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[Article]

Hemodynamic Changes, Plasma Catecholamine Responses, and Echocardiographically Detected Contractile Reserve During Two Different Dobutamine-Infusion Protocols

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Summary:

We studied hemodynamic changes, catecholamine responses, and the occurrence of improved wall thickening by echocardiography during two different dobutamine-infusion protocols. Forty-three patients were studied by using a stepwise incremental dobutamine dose-infusion protocol (10-40 μg/kg/min, 3-min intervals); a subgroup of 11 patients also underwent a continuous dobutamine-infusion protocol (10 μg/kg/min for 12 min) in random order. No patient used [beta]-blockers. At 3-min intervals, blood pressure, heart rate, and plasma concentrations of dobutamine, epinephrine, and norepinephrine were measured. The echocardiographic improvement of wall thickening was analyzed only in paired protocols by visual assessment in left ventricular regions with normal wall motion at rest. The mean heart rate increased in the continuous and stepwise protocols from 73 to 99 and 74 to 132 beats/min. There was no significant change in blood pressure response between the two protocols. The mean plasma dobutamine concentrations during the continuous and stepwise protocols at 0, 3, 6, 9, and 12 min were 0/0; 31/38; 80/203; 106/448; and 120/692 ng/ml, respectively. In each patient, a response curve was constructed for the plasma dobutamine concentration versus heart rate. The heart rate increment and dobutamine concentration at which wall thickening was detected were similar with both protocols (14 ± 5 vs. 12 ± 7 beats/min) and (80 ± 40 vs. 92 ± 48 ng/ml; mean ± SD). Wall thickening was noted in two of 11 patients between 0 and 3 min and 11 of 11 patients between 3 and 6 min in both protocols. Catecholamine responses during the continuous and stepwise protocols were epinephrine, 23 versus 28/28 versus 36, and norepinephrine 301 versus 323/347 versus 519. Only norepinephrine plasma concentrations increased significantly during the stepwise protocol. A 6-min dobutamine infusion was sufficient during both protocols to reach an adequate plasma dobutamine concentration, which induced a detectable increase of wall thickening in all patients. There is a significant differences between the two protocols with regard to the plasma catecholamine changes, so some of the hemodynamic effects during the stepwise dobutamine-infusion protocol may be mediated through release of endogenous catecholamines.

Dobutamine-atropine stress echo (DSE) is increasingly used for the evaluation of coronary artery disease and assessment of myocardial viability because of high accuracy, feasibility, safety, and low costs of the test compared with other noninvasive stress-test modalities (1,2). The detection of myocardial ischemia is important for the evaluation of chest pain, preoperative cardiac risk stratification, and prognosis of late cardiac events in patients incapable of performing adequate physical exercise. Viability testing can predict recovery of ventricular function after coronary revascularization in patients with stable coronary artery disease and severe ventricular dysfunction (i.e., myocardial stunning or hibernation) (3). In those patients, coronary revascularization may provide an attractive alternative option to heart transplantation.

For the detection of both conditions, two different protocols are used. Myocardial ischemia is detected by a protocol using stepwise increments of dobutamine at 3-min intervals, starting with 10 μg/kg/min up to 40 μg/kg/min (1). End-point of the test is target heart rate (85% of the maximal age- and sex-related heart rate), apparent myocardial ischemia, or side effects. In patients not achieving an adequate HR response at maximal dobutamine dose, atropine is added to dobutamine (4). DSE has been shown to detect coronary artery disease with a high sensitivity and specificity (2). The diagnostic gain can be further improved by adapting quantification of stress echo results instead of only presence or absence of ischemia. For instance, the HR and dobutamine-infusion rate at which ischemia occurs is related to the severity of coronary artery disease (2). By using M-mode recordings and volume changes during stress echo, additional semiquantitative analysis of wall motion can be performed (5).

For the evaluation of myocardial viability, different protocols are used, a low-dose dobutamine, starting with 2.5 or 5 μg/kg/min for 3 or 5 min, followed by 5, 7.5, or 10 μg/kg/min for 3 or 5 min (6,7). Most widely used are combinations of two increasing low doses for a total period of 15 min (5).

During "low-dose" dobutamine, a positive inotropic effect is mostly present, whereas at "high-dose," the chronotropic effect dominates (8). Echocardiographic markers of viable myocardium are improved wall motion at low dose or myocardial ischemia at any dose of dobutamine infusion. Deterioration of wall motion compared with resting value is the hallmark of ischemia. Differentiation of segments with an improved wall motion at low-dose dobutamine or only ischemia can provide additional information concerning the severity of stenosis of the supplying coronary artery or the presence of collateral blood flow. Before assessing the relative effectiveness of different stage durations and doses of a low-dose DSE test to detect viability, the physiologic and hemodynamic effect of the test must be evaluated.

Dobutamine is a selective [beta]$_1$-adrenoceptor agonist with relatively weak [alpha] and [beta]$_2$-adrenoceptor stimulant activity (8-11). The pharmacologic half-life of dobutamine is 2 min, with a steady state not obtained for <=10 min. Thus short-stage durations of stress protocols would not achieve a steady state of a dose; therefore wall-motion changes may be more related to the change in HR or dobutamine plasma concentration than the corresponding infusion rate. This purpose of this study was to evaluate physiologic responses during a standard stepwise stress test and to compare two different stress protocols in the same patients.

To assess the feasibility of using only one protocol for detection of both myocardial viability (in segments with normal functioning at rest) and ischemia, both protocols are compared.

METHODS

Patient characteristics

Forty-three patients underwent a standard DSE for the evaluation of coronary artery disease. In a subgroup of 11 patients, both protocols (i.e., stepwise increment and continuous low-dose dobutamine) in random order on two different days were performed. No patients used [beta]-blockers or had diabetes mellitus. The mean age was 56 years (range, 39-78 years). A history of myocardial infarction was present in 12 patients. Indication for the tests were preoperative cardiac risk stratification or evaluation of chest-pain complaints.

In all subjects, plasma concentrations of dobutamine, dopamine, norepinephrine, and epinephrine were measured during the test.

Dobutamine stress test

The dobutamine stress protocols were approved by the Hospital Ethical Committee. After they had given informed consent, the subjects underwent a resting two-dimensional echocardiographic examination. During the stepwise incremental dobutamine-infusion protocol, dobutamine was administered intravenously with an infusion pump, starting at 10 µg/kg/min for 3 min, followed by stepwise increments of 10 µg/kg/min every 3 min to a maximum of 40 µg/kg/min. The dobutamine infusion was stopped if a target HR (85% of a theoretic maximal HR (men, (220 - age) × 85%; women, (200 - age) × 85%) was achieved. During the continuous dobutamine-infusion protocol, 10 µg/kg/min was administrated intravenously with an infusion pump for 12 min. Blood pressure and HR were measured at rest and at the end of each infusion step with an automatic device (Accutorr A1; Datascope Corp., Paramus, NY, U.S.A.). A 12-lead electrocardiogram (ECG) was recorded at rest and at the end of every dose step. The two-dimensional echocardiogram was monitored continuously and recorded on video tape. Criteria for interruption of the test were a horizontal or downsloping ST depression > 2 mm at 80 ms after the J point, ST elevation, severe continuous chest pain, reduction in systolic blood pressure > 40 mm Hg from baseline or a systolic blood pressure < 100 mm Hg, significant cardiac arrhythmias, or any side effect regarded as resulting from dobutamine. Off-line assessment of echocardiographic images was performed by two investigators. Increased wall thickening was observed by visual assessment in left ventricular regions that showed normal wall motion at rest. When there was disagreement between these two assessors, a third investigator viewed the images without knowledge of the previous assessments, and a majority decision was achieved. The corresponding HR at which this occurred was noted in every patient.

Blood concentrations of dobutamine, dopamine, norepinephrine, and epinephrine

Blood samples were taken at 0, 3, 6, 9, and 12 min during both protocols. Dobutamine was measured in plasma as described by Alberts et al. (12). In brief, after a liquid-liquid extraction and derivatization with the fluorogenic agent 1,2-diphenylethylenediamine, dobutamine is measured by fluorometric detection after separation by high-performance liquid chromatography (HPLC). Dopamine, norepinephrine, and epinephrine were measured in plasma as described by van de Hoorn et al. (13).

Statistical analysis

Linear regression analysis was performed to determine the HR-log dobutamine response curve for each patient. Based on this relation, the plasma dobutamine concentration was estimated, corresponding with the HR at which wall thickening occurred during dobutamine infusion. Two-way analysis of variance (ANOVA) with repeated measures over time was performed, to study differences in HR, blood pressure, plasma concentrations of dopamine, epinephrine, and norepinephrine between the two protocols. A p value < 0.05 was required for significance. When a difference was found, five additional Student's *t* tests were planned. To correct for increasing type I error by multiple testing, significance was stated at the 0.01 probability level (Bonferroni's correction). All data are expressed as mean ± SD. It was calculated that to show a significant difference of 50 pg/ml in plasma norepinephrine concentration during the stepwise protocol, 40 individuals had to be investigated. Similar calculations for the continuous-infusion protocol yielded a sample size of 500 patients, which was a reason for not increasing the sample size to >11.

RESULTS

HR increased during continuous/stepwise increment dobutamine infusion from 73 ± 8/74 ± 8 to 99 ± 12/132 ± 13 beats/min (ANOVA, p = 0.001; Fig. 1). Furthermore, the HR increment was different between both protocols (ANOVA, p = 0.001; see Table 1. Systolic blood pressure increased significantly during infusion from 139 ± 20/141 ± 19 to 149 ± 23/156 ± 20 mm Hg (ANOVA, p = 0.03). However, there was no difference in response between both protocols (ANOVA, p = 0.88; see Table 1). Diastolic blood pressure decreased during both protocols from 73 ± 5/74 ± 5 to 69 ± 10/65 ± 11 mm Hg at the maximum dose of dobutamine (ANOVA, p = 0.01). Between both protocols, there were no differences (ANOVA, p = 0.55).

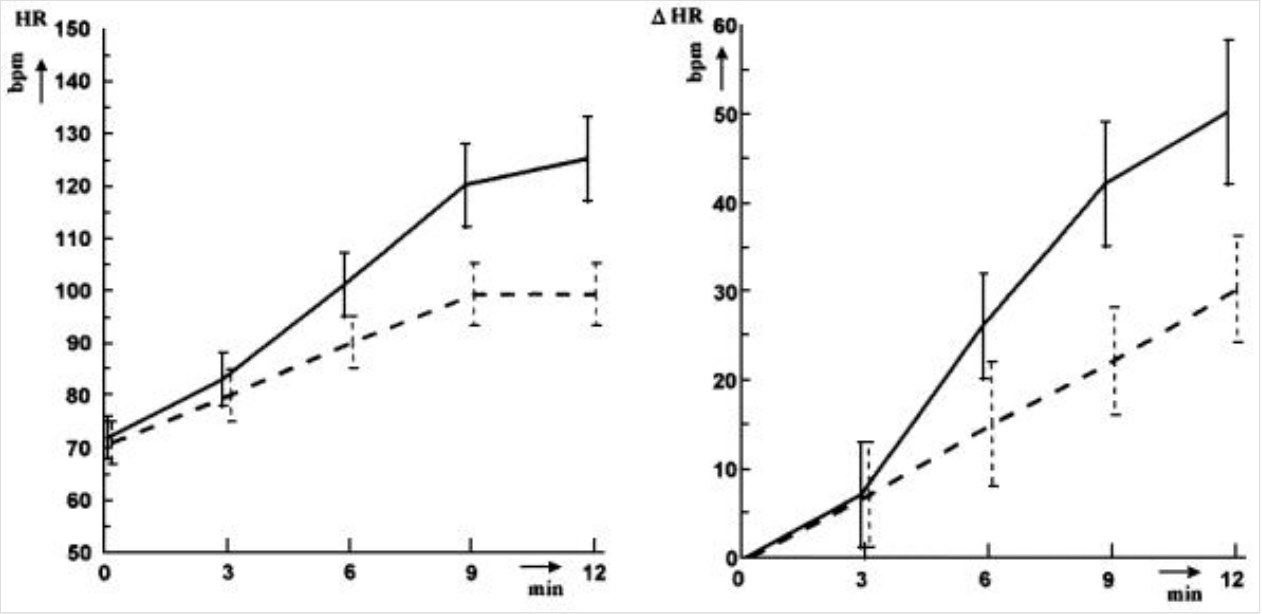

FIG. 1. Heart rate responses, absolute values, and percentage change with dobutamine during infusion. Dotted line, continuous dobutamine-infusion protocol; solid line, the stepwise incremental-infusion protocol. Values expressed as mean ± SD.

		0 min	3 min	6 min	9 min	12 min
Heart rate (beats/min)	Continuous	73 ± 8	80 ± 12	91 ± 12	99 ± 13	99 ± 12
	Stepwise	74 ± 8	84 ± 14	103 ± 14	120 ± 14	132 ± 13
ANOVA p value, 0.001	p Value	0.79	0.15	0.09	0.02	0.001
Systolic blood pressure (mm Hg)	Continuous	139 ± 20	141 ± 20	147 ± 23	149 ± 24	149 ± 23
ANOVA p value, 0.88	Stepwise	141 ± 19	149 ± 23	157 ± 22	156 ± 23	156 ± 20
Diastolic blood pressure (mm Hg)	Continuous	73 ± 10	74 ± 10	68 ± 13	65 ± 12	69 ± 13
ANOVA p value, 0.55	Stepwise	74 ± 10	71 ± 14	72 ± 17	68 ± 13	65 ± 13

Continuous, infusion of dobutamine, 10 mg/kg/min for 12 min (n = 11); stepwise, incremental infusion of dobutamine 10, 20, 30, and 40 mg/kg/min, 3-min interval (n = 43); ANOVA p value, possible interaction between protocol and time; p value, difference between the two infusion protocols.

TABLE 1. Hemodynamic changes

Plasma concentrations of dobutamine, dopamine, norepinephrine, and epinephrine are presented in Figs. 2, 3, and Table 2. Norepinephrine and dopamine plasma concentrations increased significantly during the stepwise protocol (ANOVA, p = 0.0001). Between both protocols, the increment of norepinephrine and dopamine plasma concentrations showed a significant difference (both ANOVAs, p = 0.01). The epinephrine value changed insignificantly during low-dose or stepwise incremental dobutamine infusion (ANOVA, p = 0.30. To reach a statistical difference with a power of the test of 0.80, the population size had to be increased to 500 patients.

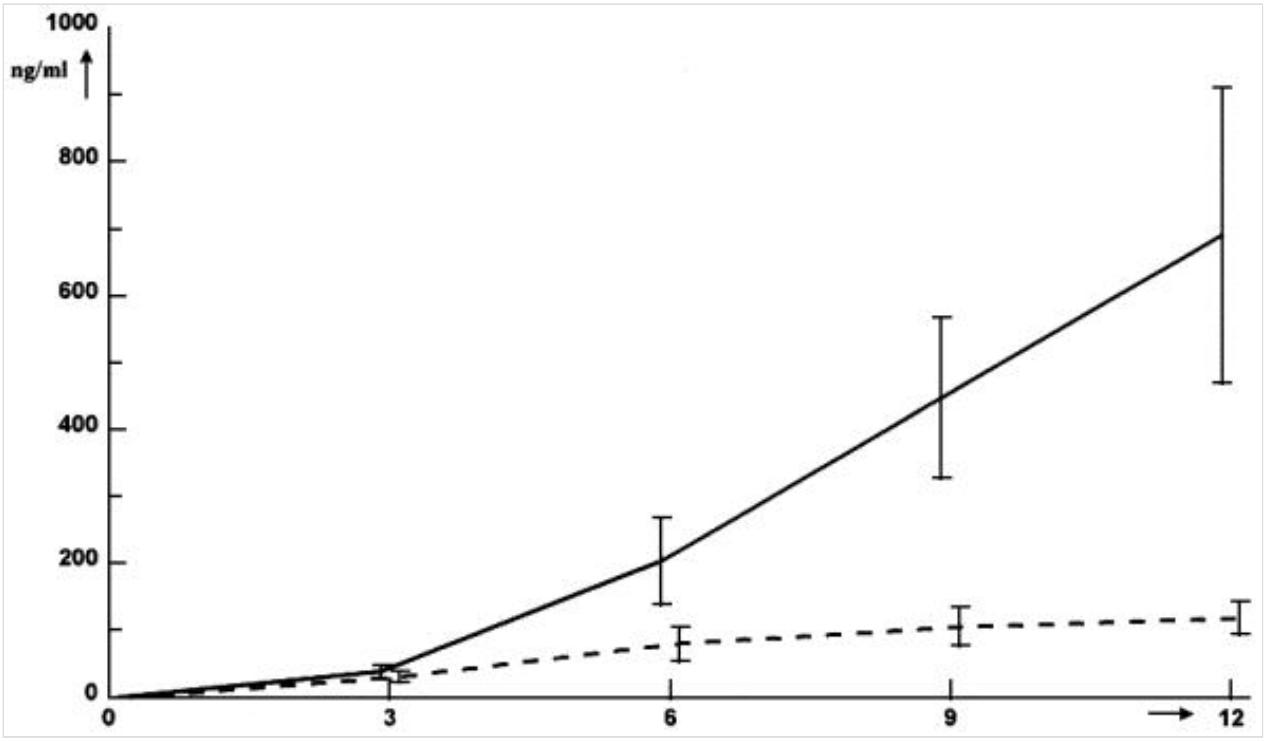

FIG. 2. Dobutamine plasma concentration during dobutamine infusion. Dotted line, continuous-infusion protocol; solid line, stepwise incremental protocol. Values expressed as mean ± SD.

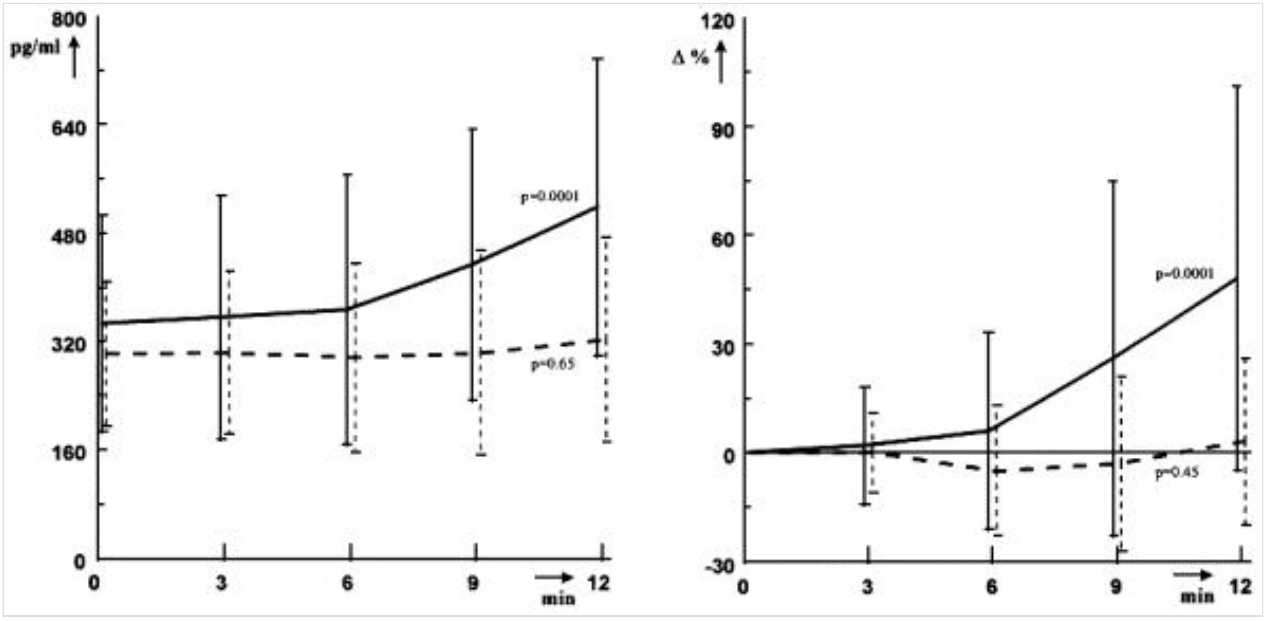

FIG. 3. Norepinephrine plasma concentration during dobutamine infusion. Dotted line, continuous-infusion protocol; solid line, stepwise incremental protocol. Values expressed as mean ± SD; p value indicates the difference between rest and 12 min.

		0 min	3 min	6 min	9 min	12 min
Dopamine (pg/ml)	Continuous	15 ± 8	18 ± 10	20 ± 11	19 ± 8	20 ± 12
ANOVA p value, 0.01	Stepwise	22 ± 15	32 ± 20	59 ± 34	62 ± 49	51 ± 22
	p Value	0.10	0.03	0.002	0.01	0.001
Epinephrine (pg/ml)	Continuous	23 ± 17	24 ± 18	27 ± 12	26 ± 10	28 ± 11
ANOVA p value, 0.30	Stepwise	28 ± 7	27 ± 11	27 ± 19	28 ± 14	36 ± 13
Norepinephrine (pg/ml)	Continuous	301 ± 106	304 ± 122	297 ± 145	304 ± 151	323 ± 152
ANOVA p value, 0.01	Stepwise	347 ± 167	356 ± 109	367 ± 114	433 ± 121	519 ± 283
	p Value	0.20	0.10	0.04	0.002	0.0001

Continuous, infusion of dobutamine, 10 mg/kg/min for 12 min (n = 11); Stepwise, incremental infusion of dobutamine 10, 20, 30, and 40 mg/kg/min, 3-min interval (n = 43); ANOVA p value, possible interaction between protocol and time; p value, difference between the two infusion protocols.

TABLE 2. Plasma catecholamine responses

During dobutamine infusion, there was a large variation in plasma dobutamine concentration between individuals (Fig. 2). However, the plasma concentration of dobutamine at which increased myocardial thickening was detected was similar with both protocols (80 ± 40 vs. 92 ± 48 ng/ml). Improved wall thickening was noted in two of 11 patients between 0 and 3 min and in 11 of 11 patients between 3 and 6 min in both protocols.

In patients 6 and 9, new wall-motion abnormalities and ECG changes were detected without the occurrence of angina pectoris. In both patients, the two segments in which new wall-motion abnormalities occurred were not used for the assessment of contractile reserve. Ischemia was induced only during the stepwise protocol, at the highest dobutamine dose-step (40 μg/kg/min).

DISCUSSION

Our results indicate that during both protocols, stepwise and continuous dobutamine infusion, myocardial contractile reserve can be detected. Endogenous catecholamine release may enhance the stress induced by dobutamine during the stepwise protocol only.

Optimal dobutamine plasma concentration for assessment of contractile reserve

The optimal duration and infusion dose of dobutamine for the assessment of myocardial viability or ischemic threshold has been studied extensively (3,6,13-16). Increased myocardial wall thickening is detected by using a two-step protocol, starting with 2.5 or 5 μg dobutamine/kg/min for 5 min each. In our study, contractile reserve, in regions with normal wall motion at rest, was detected by a dobutamine concentration of 80 ± 40 versus 92 ± 48 ng/ml or HR increment of 14 ± 5 versus 12 ± 7 beats/min (mean ± SD) for the continuous or stepwise protocol. This emphasizes the importance of plasma dobutamine concentration and not of the infused dose at a given time, especially because the plasma dobutamine concentration varies greatly between patients during the same protocol (Fig. 2) (17).

These data are in agreement with the studies of Sklenar et al. (19) and Berg et al. (20). The latter study showed, in healthy volunteers with a low-dose dobutamine infusion protocol (starting with 0.5 up to 5 μg/kg/min) at 20-min intervals, that echocardiography-enhanced systolic function occurred at dobutamine plasma concentrations >17 ng/ml. This level was reached in all of our patients after 6 min of dobutamine infusion, irrespective of using the low-dose or stepwise infusion protocol.

Sklenar et al. (19) studied maximal echocardiography-detected wall thickening in a pig model by using different dobutamine-infusion rates after coronary occlusion for evaluation of myocardial viability. Dobutamine started at 5 μg/kg/min with a 3-min interval up to 20 μg/kg/min. There was an excellent negative correlation between infarct size and wall thickening during dobutamine infusion. The optimal infusion rate was 15 μg/kg/min, but a dose of 20 μg/kg/min did not increase thickening any further. The study of Sklenar et al. differed from our study (it did not provide corresponding plasma dobutamine values). Our stepwise protocol started higher with 10 μg/kg/min dobutamine instead of 5 μg/kg/min, and wall thickening was evaluated after coronary occlusion. Both studies showed that after 6-min dobutamine infusion, adequate plasma concentrations were achieved to evaluate improved wall thickening.

The study results are in contrast to the results of Cohen et al. (15), which showed a close relation between HR increment and dobutamine-infusion rate. However, instead of 10 μg/kg/min, they used a 5-μg/kg/min dobutamine increment every 3 min. Considering the plasma half-life of dobutamine (3 min), this regimen allows more reproducible dobutamine pharmacokinetics between different patients. In all our patients, a sufficient plasma dobutamine concentration or HR increment was reached after 6 min.

For the continuous low-dose protocol, we used an infusion rate of dobutamine of 10 µg/kg/min. This dose, which is higher than most low-dose infusion protocols, was chosen because we wanted to be certain to achieve a sufficient plasma dobutamine concentration to evaluate improved wall thickening. This dose was previously determined in a study evaluating the effect of aging on dobutamine pharmacokinetics (8). Because of a large interpatient variation during a "low-dobutamine" infusion protocol (2.5 or 5 µg/kg/min), the duration of infusion may not be sufficient to achieve an adequate plasma dobutamine concentration in all patients. The optimal plasma dobutamine concentration was reached in all patients in our study at an HR increment of maximally 18 beats/min compared with resting HR in patients without [beta]-blockers. This would imply a continuation of dobutamine infusion in patients who do not have increased wall thickening at low-dose dobutamine until an HR increment of 18 beats/min compared with resting HR frequency is achieved.

For the detection of myocardial ischemia, a stepwise increment of dobutamine infusion is used. Ischemia is detected if new wall-motion abnormalities occur. A positive response at low-dose or low-HR threshold is associated with a complex coronary artery lesion (13-16). A recent development is the introduction of the semiquantitative stress test (14,15). The presence of ischemia is noted as well as the extent (number of segments), the severity at peak stress (hypokinesia vs. dyskinesia), and the stage at which ischemia occurs. Additional information can be may be provided by using tissue Doppler imaging and automatic borderline-contour detection. Considering the wide range in dobutamine plasma concentration during the first dose step, the infusion rate at which wall-motion abnormalities occur may be of limited value. More adequate for the estimation of the severity of coronary artery disease may be the HR increment at which ischemia occurs. This approach will overcome pharmacokinetic and pharmacodynamic differences between patients.

Endogenous catecholamine responses

The catecholamine responses during both infusion protocols differed. There is an increase of plasma norepinephrine and dopamine concentration during the stepwise protocol compared with a continuous infusion of dobutamine. Previous studies (18) analyzing the pharmacokinetic effect of dobutamine by using animal models, anesthetized dogs and isolated guinea-pig atria after depletion of neuronal catecholamines, showed no indirect sympathomimetic activity of dobutamine. The dobutamine-infusion dose used varied from 0.3 to 30 µg/kg/min. During the continuous infusion dose, we also found no evidence of indirect sympathetic activity. However, by using higher doses of dobutamine, <=40 µg/kg/min, we demonstrated a clear activation of the sympathetic nerve system. This alters the conclusion of previous studies, indicating that at low dobutamine plasma concentration there is no contribution of endogenous catecholamines, in contrast to high dobutamine plasma concentrations. These findings may have clinical implications in patients with severe left ventricular dysfunction; the DSE test has significantly more arrhythmogenic side effects (21). This may be caused by a further increase of circulating catecholamines during the DSE test. In these patients, a continuous dobutamine infusion may produce fewer side effects.

Clinical implications

In patients studied for the presence of myocardial viability as well as ischemia, the stepwise-infusion protocol and not the continuous-infusion protocol can be used. All patients achieve an adequate plasma dobutamine concentration at stage two, 20 µg dobutamine/kg/min, at which an increased wall thickening can be detected. For the detection of ischemia, the infusion has to be continued. In patients with severe left ventricular dysfunction and elevated circulating catecholamines, further increases during the DSE by using the stepwise incremental dobutamine-infusion protocol may induce cardiac arrhythmias.

Study limitations

Our study has several limitations. We detected contractile reserve only in wall regions with a normal function at rest without ischemia at peak stress and not in regions with resting wall-motion abnormalities. The study was not designed to evaluate "viable" myocardium in dysfunctional segments at rest, which would necessitate an independent investigation such as 18-fluorodes-oxyglucose/technetium-99m tetrofosmin studies. Also no coronary angiography as a gold standard was presented in this study.

CONCLUSIONS

1. A 6-min dobutamine infusion was required with both protocols (continuous and stepwise incremental infusion) to reach an adequate plasma dobutamine concentration to induce a visible increase of wall thickening in "normal" myocardium in all patients.

2. There is evidence that dobutamine effects during stress echocardiography by using the stepwise incremental dobutamine-infusion protocol are mediated through endogenous release of catecholamines.

3. The stepwise protocol can be used for assessment of myocardial contractility reserve, as well as for the detection of ischemia during dobutamine infusion of 10-40 µg/kg/min.

4. An HR increment of 18 beats/min is required to evaluate the presence of myocardial viability during the stepwise dobutamine-infusion protocol.

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Key Words: Dobutamine; Catecholamine; Contractile reserve

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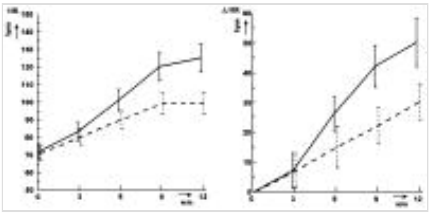
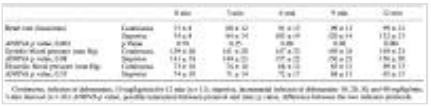


Fig. 1



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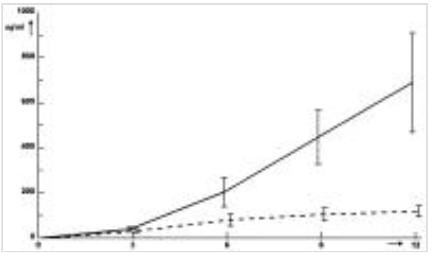

Fig. 2

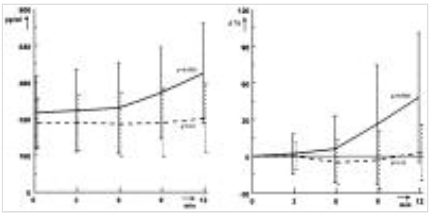

Fig. 3

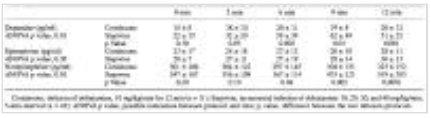

Table 2

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