Hypotensive Response during Dobutamine Stress Echocardiography in Coronary Patients: A Common Event of Well-Functioning Left Ventricle

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Summary:

Background: Hypotensive response during dobutamine stress echocardiography (DSE) is a common complication, lacking the prognostic significance of hypotension during exercise treadmill test.

Hypothesis: The present study aimed to assess the possible mechanisms of hypotensive response during DSE and to compare it with exercise treadmill test.

Methods: In all, 91 patients with known coronary artery disease (CAD) underwent both DSE and exercise treadmill test. Dobutamine-induced hypotension was defined as a systolic blood pressure drop ≥ 20 mmHg from baseline or from the previous level of infusion.

Results: Twenty-one (23%) patients, 10 of whom also had bradycardia, developed hypotension during dobutamine infusion. Five (5.5%) patients were severely symptomatic and the infusion was stopped prematurely, while in the remaining 16 the addition of atropine allowed the continuation of the test. Patients prone to hypotension were predominantly female ($p = 0.0004$), had smaller ($p = 0.01$) and better functioning left ventricles ($p = 0.0004$), were unlikely to have rest wall motion abnormalities ($p = 0.0008$) or multivessel CAD ($p = 0.02$), and had less ischemia (wall motion score difference) ($p = 0.03$). Hypotension during exercise treadmill test was observed in only one (1%) patient with left main disease.

Conclusions: Hypotension during DSE is unrelated to the anatomical or functional extent of CAD and is frequent in the setting of a well-functioning left ventricle. We suppose that vigorous contraction of a small chamber during dobutamine

infusion results in an excessive stimulation of cardiac mechanoreceptors that mediate reflex hypotension and bradycardia.

Key words: cardiac mechanoreceptors, coronary artery disease, dobutamine stress echocardiography, hypotensive response

Introduction

Dobutamine stress echocardiography (DSE) is widely used for noninvasive evaluation of coronary artery disease (CAD) and myocardial viability.^{1–4} One limitation of this modality is the development of “paradoxical” hypotension during dobutamine infusion in about 20% of subjects.⁵ This causes a degree of discomfort and sometimes leads to premature discontinuation of the test. While hypotension during exercise stress indicates severe CAD,^{6,7} hypotension during DSE is not a marker of ischemia,^{5,8} but the precise mechanism has not been entirely elucidated.

The aim of our study was to shed further light on the possible mechanisms of hypotension during dobutamine infusion in patients with CAD who also underwent exercise treadmill electrocardiography.

Methods

Study Patients

In all, 91 consecutive patients with an average age of 57.2 ± 10 years (range 37–75) and CAD were enrolled in this study. Patients with heart failure (New York Heart Association functional class III or IV), unstable angina, recent myocardial infarction (within the preceding 6 months), previous cardiac surgery or coronary angioplasty, valvular heart disease, uncontrolled hypertension, or documented serious arrhythmia were excluded, as were those unable to perform an exercise test. All patients had cardiac catheterization within 6 months prior the day of the test. Significant CAD was defined as $> 70\%$ diameter stenosis of any of the three coronary arteries

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or their primary branches, or > 50% narrowing of the luminal diameter of the left main coronary artery. All patients had significant CAD, 50 with single- and 41 with double- or triple-vessel disease (2 of whom had left main disease).

Dobutamine Infusion Protocol

Graded dobutamine infusion was administered in 3-min stages at infusion rates of 5, 10, 20, 30, and 40 $\mu\text{g/kg/min}$. If chronotropic response was inadequate (< 85% of the age-predicted maximum heart rate), 0.6 mg atropine was given intravenously and repeated up to a maximum of 1.8 mg, if necessary, while dobutamine infusion was continued for up to a further 5 min. Cardiac rhythm was continuously monitored. A 12-lead electrocardiogram was recorded every 3 min and blood pressure was measured by automatic cuff sphygmomanometer every 1 min. Dobutamine-induced hypotension was defined as a systolic blood pressure drop ≥ 20 mmHg from baseline or the previous level of infusion or the peak recorded blood pressure.

End points for termination of DSE included achievement of > 85% of the age-predicted maximal heart rate, new or worsening wall motion abnormalities, systolic blood pressure > 220 mmHg, or diastolic blood pressure > 120 mmHg, and significant arrhythmias. In the event of hypotension, if the patient was symptomatic or a drop in heart rate was also present, atropine (0.6 up to 1.8 mg) was given while continuing the infusion in an attempt to reverse the hypotensive response and complete the test. However, if the symptoms persisted or were intolerable, the infusion was discontinued prematurely.

Echocardiography

With the patients semirecumbent in the left lateral position, baseline echocardiograms were performed with a commercially available cardiac ultrasound system (Toshiba SSH 160A, Crawley, West Sussex, UK). Two-dimensional echocardiography from parasternal long- and short-axis, and apical four- and two-chamber views was continuous throughout the dobutamine stress and during recovery until resolution of wall motion abnormalities. Digitized images were also acquired on line in a quad-screen format (Image View III, DCR, Nova MicroSonics, Indianapolis, Indiana) for subsequent side-by-side analysis. Echocardiograms were selected at (1) baseline, (2) low dose (10 $\mu\text{g/kg/min}$), (3) high dose (40 $\mu\text{g/kg/min}$), and (4) peak stress ($\pm$ atropine). All studies were stored on both videotape and optical disk.

Analysis of Echocardiograms

Digitized echocardiograms were independently reviewed by two experienced observers (LR and PN) who were blinded to the angiographic data. Differences were resolved by consensus. For wall motion abnormalities, the left ventricle was divided into 16 segments according to the recommendations of the American Society of Echocardiography.⁹ Regional myocardial contractile function was graded as normal, hypo-

kinetic, akinetic, or dyskinetic, and was assigned numeric values of 1, 2, 3, or 4, respectively.

Positive DSE was defined as the development of a new wall motion abnormality or the increase of an existing wall motion abnormality in extent or severity with stress. Total wall motion score was derived by adding the score of all segments and the wall motion index by dividing the total score by the number of segments. Wall motion score difference between peak stress and rest was introduced as a measure of the extent of reversible ischemia during DSE.

Exercise Electrocardiography

A symptom-limited maximal treadmill exercise test was performed according to the modified Bruce protocol within 2 weeks (11 ± 3 days) after DSE. No alteration in patient treatment was made between the two tests. For those who discontinued their treatment for DSE, the same policy was followed for exercise test. The conventional end points were used for termination of exercise test.

Electrocardiographic Analysis

An ischemic response during exercise test was defined as the development of ≥ 0.1 mV horizontal or downsloping ST-segment depression 80 ms after the J point in a lead with a normal baseline ST segment.

Statistical Analysis

All values are expressed as mean $\pm$ standard deviation. Frequency data were compared using chi-square analysis and continuous variables using Student's *t*-test. A *p* value of < 0.05 was considered significant.

Results

Hypotensive Response during Dobutamine Infusion

Twenty-one (23%) patients developed hypotensive response during dobutamine infusion. A drop in heart rate (7 with sinus bradycardia, 3 with junctional escape rhythm) was also seen in 10 of the 21 (47.6%) hypotensive patients. Five (5.5%) patients were severely symptomatic (nausea, dizziness, sweating, with two patients having fainting episodes), could not tolerate the test, and the infusion was stopped prematurely. They were positioned flat with the legs elevated and they recovered rapidly. Two of these five patients also had bradycardia (junctional escape rhythm), but none showed ischemia prior to the discontinuation of the infusion. The DSE was considered as nondiagnostic since the achieved workload was inadequate. The remaining 16 patients were asymptomatic or mildly symptomatic, and hypotension was reversed after administration of atropine. In 9 patients the blood pressure drop was gradual, occurring over two or more stages, while in 12 it was more precipitous, occurring within one stage. The

latter group comprised all the severely symptomatic patients. The mean decrease in blood pressure was 32.1 ± 7.3 mmHg and the mean infusion time, when the blood pressure drop first occurred, was 9.8 ± 2.8 min. In the 5 patients whose symptoms led to premature discontinuation of infusion, the mean decrease in blood pressure was 37.5 ± 6.5 mmHg while in the remaining 16 it was 29.8 ± 6.4 mmHg ($p = 0.01$). The majority (76.2%) of the hypotension reactions started at the 20 to 30 $\mu\text{g/kg/min}$ stage of dobutamine infusion (Fig. 1).

Baseline Characteristics

Clinical, angiographic, and echocardiographic characteristics of the population studied are shown in Table 1. Patients who developed hypotension during dobutamine infusion were predominantly female ($p = 0.0004$), had a smaller left ventricle ($p = 0.01$) and a higher ejection fraction ($p = 0.0004$), and were unlikely to have rest regional wall motion abnormalities ($p = 0.0008$) compared with the nonhypotensive group. None of the patients with hypotension had echocardiographic evidence of ischemia prior to the onset of blood pressure drop. Patients prone to hypotension were less likely to have multi-vessel CAD than did those in the nonhypotensive group

FIG. 1 Number of patients with hypotensive response according to the stage of dobutamine infusion.

($p = 0.02$). The magnitude of reversible ischemia, as it is expressed by the wall motion score difference, was less in the hypotensive than in the nonhypotensive group ($p = 0.03$). There was no difference in the percentage of beta-blocker users between the two subgroups. Similarly, there was no difference in the number of patients who discontinued beta blockers for ≥ 48 h before the tests.

TABLE 1 Clinical, angiographic, and echocardiographic characteristics in patients according to the development of hypotensive response during dobutamine infusion

	Hypotension (n = 21)	No hypotension (n = 70)	p Value
Clinical data			
Age	57.4 ± 7.8	57.2 ± 11.4	NS
Sex (female/male)	8/13	5/65	0.0004
Body mass index (kg/m^2)	28 ± 3.7	26.9 ± 4.3	NS
History of hypertension (%)	38	31.8	NS
Beta-blocker user (%)	62	55.7	NS
Rest systolic BP (mmHg)	131.2 ± 14.8	127.6 ± 17.1	NS
Rest diastolic BP (mmHg)	82.3 ± 12.5	80 ± 10.2	NS
Rest heart rate (beats/min)	75.2 ± 12.7	73.1 ± 13.8	NS
Angiography			
Single-vessel disease (%)	76.2	48.6	0.02
Multivessel disease (%)	23.8	51.4	0.02
Ejection fraction (%)	58.1 ± 7.1	47.3 ± 12.8	0.0004
Ejection fraction < 40%	1/21	20/70	0.02
Echocardiography			
Interventricular septum (mm)	10 ± 0.97	10 ± 1.2	NS
LV end-diastolic diameter (mm)	43.7 ± 5.1	47.9 ± 7.2	0.01
LV end-systolic diameter (mm)	28.1 ± 4.6	33.8 ± 9.3	0.008
Fractional shortening (%)	35.6 ± 6	30.5 ± 9.1	0.01
Rest wall motion index	1.08 ± 0.21	1.38 ± 0.46	0.004
Peak wall motion index	1.34 ± 0.3^a	1.7 ± 0.48	0.001
(Peak-rest) wall motion score	1.2 ± 1.7^a	3.2 ± 4.1	0.03
Rest RWMA (%)	14.3	55.7	0.0008
Positive DSE (%)	50 ^a	68.6	NS

^aThe five hypotensive patients whose dobutamine infusion was terminated prematurely are not included.

Abbreviations: BP = blood pressure, DSE = dobutamine stress echocardiogram, LV = left ventricle, RWMA = regional wall motion abnormalities, NS = not significant.

Treadmill Exercise Test

One (1%) of all patients studied has a progressive drop in systolic blood pressure during the treadmill exercise test. He also developed angina with significant ST changes, and the test was terminated prematurely. This patient did not become hypotensive during dobutamine infusion. Angiogram showed left main disease with good left ventricular function. Patients with hypotensive response during dobutamine infusion had a trend toward lower frequency of positive exercise tests than the nonhypotensive group (Table II). The hemodynamic parameters at peak exercise test did not differ significantly between the hypotensive and the nonhypotensive group (Table II). However, there was a trend for those with dobutamine-induced hypotension toward higher systolic blood pressure and rate-pressure product at peak exercise.

Role of Atropine in Dobutamine-Induced Hypotension

In our laboratory, atropine is routinely given at the end of the 40 µg/kg/min infusion stage when the 85% of the maximal predicted heart rate has not been achieved. In the present study, atropine was also given promptly in all 21 patients with hypotension in an attempt to reverse it. However, in five patients the infusion was terminated prematurely because the symptoms were intolerable, and immediate measures such as supine position and leg elevation were applied to facilitate recovery. The mean increase in systolic blood pressure (blood pressure after atropine administration—blood pressure at hypotension) was 15.8 ± 15 mmHg and the mean increase in heart rate was 48.6 ± 21.3 beats/min. Compared with patients without hypotension, there was a trend toward lower rate-pressure product at the peak of the test in the 16 hypotensive patients whose tests were completed after the addition of atropine ($18,663 \pm 2,552$ vs. $20,493 \pm 3,525$, $p=NS$). The conclusion of DSE after atropine administration resulted in an ischemic response in 8 (50%) of the 16 hypotensive patients.

Discussion

This is the first study in which a direct comparison is made of the incidence of hypotensive response of the same coronary patients during dobutamine infusion and treadmill exercise test. Treadmill exercise test was performed within 2 weeks after DSE and the physician was unaware of the results of DSE. Special attention was paid to maintain the treatment of all patients between the two tests unchanged.

The incidence of hypotension during DSE in our study was 23%, while in previous studies it ranged from 14 to 38%.^{5,8,10-12} This wide range is mainly due to the different definition of hypotension and infusion protocol. Rosamond *et al.*⁸ reported a high incidence (38%), but hypotension was defined as a systolic blood pressure drop >10 mmHg from baseline. Mazeika *et al.*¹⁰ found a relatively low incidence (14%) of hypotension, but they used a 8-min stepwise infusion of dobutamine at 5, 10, 15, and 20 µg/kg/min. The occur-

TABLE II Comparison of hemodynamic responses at exercise treadmill test according to the development of hypotensive response during dobutamine infusion

Hypotension at DSE	Yes (n = 21)	No (n = 70)	p Value
Positive treadmill test (%)	42.9	60	NS
Peak			
Heart rate (beats/min)	144.2 ± 19.3	141.5 ± 22.3	NS
Systolic BP (mmHg)	180.3 ± 17.8	170.3 ± 26.6	NS
Diastolic BP (mmHg)	91.5 ± 9.9	89.4 ± 9.5	NS
% Max heart rate	85.9 ± 11.6	87.4 ± 13.2	NS
Rate-pressure product	$26,062 \pm 4,651$	$24,254 \pm 6,010$	NS
METs	8.7 ± 2.2	8.3 ± 3.2	NS
Duration (min)	13.2 ± 2.5	12.8 ± 3.6	NS

Abbreviations as in Table I.

rence of "paradoxical" hypotensive response is the main disadvantage of DSE. Although blood pressure drop rarely results in premature discontinuation of the test, hypotension is usually associated with nausea, dizziness, and even, although rarely, syncope, and therefore it adds discomfort compromising the popularity of the test.

The occurrence of hypotension is far less frequent during treadmill exercise test ranging from 2.7 to 6%.^{6,13} in our population it occurred in only 1%. Since the referral population was the same, this clearly shows that the mechanisms of hypotensive response are different in the two types of stress. Several studies of treadmill exercise test have demonstrated exertional hypotension to be a strong marker for significant CAD, impaired left ventricular function, and poor prognosis.^{7,14} The main mechanism of hypotension during exercise appears to be the reduction of ejection fraction caused by large areas of ischemic myocardium.

Characteristics of Patients Prone to Dobutamine-Induced Hypotension

In our study, hypotension during DSE was not related to the anatomical or functional severity of CAD. The majority of coronary patients with hypotensive response were female, had single-vessel disease, and the magnitude of ischemia detected by echocardiography was less in the hypotensive group. This was clearly shown by the lower wall motion score difference in the hypotensive group. This finding cannot be attributed to a lesser "stressor" effect of dobutamine due to blood pressure drop during dobutamine infusion since the rate-pressure product after atropine addition almost reached the levels of the nonhypotensive group. The relatively low percentage of positive DSE in the hypotensive group is probably due to the high proportion of patients with single-vessel disease.

It is interesting to note that hypotension occurred in the setting of good left ventricular function. Blood pressure drop was a rare event when ejection fraction of left ventricle was <40%. Lieberman *et al.*¹¹ also found that dobutamine-induced hy-

potension was more likely in patients with higher rest left ventricular ejection fraction. Our findings are in direct contrast to the exercise-induced hypotension that is related to the extent of left ventricular dysfunction.¹⁵

There was no difference in the percentage of beta-blocker users between the hypotensive and nonhypotensive group. However, a previous study¹⁶ raised the possibility of some protective effect of beta-1-adrenergic blockage on bradycardia and hypotension induced by isoproterenol infusion during upright-tilt test.

Potential Mechanisms of Hypotension during Dobutamine Infusion

Dobutamine is a sympathomimetic drug which stimulates beta-1, beta-2, and alpha-1 adrenoceptors. In the peripheral vasculature, alpha-1-mediated vasoconstriction is offset by beta-2-mediated vasodilatation, and this explains the relative lack of effect on blood pressure.¹⁷ In a previous study,¹² we found no increase in systolic blood pressure at peak of dobutamine infusion, although other investigators have reported such an increase.^{5, 18}

The exact mechanism of dobutamine-induced hypotension remains unclear and it appears that a spectrum of different mechanisms, such as vasodepressor reflexes,¹⁰ induction of dynamic left ventricular outflow tract obstruction,¹⁹ and inadequate increase in cardiac output due to impaired systolic reserve,²⁰ is involved. Our findings suggest that the main mechanism of hypotension is the excessive stimulation of cardiac vagal afferents innervating mechanoreceptors, which are more predominant in the inferior and posterior walls of the left ventricle. Such a stimulation due to forceful systolic contraction, which may squeeze and activate these cardiac nerve endings, may occur during dobutamine infusion. This may trigger sympathoinhibition and increased parasympathetic discharge, leading to bradycardia, or decrease in systemic vascular resistance, or both.¹⁰ The whole spectrum of this reflex was seen in 10 patients whose hypotension was associated with bradycardia. In these particular cases, hypotensive response bore a striking similarity with the neurally mediated reflex hypotension and bradycardia during isoproterenol infusion in conjunction with upright-tilt test.¹⁶ This resemblance suggests a similar underlying mechanism. In the remaining 11 hypotensive patients without bradycardia, we speculate that the chronotropic action of dobutamine could have partly masked the reflex bradycardia. Furthermore, the prompt administration of atropine when the patient first manifested a drop in blood pressure could have abolished the bradycardic component.

Our hypothesis is further enhanced by the observation that when the left ventricle was moderately or severely impaired, hypotension was rare. This is in agreement with the existing evidence that the activation of cardiac afferent nerves is impaired in heart failure.^{21, 22} Furthermore, Tan *et al.*²³ observed no vasodepression in patients with heart failure undergoing assessment of pump function using dobutamine infusion. Therefore, we suppose that the blood pressure response during

DSE is determined by the functional condition of the left ventricle and the variable degree of mechanoreceptor sensitivity. Although we did not perform Doppler measurements systematically, it is our experience that the vigorously contracting left ventricle during dobutamine infusion usually creates some degree of functional outflow tract obstruction, as indicated by the increased outflow tract velocity. Therefore, we believe that dynamic obstruction is not a major cause of hypotension itself, but constitutes an epiphenomenon usually preceding the neurally mediated hypotension.

Conclusions

Hypotension during DSE is a frequent event not related to the anatomical or functional severity of CAD or left ventricular impairment, as is the case in exertional hypotension. Among coronary patients it is more likely to appear in women with single-vessel disease and in the setting of a good left ventricle. Prompt administration of atropine when blood pressure drops or bradycardia appears aborts hypotensive response in most cases and allows the conclusion of a diagnostic DSE.

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