalambos Vlachopoulos, and Christodoulos Stefanadis

Background: The use of the vasodilating agent adenosine as stressor in conjunction with myocardial contrast echocardiography has not been extensively evaluated in hypertensive patients. Our aim was to evaluate the diagnostic value of adenosine myocardial contrast echocardiography (MCE) in comparison to single-photon emission computed tomography (SPECT), with reference to angiographic findings, in a hypertensive population.

Methods: Fifty hypertensive subjects, treated with standard antihypertensive treatment, were submitted to adenosine stress MCE, adenosine SPECT, and coronary angiography within a 1-month period, without any intervening events.

Results: Sensitivity, specificity, and accuracy were 88%, 89%, 88% for MCE and 80%, 94%, 85% for SPECT, respectively ($P = 0.005$ not significant). In the analysis by coronary territory, it appears that MCE and SPECT are both more accurate in detecting lesions of the anterior than of the posterior coronary system, as suggested by the good concordance to angiography results in the left anterior descending artery territory ($k = 0.640$ and 0.671, respectively). Agreement with angiographic findings was moderate for the right coronary artery ($k = 0.561$ and 0.539, respectively), whereas left circumflex artery lesions were more accurately detected by MCE than by SPECT ($k = 0.533$ and 0.400, respectively), that is, MCE appears to be superior in the left circumflex artery territory.

Conclusions: In hypertensive patients, adenosine MCE has similar overall diagnostic accuracy with SPECT for assessment of coronary artery disease but is superior in the left circumflex artery territory.

Key Words: Hypertension, adenosine, stress echocardiography, myocardial contrast echocardiography, coronary artery disease.

Coronary artery disease (CAD) is the major cause of mortality in hypertensive patients, rendering the noninvasive evaluation of CAD in this population a particularly relevant clinical issue, especially considering the alterations in myocardial perfusion pattern and flow reserve in these patients. Among imaging modalities, pharmacologic stress echocardiography and myocardial perfusion scintigraphy are widely used noninvasive techniques for the functional assessment of patients with suspected CAD.

During the past decade, the echocardiographic assessment of the extent and severity of myocardial perfusion abnormalities has become possible with the development of myocardial contrast echocardiography (MCE), which enables the assessment of myocardial perfusion, after an injection of an ultrasound contrast agent. The MCE is increasingly used for CAD detection, as well as for myocardial viability assessment. Among the various stressors used, dobutamine has been associated with decreased sensitivity in the setting of ventricular wall hypertrophy, which is frequent in patients with hypertension, thus

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making adenosine (a vasodilating stressor) a potentially attractive option for CAD diagnosis in this clinical setting.

The aim of this study was to compare the diagnostic accuracy of perfusion assessment with MCE during adenosine stress test with that of Tl-201 single-photon emission computed tomography (SPECT), with reference to angiographic findings, in detecting CAD in hypertensive patients.

**Methods**

**Study Population**

Fifty hypertensive patients (34 men, 16 women, mean age 67 ± 5 years), with an intermediate-to-high probability of CAD based on clinical criteria, who were referred for pharmacologic stress testing with adenosine or were already scheduled for coronary angiography (CAG) were approached for enrolment. None of the patients had a known history of CAD in the past. All patients were on standard antihypertensive treatment and gave informed consent to the investigators. The distribution of antihypertensive regimens and main cardiovascular risk factors in the study population is shown in **Table 1**. The hospital medical ethics committee approved of the protocol.

Exclusion criteria included myocardial infarction within 1 week, unstable angina, second- or third-degree atrioventricular block, wheezing, systolic blood pressure (BP) <90 mm Hg, ingestion of caffeine within 24 h or methylxanthine derivatives within 48 h, pregnancy or lactation. Patients not in sinus rhythm, as well as those with congestive heart failure or severe valvular heart disease were also excluded.

All patients were scheduled to undergo adenosine protocol with myocardial contrast echocardiography, TL-201 SPECT (the echocardiography and the nuclear study were previously described).5

**Table 1. Risk factor and antihypertensive treatment distribution in the study population**

<table>
<thead>
<tr>
<th>Risk factors</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>50</td>
<td>100%</td>
</tr>
<tr>
<td>Smoking</td>
<td>22</td>
<td>44%</td>
</tr>
<tr>
<td>Diabetes</td>
<td>11</td>
<td>22%</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>18</td>
<td>36%</td>
</tr>
<tr>
<td>Positive family history</td>
<td>18</td>
<td>36%</td>
</tr>
<tr>
<td>Antihypertensive medications</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diuretics</td>
<td>34</td>
<td>68%</td>
</tr>
<tr>
<td>β-blockers</td>
<td>15</td>
<td>30%</td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>26</td>
<td>52%</td>
</tr>
<tr>
<td>CCBs</td>
<td>21</td>
<td>42%</td>
</tr>
<tr>
<td>ARBs</td>
<td>12</td>
<td>24%</td>
</tr>
<tr>
<td>Centrally acting agents</td>
<td>3</td>
<td>6%</td>
</tr>
</tbody>
</table>

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; CCB = calcium-channel blocker.

**Echocardiographic Study**

The echocardiographic study was performed using a Phillips 5500 instrument (Agilent Technologies, Andover, MA). We used the S3 transducer with harmonic mode transmitting and receiving at mean frequencies of 1.3 and 2.6 MHz, respectively. The dynamic range of this system is 40 dB.

Left ventricular (LV) mass was calculated with Devereux’s formula (Penn convention) and normalized for body surface area and for height (LV mass index). Left ventricular hypertrophy was defined by an echocardiographically determined LV mass index >116 g/m² in men and >104 g/m² in women.

Adenosine was administered by a continuous infusion of 140 μg/kg during 6 min. The myocardial contrast echocardiographic protocol was performed as follows. At baseline and during the last 3 min of adenosine protocol, SonoVue (Bracco) infusion was performed at a rate of 0.8 mL/min. Power modulation and low mechanical index (0.1 to 0.2 MHz) was used. Transient high mechanical index (1.7 MHz) impulses were used to destroy microbubbles (flash echocardiography), allowing the assessment of myocardial replenishment. Before and during adenosine infusion MCE perfusion data were compared and graded for each coronary territory.

**Echocardiographic Analysis** The ventricle was divided into 16 segments. Two independent reviewers who had no knowledge of the patient’s history and hemodynamic data analyzed the echocardiographic recordings. In case of disagreement, the captured images were interpreted by a third reviewer to resolve the difference. The vascular distribution of segments was defined as previously described.5

**Myocardial Contrast Echocardiography: Qualitative Analysis** Criteria for abnormality: Normally, at rest it takes 5 sec to completely replenish the ultrasound beam after microbubble destruction using a high-MI pulse. With normal hyperemic response, the beam fills in just 1 sec.10 Any segment with normal replenishment at rest that did not fill in approximately 1 sec after adenosine infusion was considered to demonstrate a reversible perfusion defect (Fig. 1).

**Single-Photon Emission Computed Tomography**

Tomographic thallium-201 scintigraphy was performed in all patients. Adenosine protocol was followed and at the end of adenosine infusion, 2 mCi (74 MBq) of thallium-201 was administered intravenously. Thallium images were then obtained with a high-sensitivity, low-energy, medium-resolution, parallel-hole collimator (model 400 AC/T, General Electric, Milwaukee, WI) centered on the 68-keV photo peak with a 20% window. The camera was rotated 180 degrees in an elliptical orbit around the patient’s thorax from a right anterior oblique angle of 40° to the left anterior oblique angle of 40°.
degrees to a left posterior angle of 40 degrees, in 6-degree increments lasting 30 sec each. Redistribution images were obtained 3 to 4 h after exercise testing while the patients were resting. From the raw scintigraphic data, vertical short-axis and vertical and horizontal long-axis tomograms were reconstructed, and four consecutive representative slices of each view were selected for interpretation. The reconstructed stress and redistribution images were then analyzed both qualitatively and quantitatively by standard techniques. On SPECT, a perfusion defect was considered to be reversible when the defect at stress was greater in magnitude than the one at rest or when a new defect on stress not seen at rest. The results were interpreted independently by two investigators who had no knowledge of the exercise and catheterization data.

**Coronary Angiography**

All patients underwent CAG and left ventriculography by the Judkins technique. Ventriculography was performed in the 30-degree right anterior oblique and 60-degree left anterior oblique views. Eccentric stenoses were evaluated in two orthogonal views. A normal arterial segment was identified immediately proximally and distally to the lesion and measured with an electronic calliper. The minimal stenosis diameter was also measured and severity was expressed as percent reduction of normal diameter. Significant CAD was considered as a 50% reduction in luminal diameter of at least one major epicardial vessel.

**Statistical Analysis**

Data are presented as mean ± standard deviation. Numerical variables were compared using the unpaired or paired t test as suited. Categorical variables and proportions were compared using the χ² test. Sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of the different techniques for the diagnosis of CAD were assessed and compared using the McNemar’s test. Agreement among the different modalities was evaluated by k value. Values of 0.41 to 0.60 were considered to indicate moderate agreement, 0.61 to 0.80 good agreement, and 0.81 to 1.0 excellent agreement. Analysis was performed by patient and coronary territory. We performed a forward binary logistic regression analysis to further compare the power of each modality to predict the result of the angiography in each vascular territory. A P value of <.05 was considered significant. Data analysis was performed using the SPSS 10.0 statistical package for Windows (SPSS Inc., Chicago, IL).

**Results**

Of the 50 subjects studied, 32 (64%) had significant CAD, according to CAG. All patients had mild LV hypertrophy (mean interventricular septum diameter 11.7 ± 0.9 mm, mean LV posterior wall diameter 11.3 ± 0.80 mm, mean LV mass index 118 ± 3 g/m²). Duration of hypertension from diagnosis was 35 ± 18 months in CAD patients and 32 ± 16 months in patients with normal coronary arteries (P = not significant [NS]).

Mean heart rate before adenosine infusion was similar between groups (70.0 in subjects without CAD and 69.6 in those finally diagnosed with CAD, P = NS). The mean increase in heart rate with adenosine infusion was 17 ± 8 beats/min (P < .001). There was no significant difference in the chronotropic response between CAD and non-CAD patients (mean increase in heart rate 18 and 16 beats/min, respectively, P = NS).

The mean BP values obtained just before performing the stress echo, were 135 ± 10/82 ± 6 mm Hg in patients with CAD and 134 ± 19/85 ± 3 mm Hg in patients with normal coronary arteries (P = NS). At the end of adenosine infusion, these values were 130 ± 12/78 ± 6 mm Hg and 127 ± 7/75 ± 8 mm Hg, respectively (P = NS). The overall change in BP levels before and after adenosine infusion was significant both for systolic (mean reduction 6 ± 6 mm Hg, P < .001) and diastolic (mean reduction 4 ± 3 mm Hg, P < .001) arterial pressures. There was no significant difference in BP response to adenosine between CAD and non-CAD subjects (mean reduction in systolic
BP 6 mm Hg and 7 mm Hg, respectively, and mean reduction in diastolic BP 4 mm Hg and 4 mm Hg, respectively. $P$ = NS for both).

**Analysis by Patient**

Among the 50 patients who underwent adenosine MCE, SPECT, and CAG, 32 (64%) were diagnosed as suffering from CAD according to the gold standard method (CAG). Ten patients had one-vessel, 15 patients had two-vessel, and the remaining 7 had three-vessel disease.

Adenosine stress echo was performed in all 50 patients according to the protocol without any adverse events. Interpretation of thickening of LV myocardial segments and MCE images was feasible in all patients. The MCE detected perfusion defects in 30 patients; 28 of them were finally diagnosed with CAD on CAG. On the other hand, of the 20 patients with negative MCE study 4 were found to have significant CAD on CAG. Table 2 summarizes the diagnostic evaluation parameters (sensitivity, specificity, positive and negative predictive value, accuracy) for MCE, with CAG as reference method.

The SPECT results were considered nondiagnostic in two cases, due to inadequate implementation of the test protocol because of patient complaints (in both these cases the result of the SPECT study was negative, although the patients were found to suffer from CAD on CAG). These two cases were excluded from the analysis of the SPECT results. The SPECT identified 25 patients with CAD, 24 of which had significant coronary lesions on CAG. Of the 23 patients who were found negative in the SPECT study, 6 were finally diagnosed with CAD. The SPECT sensitivity, specificity, positive and negative predictive value, and accuracy are summarized in Table 2.

**Comparison of Modalities**

The MCE identified 28 of 32 (87.5%) patients with CAD, whereas SPECT identified 24 of 30 (80%) patients ($P$ = NS). Consensus by MCE, SPECT, and CAG was observed in 22 of 30 patients with CAD (the 2 cases with nondiagnostic SPECT are excluded). There was no case of a positive result in both MCE and SPECT among patients without CAD on CAG. Of the 32 patients with CAD, 2 went undiagnosed by both MCE and SPECT. The concordance data between the studied diagnostic strategies and CAG findings, as well as between MCE and SPECT, are summarized in Table 3. As shown, both MCE and SPECT demonstrate good agreement with CAG.

Furthermore, we compared the sensitivity of the two modalities according to the severity of CAD, separating patients with significant CAD on CAG into two groups: those with multivessel (2- or 3-vessel) disease and those with single-vessel disease. The MCE was non-significantly more sensitive than SPECT in detecting both multivessel (95.5% vs 81.8%) and single-vessel (70.0% vs 50.0%) disease (Fig. 2).

### Table 2. Diagnostic parameters of myocardial contrast echocardiography (MCE) and single-photon emission tomography (SPECT), with angiography as reference (PPV: positive predictive value; NPV: negative predictive value)

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
<th>Accuracy</th>
</tr>
</thead>
<tbody>
<tr>
<td>By patient analysis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MCE</td>
<td>87.5%</td>
<td>88.9%</td>
<td>93.3%</td>
<td>80.0%</td>
<td>88.0%</td>
</tr>
<tr>
<td>SPECT</td>
<td>80.0%</td>
<td>94.4%</td>
<td>96.0%</td>
<td>73.9%</td>
<td>85.4%</td>
</tr>
<tr>
<td>By vascular territory analysis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MCE</td>
<td>77.0%</td>
<td>89.9%</td>
<td>83.9%</td>
<td>81.5%</td>
<td>84.7%</td>
</tr>
<tr>
<td>SPECT</td>
<td>62.3%</td>
<td>94.4%</td>
<td>88.4%</td>
<td>78.5%</td>
<td>81.3%</td>
</tr>
</tbody>
</table>

$P$ = NS for all differences between the two methods.

### Table 3. Degree of agreement between the studied modalities on patient-by-patient basis

<table>
<thead>
<tr>
<th>Concordance between tests (by patient analysis)</th>
<th>kappa value</th>
<th>Notation</th>
</tr>
</thead>
<tbody>
<tr>
<td>MCE vs. CAG</td>
<td>0.746 ± 0.097</td>
<td>Good agreement</td>
</tr>
<tr>
<td>SPECT vs. CAG</td>
<td>0.705 ± 0.101</td>
<td>Good agreement</td>
</tr>
<tr>
<td>MCE vs. SPECT</td>
<td>0.616 ± 0.114</td>
<td>Good agreement</td>
</tr>
</tbody>
</table>

Kappa statistic values are expressed as $k ±$ standard error. Intervals of agreement are denoted as: kappa value more than 0.800 denotes excellent agreement, 0.601 to 0.800 good agreement, 0.401 to 0.600 moderate agreement, 0.400 or less poor agreement.

**FIG. 2.** Comparison of sensitivity of myocardial contrast echocardiography (MCE) (striped column) and single-photon emission computed tomography (SPECT) (gray column) in detection of single and multivessel disease. In both cases, $P$ = not significant.
The beta value was slightly higher for MCE versus SPECT. The results of the present study indicate that adenosine stress echo is a feasible and safe technique in this population of patients, who may be unsuitable for exercise testing (eg, due to prominent increases in BP during exercise), as adenosine does not increase BP or cardiac wall tension.

According to our findings, MCE with adenosine infusion exhibits slightly higher—without achieving statistical significance—sensitivity than SPECT in detecting CAD in hypertensive patients and similar overall diagnostic accuracy. We have not been able to find studies comparing real-time adenosine stress–contrast echo to SPECT, with coronary arteriography as reference, in hypertensives. Sennor et al,11 who used another vasodilator stressor—dipyridamole—in a medium risk population, reported 83% v 49% sensitivity and 58% v 92% specificity for MCE and SPECT, respectively, in CAD detection. Our results indicate substantially higher sensitivity for SPECT and higher specificity for MCE, which may reflect the fact that in our study the population was of moderate-to-high risk for CAD.

Vasodilator stress presents certain advantages, such as shorter examination time, fewer side effects, and easier image interpretation because of absence of tachycardia and tachypnea-induced cardiac motion. In hypertensive patients with LV hypertrophic remodeling, in particular, dobutamine has been shown to be associated with lower sensitivity,7,8 possibly due to decreased wall tension, resulting in lower oxygen demand and, thus, reduced potential for appearance of wall motion abnormalities. Adenosine, acting mainly through the differential induction of hyperemia between regions supplied by normal and stenotic arteries, should not be influenced by such effects. For these reasons, adenosine is an attractive alternative to dobutamine as a stressor in echocardiographic functional tests for CAD diagnosis in hypertensive patient populations with LV hypertrophy. Of course, this hypothesis should be further evaluated by clinical studies. To this end, our findings indicate that adenosine stress echocardiography with real-time perfusion imaging possesses adequate diagnostic accuracy in patients with hypertension and mild LV hypertrophy.

Another interesting point of our results is that accuracy is highest for LAD artery territory and moderate for RCA territories for both adenosine MCE and SPECT, whereas MCE demonstrated superiority in correctly identifying LCx artery disease. Heinle et al,12 in a study comparing adenosine stress echo to SPECT, without angiographic data, reported that the two modalities presented the highest concordance in the LAD artery territory and the highest discrepancy in the LCx artery territory. Our findings reiterate this observation and suggest that it may be attributed to the superior diagnostic accuracy of MCE in the regions supplied by the LCx artery.

From the practical point of view, our findings suggest that the assessment of perfusion defects during a vasodilator stress echo may be sufficient to detect CAD in hypertensive patients.
lator stress echo study is a well-founded diagnostic approach given the reports that vasodilator stress does not consistently provoke functional ischemia\(^\text{13}\) (and thus wall motion abnormalities), and, as a result, may not be optimally suited for use with techniques that use regional wall thickening abnormalities (such as conventional stress echo), as a sole marker of ischemia for the diagnosis of CAD.

**Study Limitations**

The two adenosine stress protocols were performed separately, in a 1-week period. Preferably, both echo and nuclear tests should be performed during the same stress protocol. Moreover, the studied population consisted of patients referred for evaluation and possible catheterization to our institution, which means that they had high probability to be positive for CAD. This fact may entail an overestimation of the diagnostic power (especially specificity) of the techniques in the general population. Finally, it should be noted that all patients in our study population exhibited mild LV hypertrophy, consistent with their history of hypertension. It may, thus, be unwise to extrapolate the herein reported results to hypertensive patients with no LV hypertrophy.

In conclusion, the present study provides evidence that real-time adenosine stress-contrast echocardiography is a feasible alternative to SPECT, with high diagnostic accuracy for the detection of CAD in hypertensive patients. Further studies, involving larger numbers of patients are needed to better define the relative merits of each modality and possibly investigate subsets of patients who may be better suited for one method than for the other.

**References**