Prognostic Significance of Systolic Blood Pressure Changes During *Dobutamine-Atropine* Stress Technetium-99m Sestamibi Perfusion Scintigraphy in Patients With Chest Pain and Known or Suspected Coronary Artery Disease

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To investigate the prognostic value of dobutamine stress-induced changes in systolic blood pressure (BP) 418 patients (mean age 60 years, 238 men) with chest pain and known or suspected coronary artery disease, who underwent a dobutamine-atropine stress technetium-99m sestamibi myocardial perfusion scintigraphic study, were followed up for 25 ± 15 months. Blood pressure was measured by automatic sphygmomanometry every 3 minutes. A marked decrease and increase in systolic BP from rest to peak were defined as changes of ≥20 mm Hg, and ≥30 mm Hg, respectively. Worst outcome events were cardiac death (n = 30), nonfatal myocardial infarction (n = 17), and hospitalization for congestive heart failure (n = 8). A decrease in systolic BP (prevalence 16%) was associated with older age and higher baseline systolic BP. Fixed and reversible sestamibi perfusion defects and follow-up results were similar to patients without a systolic BP decrease. In contrast, an increase in systolic BP (prevalence 24%) was associated with younger age, lower baseline systolic BP, and with absence of a history of prior congestive heart failure or treatment with angiotensin-converting enzyme inhibitors. Furthermore, these patients had fewer fixed perfusion defects and tended to have fewer annual event rates (3.5% vs 7.5%, p <0.10). In a multivariate model, an increase in systolic BP was not an independent predictor for subsequent events. In conclusion, a dobutamine-induced decrease in systolic BP is not associated with fixed or reversible sestamibi defects or adverse prognosis. An increase in systolic BP, however, is associated with less fixed sestamibi defects and a tendency toward less annual event rates. ©1997 by Excerpta Medica, Inc.

(Am J Cardiol 1997;79:1031–1035)

Dobutamine stress technetium-99m sestamibi myocardial perfusion scintigraphy is a pharmacologic stress modality with diagnostic[1–5] and prognostic[6] properties comparable to dobutamine stress echocardiography. Previous dobutamine stress echocardiographic studies have reported that dobutamine stress-induced hypotension is—unlike exercise—induced hypotension[7–10] not related to new or worsening wall motion abnormalities[11–14] and the presence or extent of coronary artery disease.[11,12] Furthermore, a relatively small echocardiographic study[12] has supported these results with prognostic data that were similar for the hypotensive and the nonhypotensive group. To date, however, these findings were not confirmed by myocardial perfusion scintigraphic data. Also, it is not known whether a substantial increase in systolic blood pressure (BP) reflects, as in exercise studies,[15,16] less myocardial damage and better prognosis.

METHODS

Patient selection: Over a 4-year period, between November 1990 and October 1994, 418 consecutive patients with chest pain were referred to the nuclear cardiology laboratory at the Thoraxcentre for the evaluation of suspected myocardial ischemia with dobutamine-atropine technetium-99m sestamibi single-photon emission computed tomographic imaging. All patients were unable to perform an adequate exercise test and none had prior heart transplantation, significant congenital or valvular heart disease, unstable angina, or known primary dilated cardiomyopathy. Mean age of the patients was 60 ± 12 years (range 23 to 85); 238 were men (57%), 203 patients (49%) had a previous myocardial infarction, and 55 patients (13%) had coronary artery disease without known myocardial infarction. One hundred four patients (25%) had typical angina, 205 (49%) had atypical angina, and 109 (26%) had nonanginal chest pain. At the time of the study 301 patients (72%) were receiving antianginal therapy including β blockers in 180 (43%).

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TABLE I Patient Characteristics of 418 Patients Studied With Dobutamine-Atropine Stress Sestamibi Scintigraphy

	BP Fall ≥20 mm Hg (n = 65)	Others (n = 353)	p Value	BP Rise ≥30 mm Hg (n = 101)	Others (n = 317)	p Value
Age (mean ± SD)	65 ± 10	59 ± 12	0.0002	54 ± 12	62 ± 11	0.0000
Men	38 (59)	200 (57)	0.7872	63 (62)	175 (55)	0.2050
Prior MI (history)	28 (43)	177 (50)	0.2951	49 (49)	156 (49)	0.9029
CHF (history)	13 (20)	69 (20)	0.9326	11 (11)	71 (22)	0.0112
Angina (history)	14 (22)	90 (26)	0.4977	25 (25)	79 (25)	0.9721
Hypertension (history)	32 (49)	147 (42)	0.2559	42 (42)	137 (43)	0.7726
β blockers	28 (43)	152 (43)	0.9935	42 (42)	138 (44)	0.7305
ACE inhibitors	12 (19)	85 (24)	0.3242	15 (15)	82 (26)	0.0224
Diuretics	16 (25)	70 (20)	0.3805	16 (16)	70 (22)	0.1767

Unless otherwise indicated, data are expressed as number of patients (%).
ACE = angiotensin-converting enzyme inhibitors; BP = blood pressure; CHF = congestive heart failure; MI = myocardial infarction.

Dobutamine stress test: Infusion rate was 10 μg/kg/min for 3 minutes, increasing by 10 μg/kg/min every 3 minutes up to a maximum of 40 μg/kg/min. In patients not achieving 85% of the predicted maximal heart rate and without symptoms or signs of myocardial ischemia, atropine was administered in addition to the maximal dose of dobutamine, starting with 0.25 mg adminstered intravenously and repeated up to a maximum of 1.0 mg within 4 minutes with continuation of dobutamine infusion. Throughout dobutamine infusion the electrocardiogram was continuously monitored (3 leads) and recorded (12 leads) at 1-minute intervals. Blood pressure was measured and recorded by automatic sphygmomanometry in the supine position at rest and at the end of each dobutamine (or atropine) stage. A hypotensive response was defined as a decrease in systolic BP from rest to peak of ≥20 mm Hg, in accordance with most previous studies.[12–14] An increase in systolic BP was defined as an increase of ≥30 mm Hg from rest to peak, also in accordance with previous (exercise) studies.[15,16] Reasons for interruption of the test were: horizontal or downsloping ST-segment depression >0.2 mV at an interval of 80 ms after the J point compared with baseline, ST-segment elevation >0.1 mV in patients without previous myocardial infarction, severe angina, a symptomatic reduction in systolic BP >40 mm Hg, hypertension (BP >240/120 mm Hg), and significant tachyarrhythmias.

Perfusion imaging: At peak stress, 370 MBq of technetium-99m sestamibi was injected intravenously, while dobutamine infusion was continued for at least 1 minute. Stress scintigraphic images were acquired on average 1 hour after the termination of the dobutamine infusion. For resting studies, patients were reinjected with 370 MBq of technetium-99m sestamibi ≥24 hours after the stress study. Image acquisition was performed with a Gammasonics single-head Orbiter Camera (Siemens, Des Plaines, Illinois). As described previously,[6] the tomographic views were grouped into 6 major segments: anterior, septum anterior, septum posterior, inferoposterior, lateral, and apical. Myocardial radiotracer uptake was evaluated visually (with the assistance of circumferential profiles analysis, including the normal values) for each of the 6 major segments both during rest and stress with a 4-point scoring method (0 = normal, 1 = equivocal or minimally reduced uptake, 2 = moderately reduced uptake, and 3 = severely reduced or absent uptake).

Coronary angiography: Coronary angiography was performed within 6 months in 164 patients (39%). Significant coronary artery disease was defined as a diameter stenosis ≥50% in a major epicardial artery at quantitative coronary angiography.[17]

Follow-up: Follow-up data were obtained over a 25 ± 15-month period (range 6 to 54 months) by outpatient clinic assessment, review of case notes and contacting the patient, general practitioner or other hospitals when necessary. Outcome events were death (defined as cardiac death), nonfatal myocardial infarction, and hospitalization for congestive heart failure. Follow-up was complete in 413 patients (99%).

Statistical analysis: Values were expressed as value ± SD, when appropriate. Comparisons (2-tailed) of patients with and without significant changes in systolic BP were performed with the Student's *t* test for continuous variables and chi-square test for discrete variables. Differences in the p value <0.05 were considered significant. Differences of <0.10 were described as a tendency toward significance. Multivariate logistic regression using the BMDP package[18] was performed to identify factors that were related to events. A forward and backward stepping algorithm was used with a p value of <0.05 to identify independent predictors for events.

RESULTS

Dobutamine-induced decrease in systolic blood pressure: A decrease in systolic BP ≥20 mm Hg was present in 65 patients (16%), and was associated with older age (p <0.001) and higher baseline systolic BP (p <0.0001). Severe, symptomatic hypotension as a test end point was present in only 4 patients (1%). Gender, history of prior myocardial infarction or congestive heart failure, and the use of β blockers, angiotensin-converting enzyme inhibitors or diuretics were not associated with a hypotensive systolic BP response (Tables I and II). There were no significant differences between patients with and without

TABLE II Hemodynamic, Sestamibi Scintigraphic, and Angiographic Data

	BP Fall ≥20 mm Hg (n = 65)	Others (n = 353)	p Value	BP Rise ≥30 mm Hg (n = 101)	Others (n = 317)	p Value
Heart rate						
Rest	71 ± 17	69 ± 13	0.2647	68 ± 11	70 ± 14	0.1930
Peak	132 ± 17	135 ± 17	0.2612	137 ± 16	134 ± 17	0.0841
Increase	61 ± 19	66 ± 18	0.0547	69 ± 17	64 ± 18	0.0082
Systolic blood pressure						
Rest	151 ± 23	136 ± 22	0.0000	133 ± 21	140 ± 24	0.0040
Peak	119 ± 25	154 ± 29	0.0000	177 ± 28	139 ± 26	0.0000
Increase	−33 ± 14	18 ± 22	0.0000	45 ± 18	−1 ± 20	0.0000
Dobutamine dose	38 ± 6	38 ± 4	0.6519	38 ± 4	38 ± 5	0.6305
Atropine dose	0.58 ± 0.30	0.58 ± 0.28	0.9637	0.63 ± 0.28	0.56 ± 0.28	0.1557
Sestamibi scan						
Fixed defect score	2.4 ± 2.6	2.6 ± 3.2	0.6263	1.9 ± 2.5	2.8 ± 3.2	0.0227
Reversible defect score	1.8 ± 2.4	1.6 ± 2.0	0.4550	1.4 ± 1.8	1.7 ± 2.2	0.2184
Total defect score	4.2 ± 3.8	4.2 ± 3.8	0.9881	3.3 ± 3.3	4.4 ± 4.0	0.0127
Coronary angiography						
Total number	22 (34)	142 (40)	0.3330	38 (38)	126 (40)	0.7034
Normal arteries	6 (27)	34 (24)	0.7351	9 (24)	31 (25)	0.9079
Diseased arteries	16 (73)	108 (76)	0.7351	29 (76)	95 (75)	0.9079
Single-vessel disease	6 (27)	56 (39)	0.2736	15 (40)	47 (37)	0.8088
Multivessel disease	10 (46)	52 (37)	0.4265	14 (37)	48 (38)	0.8889

Apart from angiographic data, which are expressed as number of patients (%), data are expressed as mean ± SD.
Abbreviations as in Table I.

TABLE III Clinical End Points at Follow-Up

	BP Fall ≥20 mm Hg (n = 65)	Others (n = 353)	p Value	BP Rise ≥30 mm Hg (n = 101)	Others (n = 317)	p Value
Follow-up (mean ± SD)	23 ± 14	25 ± 15	0.2024	31 ± 15	23 ± 14	0.0000
Cardiac events						
Death	5 (8)	25 (7)	0.8610	5 (5)	25 (8)	0.3195
Death/MI	8 (12)	39 (11)	0.7677	7 (7)	40 (13)	0.1151
Death/MI/CHF	9 (14)	46 (13)	0.8582	9 (9)	46 (15)	0.1471

Unless otherwise indicated, data are expressed as number of patients (%).
Abbreviations as in Table I.

systolic BP decrease with respect to dobutamine and atropine doses, fixed, reversible, and total sestamibi perfusion defect scores, presence and extent of coronary disease, and events during follow-up (Tables II and III).

Dobutamine-induced increase in systolic blood pressure: An increase in systolic BP ≥30 mm Hg was present in 101 patients (24%) and was associated with younger age ($p < 0.0001$), lower baseline systolic BP ($p < 0.005$), absence of history of congestive heart failure ($p < 0.02$), absence of the use of angiotensin-converting enzyme inhibitors ($p < 0.03$), and a higher increase in heart rate ($p < 0.01$) (Tables I and II). Patients with this systolic BP response had lower fixed ($p < 0.03$) and total ($p < 0.02$) sestamibi perfusion defect scores. However, the reversible defect score as well as the presence and extent of coronary disease were similar for both groups. Cardiac events during follow-up tended to occur less in patients with an increase in systolic BP, especially when the longer mean follow-up period was taken into consideration (Table III). Figure 1 shows that the annual death rates were 2.0% in patients with versus 4.0% in patients without an increase in systolic BP (p = NS); the annual death or nonfatal myocardial infarction rates were 2.7% versus 6.5% ($p < 0.10$), respectively, and all event rates (death, nonfatal myocardial infarction, hospitalization for heart failure) were 3.5% versus 7.5% ($p < 0.10$), respectively. In a multivariable stepwise logistic regression model (including the patient characteristics listed in Table I, an increase in systolic BP, and fixed and reversible perfusion defects), only age, gender, history of congestive heart failure, and the presence of reversible defects were independent predictors of clinical outcome (Table IV). An increase in systolic BP was not an independent predictor.

DISCUSSION

Generally, dobutamine stress causes an increase in heart rate, a reduction in systemic vascular resistance, a reduction in stroke volume (after an initial increase), and an increase in cardiac output.[12,19,20] Previous dobutamine stress studies have shown that as a net result, in general, there is a mild but significant increase in systolic BP.[6,21] This would suggest that, on average, an increase in cardiac output corrects for the decrease in systemic vascular resistance. Although the pathophysiology of hypotension during dobutamine infusion has not been completely de-

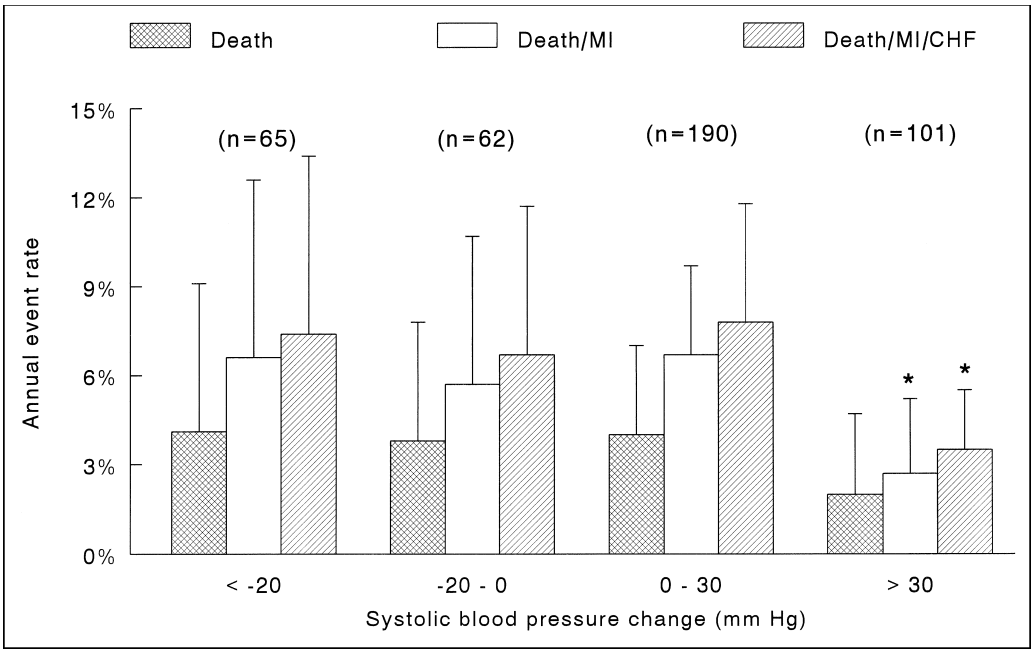

FIGURE 1. Annual event rates for the different systolic blood pressure responses. CHF = congestive heart failure; MI = myocardial infarction; *The 101 patients with an increase in systolic BP ≥30 mm Hg tended to have less events (p <0.10) than the combined 317 patients without such a blood pressure response.

TABLE IV Independent Predictors of Cardiac Events (odds ratios, 95% CI)

	Death	Death/MI	Death/MI/CHF
Age >65 years	NS	2.3 (1.1–4.8)	2.1 (1.0–4.3)
Male gender	2.4 (1.0–6.1)	2.3 (1.1–4.8)	2.6 (1.3–5.3)
CHF (history)	3.5 (1.6–7.8)	2.8 (1.4–5.5)	4.5 (2.4–8.4)
Reversible defects	2.1 (1.0–4.6)	3.0 (1.6–5.9)	1.9 (1.0–3.5)

Variables included in the model were the patient characteristics of Table I, an increase in systolic BP, and fixed and reversible perfusion defects. Variables that were not significant for any end point are not displayed.

CI = confidence interval; other abbreviations as in Table I.

fined, theoretically, it may result from (1) an inadequate increase in cardiac output to compensate for an expected decrease in systemic vascular resistance, and/or (2) a disproportionate decrease in systemic vascular resistance. An inadequate increase in cardiac output may be due to inadequate contractile reserve, severe ischemic left ventricular dysfunction, or left-sided obstructive heart disease. Dynamic left ventricular cavity obliteration due to strong inotropic stimulation was proposed as an important cause for reduced cardiac output and hypotension,[22] especially in patients with dehydration, but later studies could not confirm this mechanism,[14] and the proposed bolus of saline before dobutamine[22,23] did not prevent cavity obliteration in a canine model.[24] The second mechanism, a disproportionate decrease in systemic vascular resistance may be due to excessive sensitivity of the peripheral circulation to β_2-receptor stimulation, increased β_2-receptor density (deconditioned patients), or to a neurally mediated mechanism in which vigorous myocardial contraction stimulates the intramyocardial mechanoreceptors, resulting in sympathetic withdrawal and enhanced parasympathetic activity (the Bezold-Jarisch reflex).[25] Based on the described mechanisms, mandatory for a marked increase in systolic BP are (1) absence of dramatic decrease in systemic vascular resistance, and (2) an increase in cardiac output by increase in heart rate and/or contractility.

The 16% prevalence of a hypotensive response in this study is in agreement with that reported in previous dobutamine stress echocardiographic studies with comparable hypotension definitions.[12–14] In agreement with these previous reports, hypotension was associated with older age and higher baseline systolic BP. The consistent absence of histories of prior myocardial infarction or congestive heart failure, ischemia (whether assessed by stress echocardiography or perfusion imaging) or coronary artery disease, and worse prognosis in this and other studies[11–14,22,23,26] is strong indirect evidence of a dobutamine-induced hypotension mechanism that is primarily based on an excessive decrease in systemic vascular resistance, instead of a mechanism principally involving inadequate cardiac output. Because of the associations with older age and higher baseline systolic BP, a diminished baroreceptor reflex could play an additional role.[27] Some investigators proposed that β blockers offered some protection against hypotension by blocking peripheral vasodilatory β_2-receptors or diminishing vigorous contraction, resulting in less intramyocardial mechanoreceptor stimulation and dynamic obstruction.[12] However, as in most previously reported studies,[11,14] β blockers were not associated with a hypotensive response in the present study. Atropine can, by its vagolytic effects, increase systemic vascular resistance and pre-

vent the development of a vasovagal reflex. However, the addition and dose of atropine was similar in both patient groups.

As mentioned before, a substantial increase in systolic BP generally requires an adequate increase in cardiac output. Patients without an increase in systolic BP were older, had lower increase in heart rate (as a consequence of their lower target heart rate), and had more fixed sestamibi perfusion defects, indicating damaged myocardium, with probably less contractile reserve. Additional evidence for a mechanism involving inadequate contractile reserve is the higher prevalence of histories of congestive heart failure in these patients. Hogue et al,[28] although not dealing with this issue, reported that none of the 13 patients with a systolic BP increase $\geq$20 mm Hg had histories of congestive heart failure, compared with 5 of 23 patients without such a systolic BP response. Patients with a marked increase in systolic BP in the present study had a 50% reduction in annual cardiac events. We believe that this is further support for a better contractile reserve in these patients, because the extent and severity of fixed sestamibi perfusion defects are known to be related to prognosis.[6] The more significant results in prediction of survival by systolic BP response in exercise studies[15,16] can be a result of different (postmyocardial infarction) patient populations and the presence of the Bezold-Jarisch reflex, which will be more prevalent in patients stressed with a strong inotropic agent such as dobutamine, and in patients with preserved left ventricular rest function and contractile reserve. Indeed, this reflex will flaw the expected increase in systolic BP in more ''normal'' patients. Angiotensin-converting enzyme inhibitors were used more often in patients without a substantial increase in systolic BP. Apart from the accentuation of the vasodilatory effects of dobutamine, the more frequent use of these medications probably reflect the higher incidence of histories of congestive heart failure in these patients.

Clinical implications: It seems likely that a dobutamine stress-induced decrease in systemic vascular resistance plays a major role in the development of hypotension. Patients with hypotension during dobutamine stress are therefore not at higher risk for future events. Patients with a marked increase in systolic BP, however, are probably those with good contractile reserve (and without a marked decrease in systemic vascular resistance) and potentially better clinical outcome.

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