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Adenosine Pharmacologic Stress Myocardial Perfusion Tomographic Imaging in Patients With Significant Aortic Stenosis

Diagnostic Efficacy and Comparison of Clinical, Hemodynamic and Electrocardiographic Variables With 100 Age-Matched Control Subjects

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Objectives. **This study assessed the safety and diagnostic accuracy of adenosine stress myocardial perfusion scintigraphy for the detection of coronary artery disease using single-photon emission computed tomography (SPECT) in patients with significant aortic stenosis.**

Background. **Exercise cardiac stress testing in patients with significant aortic stenosis is generally avoided because of concerns for safety. In addition, those studies that have analyzed the utility of exercise testing both with and without myocardial thallium-201 scintigraphy for the diagnosis of coronary artery disease have yielded low specificity. Currently, no safe and accurate means exists to noninvasively assess the presence, extent and severity of coronary artery disease in patients with significant aortic stenosis.**

Methods. **The study included 35 patients with moderate to severe aortic stenosis (mean [±SD] aortic valve area 0.84 ± 0.16 cm^2, range 0.5 to 1.2; mean maximal instantaneous aortic valve gradient 44.4 ± 15.9 mm Hg, range 20 to 84). All patients underwent a 6-min adenosine infusion (140 μg/kg body weight per min) protocol and either separate acquisition rest thallium-201/stress technetium-99m sestamibi or stress and 4-h redistribution thallium-201 SPECT. Visual 20-segment SPECT analysis used a standard five-point scoring system from 0 (normal tracer uptake) to 4 (absent uptake). The SPECT results were considered abnormal if more than two segments had a stress score ≥2. Hemodynamic, electrocardiographic and clinical responses were compared with those in a reference group of 100 consecutive age-matched patients undergoing adenosine SPECT who did not have aortic stenosis.**

Results. **Hemodynamic responses during adenosine stress testing between the study and control patients demonstrated no significant difference in the net change in systolic blood pressure (18% of baseline vs. 14%, patients with aortic stenosis vs. control subjects), heart rate (21% vs. 19%), rate-pressure product (0% vs. 2%) or incidence of chest pain (23% vs. 35%) or transient second- (9% vs. 9%) or third-degree atrioventricular block (3% vs. 1%). In the 20 patients who had coronary angiography, sensitivity for detection of coronary artery disease was 92% (12 of 13) and specificity was 71% (5 of 7).**

Conclusions. **In this preliminary study, adenosine was found to be well tolerated and diagnostically accurate in patients with moderate to severe aortic stenosis.**

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The use of exercise cardiac stress testing in patients with significant aortic stenosis has been controversial. Well described complications of exercise include hypotension, syncope (1–5) and sudden death (1,2,6). The incidence of these events is not well known, and some investigators have suggested that patients with aortic stenosis may safely undergo exercise testing when performed cautiously (6–8). However, a depressed left ventricular stroke volume response to exercise with a concomitant decrease in cardiac output is commonly found in patients with aortic stenosis (9,10), and published reports continue to counsel avoidance of exercise testing in patients with significant aortic stenosis (11–13). Furthermore, ischemia can also occur with or without coronary artery disease in patients with aortic stenosis (14,15). Traditional exercise electrocardiographic (ECG) and exercise thallium-201 studies, when performed, have been shown (6,16–18) to yield low specificity in detecting coronary disease among patients with aortic stenosis.

Pharmacologic stress testing with adenosine offers several theoretic advantages over exercise in patients with aortic stenosis. A potent coronary vasodilator, adenosine, used in association with myocardial perfusion scintigraphy, has been shown to be highly accurate in the detection of coronary artery disease (19–25) but has never been tested in patients with

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Table 1. Demographic Data

	Patients With AS (n = 33)	Control Subjects (n = 100)	p Value
Age (yr)	76 ± 15	74 ± 9	NS
Male gender	16 (48%)	46 (46%)	NS
Angina	17 (54%)	44 (44%)	NS
Hx HTN	21 (60%)	60 (60%)	NS
Hx MI	12 (36%)	41 (41%)	NS
Hx PTCA	5 (15%)	8 (8%)	NS
Hx CABG	10 (30%)	28 (28%)	NS
LVH	12 (36%)	20 (20%)	NS
Pretest prob	0.47 ± 0.17	0.46 ± 0.20	NS
AV area (cm^2)	0.84 ± 0.19		
AV grad (mm Hg)	43 ± 15		

Data presented are mean value ± SD or number (%) of patients. AS = aortic stenosis; AV area = aortic valve area; AV grad = aortic valve gradient; CABG = coronary artery bypass graft surgery; HTN = hypertension; Hx = history of; LVH = left ventricular hypertrophy; MI = myocardial infarction; Pretest prob = pretest likelihood of coronary artery disease; PTCA = percutaneous transluminal coronary angioplasty.

aortic stenosis. However, because this agent does not generally cause a significant elevation in the rate-pressure product, oxygen demand does not increase, and myocardial ischemia is rarely precipitated (26,27). Therefore, we hypothesized that patients with aortic stenosis would have a lower risk from cardiac stress testing with adenosine and that diagnostic specificity for the detection of coronary artery disease might be improved. Thus, the purpose of this study was to assess preliminarily the safety and diagnostic efficacy of adenosine stress myocardial perfusion single-photon emission computed tomography (SPECT).

Methods

Patients. Two patient groups were included: a study group and a reference group. The study group included 35 consecutive patients who fulfilled the following criteria: All had undergone adenosine stress myocardial perfusion SPECT and a two-dimensional echocardiography Doppler study within 6 months of each other and had evidence of aortic stenosis by the latter, with a calculated aortic valve area ≤1.2 cm^2 or a peak instantaneous aortic valve gradient ≥50 mm Hg, or both.

The reference group included 100 age-matched patients who underwent adenosine pharmacologic stress testing. These patients had no clinical evidence of aortic stenosis. The comparative demographic data is summarized in Table 1. The pretest likelihood of coronary artery disease is a numeric variable based on age, gender, risk factors and symptom classification, as published previously (28,30). Table 2 describes the clinical profile, hemodynamic and ECG variables of the study subjects.

Echocardiography. All study patients underwent conventional two-dimensional echocardiography with continuous wave and color flow Doppler analysis. Aortic valve gradients were calculated using continuous wave Doppler signals obtained in the echocardiographic window that afforded the highest peak instantaneous velocity across the aortic valve. Aortic valve area was calculated using the continuity equation, as described elsewhere (31–35). The studies were interpreted by a physician who had no knowledge of the results of the adenosine perfusion data.

Adenosine infusion protocol. Antianginal medications were maintained at their usual dosages, except for oral dipyridamole, which was withheld for 24 h. Xanthine derivatives and caffeine-containing products were discontinued 48 and 12 h before testing, respectively. The infusion was performed with the patient in the supine position. Adenosine was administered intravenously at a dose of 140 μg/kg body weight per min for 6 min, and a bolus of 3.5 to 4 mCi of thallium-201 or 20 to 30 mCi of technetium-99m sestamibi was given through a contralateral vein at minute 3. Vital signs and a 12-lead ECG were recorded at baseline and every minute thereafter for at least 10 min. The ECG was monitored continuously (leads V_1, V_5 and AVF) for development of arrhythmia or ST segment deviation. Blood pressure was taken from the contralateral arm to the adenosine infusion site. The protocol allows for the adenosine infusion to be reduced or prematurely terminated or for conversion with aminophylline at the discretion of the cardiologist performing the test.

Acquisition of myocardial perfusion SPECT. Myocardial perfusion SPECT acquisition used the previously published methods for both thallium-201 (36) and technetium-99m sestamibi (30,37) imaging. In brief, for thallium imaging, SPECT acquisition was performed 10 to 15 min after completion of adenosine infusion. Redistribution images were performed 4 h after thallium injection. Reinjection of thallium (1 to 1.5 mCi) was performed if the patient had a previous myocardial infarction, ST changes on the ECG during pharmacologic stress or evidence of a perfusion defect on the initial thallium images. Late redistribution studies (18 to 72 h) were performed for patients with a 4-h nonreversible defect (38). Patients injected with sestamibi during adenosine stress followed a previously validated rest thallium/stress technetium-99m sestamibi separate acquisition dual-isotope myocardial perfusion SPECT protocol (37–39), with technetium-99m sestamibi SPECT beginning 1 h after sestamibi injection.

SPECT Image interpretation. For purposes of visual interpretation, all short-axis and vertical long-axis tomograms were displayed on transparency film, with the intensity of each image normalized to the maximal pixel value in that image. The myocardial perfusion tomograms were divided into 20 segments for each patient (37). These segments were assigned to six evenly spaced regions in the apical, midventricular and basal slices of the short-axis views and two apical segments of the midvertical long-axis slice. Each segment was scored by an experienced observer using a previously published (37) five-point scoring system (0 = normal; 1 = equivocal; 2 = moderate; 3 = severe reduction; 4 = absent thallium-201 uptake), without knowledge of the clinical history, ECG results or the results of coronary angiography. A SPECT study was

Table 2. Clinical Profile and Hemodynamic and Electrocardiographic Variables of 35 Study Subjects

Pt No.	Age (yr)/ Gender	Hx of Angina	Heart Rate (beats/min)		Systolic Blood Pressure (mm Hg)		Chest Pain	AV Block	ECG Dx	AV Grad (mm Hg)	AV Area (cm^2)
			Baseline	Peak	Baseline	Lowest					
1	77/M	Y	81	95	171	112	Y	3rd	A	51	0.5
2	77/M	N	62	73	190	170	N	0	E	58	0.7
3	79/F	Y	100	108	230	199	N	N	Nl	28	0.8
4	87/M	Y	60	77	137	116	N	0	E	55	0.6
5	69/M	N	61	77	147	114	N	0	Nl	20	1.0
6	87/F	Y	120	121	132	110	N	0	E	74	0.5
7	88/F	N	62	73	162	147	Y	0	Nl	49	0.8
8	79/M	Y	65	83	153	184	N	0	Nl	51	0.7
9	85/F	N	79	98	146	111	N	0	E	29	0.6
10	89/F	N	70	70	190	136	N	0	Nl	56	0.7
11	66/F	N	70	94	158	120	N	0	Nl	34	0.7
12	74/M	Y	72	106	174	154	Y	2nd	E	67	0.9
13	67/M	Y	59	95	180	134	Y	0	Nl	34	0.9
14	64/M	N	67	84	163	128	N	1st	Nl	40	0.9
15	79/M	N	82	94	140	112	N	0	E	32	1.2
16	81/M	N	68	75	188	154	N	1st	Nl	38	0.9
17	79/F	N	66	82	193	145	N	2nd	E	60	0.7
18	71/F	N	91	118	151	113	Y	0	Nl	31	1.2
19	81/M	Y	72	86	107	152	N	0	Nl	66	0.8
20	74/F	N	69	83	155	127	N	0	Nl	84	—
21	81/M	N	95	117	126	109	N	0	Nl	23	0.9
22	90/M	N	73	86	164	132	N	0	Nl	36	1.0
23	73/M	N	84	88	134	133	N	2nd	Nl	22	1.0
24	83/M	N	95	109	130	102	N	0	Nl	58	—
25	81/F	N	66	66	194	217	N	0	Nl	56	0.8
26	79/F	N	81	93	140	110	N	0	E	54	1.1
27	69/F	N	75	100	173	139	N	0	Nl	50	0.9
28	80/M	Y	63	55	105	90	N	0	Nl	31	1.0
29	78/F	N	55	84	200	174	Y	0	A	30	1.0
30	63/F	Y	64	84	225	164	N	0	Nl	41	0.6
31	90/M	N	57	68	184	142	N	0	Nl	24	1.0
32	84/F	Y	72	81	176	206	N	0	Nl	49	0.6
33	78/F	N	82	95	129	72	Y	0	E	43	0.8
34	78/F	N	106	83	100	164	N	0	Nl	58	0.7
35	74/F	Y	95	107	143	131	Y	0	Nl	22	1.0

AV = atrioventricular; ECG Dx = electrocardiographic diagnosis (Nl = normal, A = abnormal, E = equivocal); N = no; Pt = patient; Y = yes; other abbreviations as in Table 1.

considered abnormal if two or more segments had a stress score ≥2.

For the purposes of comparison between the reference and study groups with respect to the scintigraphic findings, two scintigraphic variables were used: the summed stress score and the summed reversibility score (40). The summed stress score is defined as the sum of the stress scores for the 20 segments analyzed, and the summed reversibility score is defined as the sum of the difference between the stress and rest scores for the 20 segments analyzed.

Each of the 20 myocardial SPECT segments was assigned to one of the three major coronary territories, using a previously published algorithm (30).

Interpretation of clinical and ECG response to adenosine infusion. Any symptoms of chest discomfort, shortness of breath, flushing, dizziness, headache and nausea were recorded both during adenosine infusion and in the recovery period. The ECG response was considered ischemic if ≥0.5 mm of downsloping, ≥1.0 mm horizontal or ≥1.5 mm of upsloping ST segment depression was noted at 0.08 s after the J point compared with the baseline ECG. These ECG changes were deemed borderline if the baseline ECG revealed rest ST segment depression secondary to left ventricular hypertrophy or digitalis use. Both ischemic and borderline ischemic responses were considered to be positive ECG responses.

Coronary angiography. Coronary angiography was only evaluated in the study group. There were a total of 20 patients who underwent coronary angiography within 6 months of adenosine stress myocardial perfusion imaging (mean 67 ± 22 days, range 1 to 190). Coronary angiography was performed with the standard Judkins approach, and all coronary angiograms were interpreted by two experienced physicians who

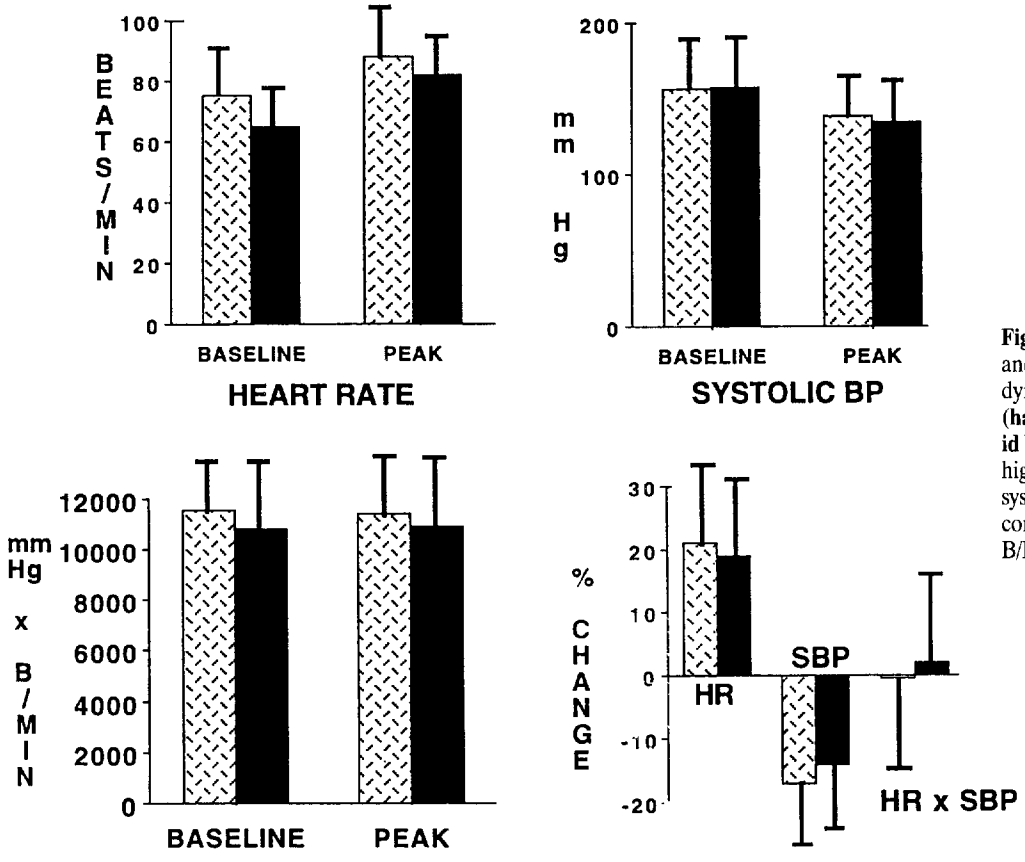

Figure 1. Comparison of baseline and pharmacologic stress hemodynamic variables in the study (**hatched bars**) and reference (**solid bars**) groups (p = NS). PEAK = highest heart rate (HR) or lowest systolic blood pressure (SBP) recorded during adenosine infusion; B/MIN = beats/min.

were unaware of the adenosine stress scintigraphic perfusion results. A significant coronary stenosis was defined as ≥70% maximal lumen diameter narrowing.

Statistical analysis. Observational data are reported as mean value ± SD when appropriate. Continuous variables were compared by Student *t* test. For categoric variables, the chi-square or Fisher exact test was used. For all purposes, a two-tailed significance level of p = 0.05 was considered significant.

Results

Patient demographics. For the patients in the study group, the mean aortic valve area was 0.84 ± 0.16 cm^2 with a mean peak valve gradient of 44.4 ± 15.9 mm Hg (Table 1). As shown in Table 2, there were no differences in age and gender distribution between the study and reference patients. There were also no differences in the frequency of history of angina, previous myocardial infarction, coronary artery disease, ECG documented left ventricular hypertrophy or calculated pretest likelihood of coronary artery disease between the two groups.

Hemodynamic effects of adenosine infusion. In the study group, systolic blood pressure decreased by a mean of 29 ± 16 mm Hg during testing, or 18 ± 10% of the baseline value (range 0% to 44%). Heart rate in the study patients increased by a mean of 15 ± 9 beats/min, or 21 ± 14% of the baseline. Compared with the reference group, there was no significant difference in either the degree of heart rate increase (19% from baseline) or systolic blood pressure decrease (14% from baseline) induced by pharmacologic stress (Fig. 1). In addition, mean rate-pressure product did not increase during testing in the study patients (0.5 ± 14%), and there was no significant difference compared with the reference patients (2.0 ± 16%).

To determine whether the severity of aortic stenosis had a direct impact on the hemodynamic response to adenosine stress, we further characterized the study group as those with an aortic valve area either more (Group A) or less (Group B) than the mean value of 0.84 cm^2. Group A (mean aortic valve area 1.0 ± 0.1 cm^2) had a mean decrease in systolic blood pressure of 17 ± 7% and a mean increase in heart rate of 25 ± 16% from baseline values. Group B (mean aortic valve area 0.68 ± 0.11 cm^2) had a decrease in systolic blood pressure of 18 ± 11% and an increase in heart rate of 18 ± 10%. These differences between Groups A and B were not statistically significant.

Electrocardiographic effects of adenosine infusion. Three (9%) of the patients with aortic stenosis developed second-degree heart block, and there was one patient (3%) with third-degree heart block in the study group. In comparison, nine patients (9%) in our reference group developed second-degree and one (1%) developed third-degree atrioventricular (AV) block. These differences were not statistically significant.

Table 3. Symptoms Experienced During Adenosine Stress Testing

	Patients With AS (n = 33)	Control Subjects (n = 100)	p Value
Chest pain	8 (24%)	32 (32%)	NS
Flushing	12 (36%)	27 (27%)	NS
Dyspnea	9 (27%)	19 (19%)	NS
Headache	5 (15%)	19 (19%)	NS
Dizziness	4 (12%)	7 (7%)	NS
Nausea	1 (3%)	4 (4%)	NS

Data presented are number (%) of patients. AS = aortic stenosis.

All episodes of heart block observed were transient and terminated either spontaneously or with cessation or reduction of adenosine infusion.

In contrast to the reference group, ST segment depression in the study group, which occurred during adenosine stress, was more likely to be interpreted as nondiagnostic because of the presence of a left ventricular hypertrophy pattern on the baseline ECG (9 [26%] of 35 vs. 9 [9%] of 100, p = 0.05). However, the incidence of definite ischemic changes induced by pharmacologic testing was not different between the two groups (2 [6%] of 35 vs. 5 [5%] of 100, p = NS).

Symptoms experienced during adenosine infusion. Table 3 outlines the incidence of the six most commonly encountered symptoms occurring during adenosine infusion. In the reference patients, the symptoms, in order of decreasing frequency, were chest discomfort, flushing, dyspnea, headache, dizziness and nausea. Patients with aortic stenosis reported more flushing (36% vs. 27%) and less chest discomfort (24% vs. 32%) than the control patients. However, the differences were not found to be statistically significant.

Incidence of adenosine protocol deviation. Four patients (Patients 1, 17, 12 and 30 [Table 2]) underwent an adenosine infusion that was either slowed or prematurely terminated in either the third or fourth minute of the test. All had significant chest discomfort that resolved within 1 min after termination of the test. Two patients (Patients 1 and 30) had a significant hypotensive response (34% and 27% decrease in systolic blood pressure from baseline, respectively) that resolved within 1 min of termination or slowing of adenosine infusion. One patient (Patient 12) had transient second-degree AV node block, and one (Patient 1) had transient third-degree AV node block. Aminophylline was not required in any of our study patients. Mean aortic valve area of these four patients was 0.72 ± 0.13 cm^2, and mean aortic valve gradient was 52 ± 9.4 mm Hg (p = NS vs. the remaining patients in the aortic stenosis group).

Myocardial perfusion SPECT analysis. Severity of perfusion defects as measured by either the summed stress severity or summed reversibility score were similar for the two groups. The mean stress score for the patients with aortic stenosis was 11.9 ± 9.2, and the mean score for the reference group was 9.7 ± 9.1 (p = NS). Mean reversibility scores were also not significantly different between the two groups (8.3 ± 7.5 vs. 6.0 ± 6.3, patients with aortic stenosis vs. control subjects, p = NS).

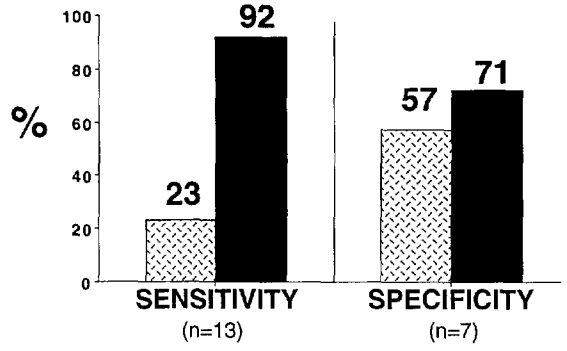

Figure 2. Sensitivity and specificity for detection of coronary artery disease by pharmacologic stress electrocardiography (**hatched bars**) and by myocardial perfusion single-photon emission computed tomography (**solid bars**).

Diagnostic accuracy of adenosine ECG and myocardial perfusion SPECT for the detection of coronary artery disease. Twenty of the patients with aortic stenosis underwent cardiac catheterization, 13 of whom (65%) had angiographically evident coronary artery disease (≥70% stenosis), and 7 (35%) had normal coronary arteriograms (Fig. 2). For the purpose of determining diagnostic accuracy, two patients with patent saphenous grafts in both the left and right systems were considered as having negative findings for coronary artery disease.

Fourteen patients had a normal ECG response to adenosine stress. Only one patient had a definitively ischemic ECG response, and the remaining five had borderline responses due to rest ST segment depression. For purposes of a dichotomous classification, both ischemic and borderline ischemic responses were considered positive ECG responses. Three of the 13 patients with coronary artery disease by angiography had a positive ECG response (sensitivity 23%). Of the seven patients with normal coronary arteriographic results, four had a normal stress ECG response (specificity 57%).

For myocardial perfusion SPECT, perfusion defects were present in 12 of 13 patients with angiographically significant coronary artery disease, yielding a sensitivity of 92% for the detection of coronary artery disease. Among the seven patients who had normal coronary arteriographic results, two had abnormal myocardial perfusion findings after adenosine stress, producing a specificity of 71%.

Discussion

Hemodynamic response during adenosine stress myocardial perfusion SPECT in patients with aortic stenosis. Many published reports (1–5,11–14) discuss the dangers of exercise testing in patients with aortic stenosis. Clyne et al. (9) showed that even asymptomatic patients with aortic stenosis develop a decrease in left ventricular stroke volume and cardiac output during exercise. Nylander et al. (7) studied 91 patients (mean valve area 0.83 cm^2) and found that 38% of patients undergoing upright exercise testing developed significant hypotension.

Animal and human studies suggest that the well described complication of syncope during exercise is caused by an elevation of left ventricular systolic pressure with resultant stimulation of left ventricular baroreceptors (1–3,41,42), reflexive peripheral vasodilation (41,42) and bradycardia (2).

Exercise-induced myocardial ischemia has been shown to occur in aortic stenosis, even in the absence of coronary artery disease. In response to stress, patients with aortic stenosis have a markedly reduced coronary vasodilatory reserve (14) and increased myocardial lactate production (15). It is reasonable to believe, as some have suggested (1), that the aforementioned hemodynamic consequences of exercise may be exacerbated by ischemia, with or without the presence of coronary artery disease.

Pharmacologic stress testing with adenosine or dipyridamole is an attractive alternative to exercise testing in the patient with aortic stenosis. Because peripheral and left ventricular systolic pressures decrease during dipyridamole or adenosine infusion, complications of left ventricular systolic hypertension and baroreceptor stimulation would be avoided. Furthermore, coronary blood flow increases during pharmacologic stress and scintigraphic perfusion defects are usually caused by only relative but not absolute decreases in coronary blood flow. Because the rate-pressure product has been shown to increase no more than 10% during pharmacologic testing (43), there is no significant increase in myocardial oxygen demand such as occurs during exercise. Although true myocardial ischemia during pharmacologic stress caused by either coronary steal (44) or a decrease in coronary perfusion pressure from systemic hypotension (45) has been described, the occurrence is far less frequent than that with exercise (26).

There are few published reports of pharmacologic stress testing in patients with aortic stenosis. Huikuri et al. (46) described a series of 27 patients with aortic stenosis (mean aortic valve area 1.0 ± 0.6 cm^2) who underwent planar thallium myocardial imaging after combined intravenous dipyridamole infusion and isometric handgrip testing. Only two patients had dizziness associated with a modest decrease in blood pressure, and two patients developed angina during handgrip testing. All symptoms resolved after the administration of aminophylline and nitroglycerin.

Compared with dipyridamole, adenosine is a more potent vasodilator with a significantly higher incidence of symptoms, such as chest pain, dyspnea and flushing. However, it has a significantly shorter half-life (<2 s), which leads to a very short duration of any symptoms or hemodynamic effects (24,46). However, it is unknown whether the symptoms or the hemodynamic response induced during adenosine stress would be more severe in the setting of aortic outflow obstruction.

With respect to hemodynamic response, our results showed that the change in blood pressure, heart rate and rate-pressure product during adenosine stress among the patients with aortic stenosis was similar to the reference group. Of the four patients whose infusion protocols were modified or terminated early at the discretion of the physician, two had a significant hypotensive response (34% and 27% decrease in blood pressure, respectively) to adenosine stress. However, each of these patients was severely hypertensive (systolic blood pressure 171 and 225 mm Hg, respectively) at the start of the study, and their lowest systolic blood pressure remained >110 mm Hg. Although their mean aortic valve area of 0.59 cm^2 is lower than the mean value of the study group (0.84 cm^2), we found that the hypotensive and tachycardic response during adenosine stress in those patients with aortic stenosis with lower aortic valve areas (less than the mean value of 0.84 cm^2) was not significantly different from those with a higher aortic valve area (>0.84 cm^2). However, to maximize safety in high risk patients with severe aortic stenosis, it may be prudent to begin the adenosine infusion at a lower dose and to increase it in a stepwise manner (19).

In a recent review of the safety of adenosine stress perfusion imaging in >9,000 patients from a multicenter registry, Cerqueria et al. (43) reported a mean increase in heart rate of 18.9% of the baseline value, which is similar to the 19.2% increase seen in our reference patients. However, the mean change in systolic blood pressure in the registry patients was only 6.7%, whereas the mean decrease in systolic blood pressure in our reference patients was 14.1%. In addition, the incidence of second-degree AV block in the registry patients was 4%, whereas the incidence in our reference patients was 9%. One possible explanation for these discrepancies is that 13% of the registry patients had a premature reduction in the rate of their adenosine infusion, whereas only 3% of our patients' studies were similarly altered. Although adenosine infusions were more likely to be terminated prematurely at our center compared with the registry study (15% vs. 7%), 50% of our reference patients whose tests were terminated completed at least 5 min of the 6-min infusion, and 86% completed at least 4 min of the protocol.

The common symptom of chest discomfort that occurs during adenosine infusion is clinically difficult to distinguish from angina but appears very frequently even in normal volunteers (24,45). The origin is thought to be due at least in part to neurohormonal receptor stimulation (47). Given that this side effect occurred with essentially equal frequency in both the study and the reference groups, the precipitation of chest discomfort in patients with aortic stenosis during adenosine infusion is unlikely to be secondary to ischemia. The incidence of other common side effects, such as dyspnea and flushing, was also not significantly different between the patients with aortic stenosis and control subjects.

Although the numbers of patients in the present study are small, our study suggests that adenosine myocardial perfusion SPECT is safe in patients with significant aortic stenosis.

Diagnostic accuracy of adenosine stress myocardial perfusion SPECT for detection of coronary artery disease in patients with aortic stenosis. Aside from concerns of safety, exercise stress testing in patients with aortic stenosis for the purpose of coronary artery disease detection has generally been found to be inaccurate with low specificity. As described earlier, ischemia can be precipitated in patients with aortic stenosis in the absence of significant coronary artery disease.

ST segment depression in patients with aortic stenosis is known to lack specificity for the diagnosis of coronary artery disease (1,9,16). In addition, symptoms of angina have been unreliable in predicting coronary disease in these patients (6,7,48). In a series of patients with aortic stenosis, only 27% of those with angina had any coronary lesions on angiography (7). Furthermore, many patients with significant aortic stenosis are severely limited in their ability to exercise and often do not reach their target heart rate.

Because of the unreliability of anginal symptoms and stress ECG findings in patients with aortic stenosis, several investigators (6,17,18) have utilized exercise thallium myocardial perfusion imaging to assist in the detection of coronary artery disease. The results of these studies have also been disappointing. Bailey et al. (6) performed exercise redistribution thallium studies with the planar method in 22 patients with aortic stenosis and described a pattern of left ventricular wall "thinning" that was thought to represent diffuse subendocardial ischemia unrelated to coronary disease. They concluded that thallium exercise testing was unable to accurately diagnose coronary artery disease in patients with aortic stenosis. Pfisterer et al. (17) described reversible apical planar perfusion defects in many patients with aortic stenosis without coronary disease and concluded that the test was therefore not specific. Similarly, Kupari et al. (18) found planar thallium testing to have a high false positive rate (specificity 57%) but suggested that negative test results may be helpful in excluding coronary artery disease.

Because true myocardial ischemia is infrequently provoked during pharmacologic stress testing, we hypothesized that adenosine myocardial perfusion SPECT would be more accurate than conventional exercise testing in the detection of coronary artery disease. Our results showed that among the subgroup of patients with aortic stenosis who underwent coronary angiography in our study, adenosine stress testing accurately detected the presence of coronary artery disease in 12 of 13 patients. The specificity of 71% in our small study group was higher than in those studies utilizing exercise testing in patients with aortic stenosis (6,17,18) and is consistent with previous reports (30,45) of the accuracy of adenosine pharmacologic stress in the general nonvalvular disease test population undergoing myocardial perfusion SPECT.

Because patients who have aortic stenosis, especially with hypertension and left ventricular hypertrophy, can have a decreased coronary flow reserve in normal coronary arteries (14,49), there is a theoretic possibility that perfusion imaging of heterogeneous flow patterns may be jeopardized because of abnormal vasodilatory reserve of patent vessels. This warrants consideration in further studies with larger patient populations.

Indications and contraindications for adenosine myocardial perfusion SPECT in patients with aortic stenosis. Patients with aortic stenosis will at times benefit from noninvasive testing for coronary artery disease. Because chest pain is often atypical and difficult to interpret in the patient with aortic stenosis, a normal noninvasive test for coronary artery disease may reassure the patient as well as the physician and obviate the need for further workup or therapy. In those patients who are either not candidates for or who have refused aortic valve replacement surgery, a noninvasive test in a patient with suspected coronary artery disease may help guide the decision toward medical management or coronary angioplasty. Patients with aortic stenosis who had previous coronary artery bypass graft surgery or percutaneous transluminal coronary angioplasty may also benefit from noninvasive testing to evaluate the possibility of graft closure or restenosis. Some have also suggested (50,51) that a sufficiently sensitive noninvasive test for coronary artery disease in patients with aortic stenosis would allow those with normal study results to proceed directly to aortic valve replacement without requiring coronary angiography. In a small number of patients, we demonstrated a high degree of sensitivity and specificity. If this result holds up in a larger patient cohort, the presence of significant coronary artery disease may be ruled out by a negative test result. Contraindications to adenosine stress testing in patients with significant aortic stenosis are the same as those for the general test population and include significant hypotension, congestive heart failure, unstable angina and second- or third-degree AV block.

Conclusions. On the basis of this preliminary study, adenosine myocardial perfusion SPECT was found to be safe and diagnostically accurate for the presence of coronary artery disease among patients with significant aortic stenosis.

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