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Cardiac Chronotropic Responsiveness to Beta-Adrenoceptor Stimulation Is Not Reduced in the Elderly

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Objectives. **This study evaluated cardiac beta-adrenoceptor responsiveness in the elderly.**

Background. **The hypothesis of reduced cardiac beta-adrenoceptor responsiveness in the elderly is based on a smaller increase in heart rate after administration of isoproterenol, a nonselective $beta_1$- and $beta_2$-adrenoceptor agonist. By means of dobutamine–stress–echocardiography we were able to retest the hypothesis more accurately because dobutamine is a relatively selective $beta_1$-adrenoceptor agonist with weak $beta_2$- and alpha-adrenoceptor stimulant activity that prevents baroreflex-mediated changes in heart rate.**

Methods. **After administration of stepwise incremental infusions of dobutamine, we measured heart rate and blood pressure responses in 360 patients who had no beta-adrenergic blocking agent therapy and no side effects during the stress test. For each patient we calculated the dose of dobutamine required to increase heart rate by 50% of the maximal heart rate during the highest dose of dobutamine.**

Results. **No relation was found between age and sensitivity to dobutamine (n = 293). Power analysis revealed that this negative finding was not the result of inadequate sample size. In contrast to the prevailing hypothesis, an increased heart rate response to dobutamine was found even in a subgroup of "healthy" elderly subjects (i.e., those without concomitant disease or acute myocardial ischemia, n = 67) that was not related to changes in blood pressure during stress. However, in subjects with acute ischemia (n = 109), smokers (n = 151) or patients with a history of a previous myocardial infarction (n = 148), dobutamine sensitivity was reduced in the elderly despite a diminished change in systolic blood pressure with advanced age during dobutamine infusion. This phenomenon could be explained by a decrease in efferent cardiac baroreflex sensitivity, as has been observed during acute myocardial ischemia. There were no age-related differences in plasma concentrations of dobutamine.**

Conclusions. **No evidence for reduced beta-adrenoceptor responsiveness to dobutamine was found in "healthy" elderly subjects.**

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Adrenergic responsiveness in humans changes with aging (1,2). Changes in responses to neurotransmitters may have important clinical consequences for drug therapy in elderly subjects. The beta-adrenoceptor has been the subject of extensive pharmacologic and physiologic studies (3–6). Beta-adrenoceptor activation induces a positive inotropic and chronotropic effect on the heart, and $beta_2$-adrenoceptor stimulation induces vascular relaxation. The beta-$_1$-adrenoceptor is thought to become less sensitive with aging. Evidence for this hypothesis is circumstantial: Basal concentrations of norepinephrine are increased in the elderly, and beta-adrenoceptor densities and affinities are unchanged (2); yet, the chronotropic response to bolus infusions of isoproterenol (a $beta_1$- and $beta_2$-adrenoceptor stimulant) in older animals and senescent humans is decreased (4,7,8). In the elderly, the reduced effect of isoproterenol on heart rate may be caused by an attenuated direct chronotropic response mediated by $beta_1$- and $beta_2$-adrenoceptors or a reduced activation of the baroreflex in response to $beta_2$-adrenoceptor–mediated vasodilation induced by isoproterenol. In previous animal studies (7,8), chiefly in the rat, baroreflexes were intact, and isoproterenol was given as a bolus injection. In pithed rats, where the baroreflex response was eliminated, no difference was found in the chronotropic effect of isoproterenol in young and elderly rats (5).

The present study evaluates the chronotropic responsiveness to incremental stepwise infusions of dobutamine, a relatively selective $beta_1$-adrenoceptor agonist with weak alpha- and $beta_2$-adrenoceptor stimulant activity in relatively low dosages (9), which, in contrast to isoproterenol, does not evoke the baroreflex-induced changes in heart rate induced by vasodilation (10). Our analysis is based partly on a previously published study of dobutamine stress echocardiography (11). Data for subjects with hypertension, diabetes mellitus, previous myocardial infarction, angina pectoris, echocardiographic evidence of myocardial ischemia during dobutamine infusion and a history of smoking were analyzed separately.

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Methods

Patient characteristics. Four hundred fifty-one patients underwent dobutamine stress echocardiography during the period 1992 to 1994. Patients taking a beta-adrenergic blocking agent and those who experienced side effects during dobutamine infusion, necessitating interruption of the test, were excluded from this study, leaving a total of 360 patients for analysis (243 men, 117 women; mean age 61 years, range 22 to 90). One hundred twelve patients (31%) were >70 years old; 148 (41%) had a previous myocardial infarction; 104 (28%) had angina pectoris; 39 (11%) had diabetes mellitus (with drug therapy); and 123 (34%) had hypertension, defined as sustained elevated diastolic blood pressure ≥90 mm Hg with or without drug treatment. Indications for examination were evaluation of chest pain (n = 123 [34%]) and preoperative cardiac risk stratification (n = 237 [66%]) (11). Dobutamine plasma concentrations were measured during the test in 34 patients (mean age 62 years, range 40 to 77).

Dobutamine stress test. The dobutamine stress protocol was approved by the hospital ethics committee. After giving informed consent, the patients underwent a two-dimensional echocardiographic examination at rest. Dobutamine was administered intravenously with an infusion pump, starting at 10 μg/kg body weight per min for 3 min, followed by stepwise increments of 10 μg/kg per min every 3 min to a maximum of 40 μg/kg per min. The dobutamine infusion was stopped if the target heart rate (85% of a theoretic maximal heart rate was achieved: for men, (220 − age) × 85%; for women, (200 − age) × 85% (12). Blood pressure and heart rate were measured at rest and at every infusion step with an automatic device (Accutorr A1, Datascope Corp.). 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 videotape during the last minute of every dose step. Criteria for interruption of the test were horizontal or downsloping ST segment depression >2 mm at 80 ms after the J point; ST segment 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 caused by dobutamine. Off-line assessment of echocardiographic images was performed by two investigators (D.P., P.M.F.) Reduced wall thickening and new wall motion abnormalities are the hallmarks of ischemia (13). A new wall motion abnormality was defined as an increase in score between rest and stress.

Dobutamine measurement in plasma. Blood samples were taken at the end of every dose step. Dobutamine was measured in plasma as described by Alberts et al. (14). In brief, after a liquid/liquid extraction and derivatization with the fluorogenic agent 1,2-diphenylethylenediamine, dobutamine was measured by fluorometric detection after separation by high performance liquid chromatography.

Statistical analysis. The effect of dobutamine on blood pressure was assessed by the paired *t* test. By linear regression analysis the equations of the heart rate-log dose–response curves were calculated for each individual patient. The sensitivity for dobutamine was calculated as ED_{50}-HR, which is the dose required to increase heart rate by 50% of the maximum at the highest dose of dobutamine. "Healthy" patients were defined as those without the presence of any of the clinical variables (angina, previous infarction, hypertension, diabetes and smoking) and acute myocardial ischemia. Dobutamine sensitivity, systolic and diastolic blood pressure change in relation to clinical variables and acute myocardial ischemia (echocardiographically detected ischemia, ECG changes or angina during dobutamine infusion) were compared between various groups and between healthy subjects by multivariate linear regression analysis, including an interaction term. A two-tailed p value <0.05 was required for significance. A power analysis was performed to determine the possibility of a beta-error. All data are expressed as mean value ± SD.

Results

Heart rate increased from 72 ± 8 to 132 ± 14 beats/min (p = 0.0001, n = 360). Systolic blood pressure increased during dobutamine infusion from 144 ± 24 to 150 ± 28 mm Hg (p = 0.001). Diastolic blood pressure decreased from 82 ± 12 to 76 ± 18 mm Hg at the maximal dose of dobutamine (p = 0.01).

Ages for all subjects as well as for various subgroups by clinical variable are presented in Table 1. Between-group comparisons did not reveal statistically significant differences in age, except for subjects with a history of angina pectoris (p = 0.02).

Between-group comparisons of ED_{50}-HR for all subjects as well as for various subgroups did not reveal statistically significant differences in dobutamine sensitivity (Table 1).

No relationship was found between age and sensitivity to dobutamine (n = 293). In this group, a slope (ED_{50}-HR vs. age) of less than −0.07 would have been detected with a power of 80%. Subsequently within-group analyses of the relation between age and ED_{50}-HR were performed. In four groups a relation was found between age and ED_{50}-HR ($p < 0.05$): "healthy" subjects, in whom an increased sensitivity was noted with advancing age (p = 0.03); and subjects with a previous myocardial infarction (p = 0.01), those with acute myocardial ischemia (p = 0.03) and those who smoked (p = 0.03), in whom a decreased sensitivity was noted with advancing age.

This higher sensitivity of the "healthy" elderly to dobutamine was not related to the reduced increase in systolic pressure during dobutamine infusion (ED_{50}-HR vs. systolic blood pressure change [mm Hg], p = 0.12) (Table 1). Diastolic blood pressure remained unchanged in healthy elderly subjects and in different subgroups.

In all subjects, except for those classified as "healthy" or diabetic, a positive correlation was present between systolic blood pressure increment and ED_{50}-HR, which may be explained by an inhibition of dobutamine-induced tachycardia by a baroreflex-mediated increase in vagal activity to the heart, which inhibits the chronotropic response to dobutamine.

Table 1. Influence of Age on Heart Rate and Blood Pressure Response to Infusion of Dobutamine and Relation of Dobutamine-Induced Heart Rate Response Versus Systolic Blood Pressure Change

						ED_{50}-HR Versus Age			Change in SBP Versus Age			Change in ED_{50}-HR Versus SBP		
	No. of Pts	Age (yr) (mean ± SD)	p Value*	ED_{50}-HR (μg/kg per min)	p Value*	Slope	p Value†	p Value‡	Slope	p Value†	p Value‡	Slope	p Value†	p Value‡
All patients	293	61.8 ± 1.4	0.06§	20.9	0.16§	+0.05	0.06§	0.007	−0.42	0.002	0.14§	+0.05	0.003	0.90§
Diabetes	39	62.1 ± 4.1	0.22§	20.5	0.15§	+0.10	0.15§	0.02	+0.13	0.82§	0.04	+0.04	0.32§	0.90§
Hypertension	123	62.1 ± 1.9	0.08§	21.0	0.22§	−0.03	0.50§	0.06§	−0.23	0.34§	0.06§	+0.08	0.005	0.70§
Smoking	151	61.4 ± 2.0	0.06§	21.0	0.25§	+0.08	0.03	0.003	−0.40	0.005	0.15§	+0.06	0.003	0.90§
History of AP	104	59.4 ± 2.2	0.02	21.1	0.2§	−0.07	0.21§	0.08§	−0.68	0.001	0.90§	+0.06	0.04	0.90§
History of MI	148	61.2 ± 1.8	0.06§	20.8	0.1§	+0.11	0.01	0.003	−0.40	0.002	0.15§	+0.07	0.004	0.80§
Acute ischemia	109	60.2 ± 2.1	0.06§	21.6	0.62§	+0.11	0.03	0.003	−0.52	0.004	0.40§	+0.05	0.01	1.0§
"Healthy"	67	65.0 ± 2.9		21.9		−0.14	0.03		−0.69	0.002		+0.05	0.12§	

*Unpaired *t* test of subgroups versus "healthy" patients. †Stepwise logistic regression analysis on slopes of linear regression analysis within one subgroup. ‡Stepwise logistic regression analysis on slopes of linear regression analysis between subgroups of patients and "healthy" patients. §Not significant. Acute ischemia = presence of new wall motion abnormalities or electrocardiographic changes or angina pectoris (AP) during stress; DBP (SBP) = diastolic (systolic) blood pressure change (mm Hg) during dobutamine infusion; ED_{50}-HR = dobutamine dose required to achieve 50% of maximal heart rate; "Healthy" = absence of smoking, hypertension, diabetes mellitus, previous myocardial infarction (MI) and ischemia during stress.

In subjects who smoked or who had a previous myocardial infarction, a decreased sensitivity to dobutamine was found in the elderly despite a diminished increase in systolic blood pressure change during dobutamine infusion. In subjects with a history of angina no relation was present between age and dobutamine sensitivity despite a decrease in systolic blood pressure change. In subjects with acute myocardial ischemia, a reduced sensitivity in the elderly was present despite an unchanged systolic blood pressure (a comparison between healthy subjects and those with acute ischemia is presented in Fig. 1). All four subgroups (history of infarction or angina, smoking or acute ischemia) showed evidence of a reduced dobutamine sensitivity in elderly patients.

In senescent subjects with diabetes or hypertension, no relation between age and sensitivity to dobutamine or systolic blood pressure change was found. The relation of age and ED_{50}-HR in "all" patients, acute ischemia, smoking, diabetes and a previous myocardial infarction was significantly different

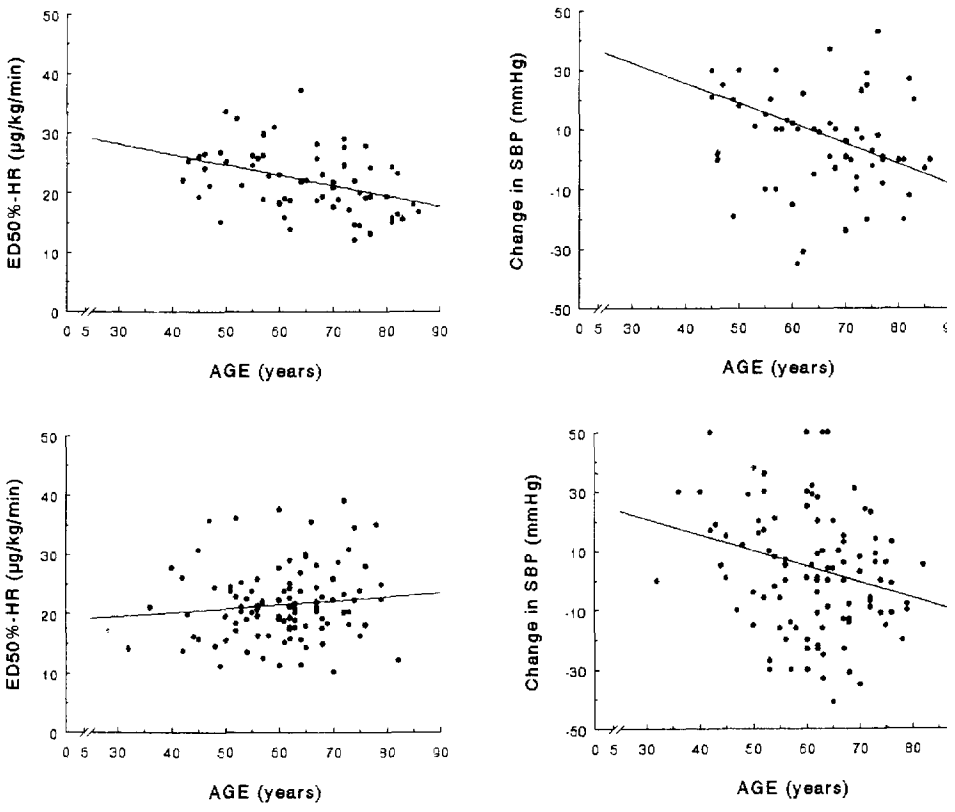

Figure 1. Changes in heart rate **(left)** and systolic blood pressure **(right)** during dobutamine infusion in "healthy" patients with no diabetes, hypertension, smoking, previous myocardial infarction or echocardiographic evidence of myocardial ischemia (n = 67) **(top)** and patients with acute myocardial ischemia during dobutamine infusion (echocardiographically detected ischemia or electrocardiographic changes or angina during dobutamine infusion) (n = 109) **(bottom)**. $ED_{50\%}$-HR = dobutamine dose (μg/kg per min) required to increase heart rate by 50% of the maximum at the highest dose of dobutamine; SBP = systolic blood pressure.

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Table 2. Increase in Plasma Concentrations of Dobutamine During Different Test Stages in Patients ≤60 and >60 Years Old

Dobutamine Infusion (μg/kg per min)	Dobutamine Plasma Concentration (ng/ml)		p Value
	Age ≤60 yr (n = 20)	Age >60 yr (n = 14)	
0	0	0	NS
10	32 ± 17	26 ± 9	NS
20	220 ± 55	220 ± 43	NS
30	552 ± 62	542 ± 59	NS
40	917 ± 118	910 ± 90	NS

Data presented are mean value ± SD.

from those of healthy subjects (Table 1). They all showed a reduced dobutamine sensitivity compared with that in healthy subjects, which could only be explained on the basis of systolic blood pressure changes during the test in subjects with diabetes, whereas the relation of ED_{50}-HR and systolic blood pressure change was not different. Analyses of the sensitivity to dobutamine in absolute terms (beats/min) rather than relative changes (ED_{50}-HR) yielded similar results.

During dobutamine infusion there was a large variation in plasma dobutamine concentration between individual subjects. When subjects >60 and <60 years old were compared, there was no significant interpatient difference in the increase of dobutamine plasma concentrations during the stress test between these two groups (Table 2).

Discussion

The effects of aging on beta-adrenoceptor–mediated responses have been studied mainly by observing the chronotropic effects of bolus injections of isoproterenol in rats (7,8). The finding of reduced cardiac chronotropic responsiveness to beta-adrenoceptor stimulation by isoproterenol has been confirmed in humans, where elderly subjects were screened for the absence of coronary artery disease by history and physical examination only (3,4). A decreased heart rate response to isoproterenol in the elderly can be caused by a reduced direct $beta_1$- or $beta_2$-adrenoceptor–mediated chronotropic response or a reduced baroreflex sensitivity to $beta_2$-adrenoceptor–mediated vasodilation occurring during isoproterenol infusion. A study by Docherty et al. (5) in pithed rats, where the baroreflex interference was abolished, showed no difference of isoproterenol-induced tachycardia in young and old rats.

In contrast to isoproterenol, dobutamine has little effect on blood pressure because of its weak stimulation of $alpha_1$- and $beta_2$-adrenoreceptors in peripheral blood vessels in the low dose range. Indeed, in our study diastolic blood pressure did not increase but in fact decreased significantly, but only by an average of 6 mm Hg. The cardiac chronotropic effect of dobutamine is mainly due to $beta_1$-adrenoceptor stimulation (9).

Beta-adrenoceptor and aging. The present study shows no evidence of reduced beta-adrenoceptor sensitivity to dobutamine in senescent subjects. In subgroups of "healthy" elderly subjects (i.e., those without diabetes, hypertension, smoking and angina and with normal echocardiographic findings at rest with no evidence of ischemia during dobutamine stress), an increased sensitivity for dobutamine-induced tachycardia was found. In these healthy subjects this response could not be explained by a reduced increase in systolic pressure in the elderly because there was no correlation between blood pressure changes and dobutamine sensitivity. Compared with previous findings, the present results might be explained by the absence of silent coronary artery disease in otherwise appealingly healthy elderly subjects because dobutamine stress echocardiography testing is a highly sensitive method for detecting silent myocardial ischemia (13).

Effect of acute myocardial ischemia. In the present study we found a decreased sensitivity to dobutamine in elderly subjects with acute myocardial ischemia during stress. Hageman et al. (15) recently described an attenuated baroreflex sensitivity and reduced efferent cardiac sympathetic activity during experimental acute myocardial ischemia in a canine model. Such a phenomenon could have contributed to the apparent reduced sensitivity to dobutamine in our subjects with acute myocardial ischemia induced by dobutamine. In subjects with diabetes or hypertension, no relation between age and sensitivity to dobutamine or between heart rate and blood pressure changes and dobutamine sensitivity was found. In patients with diabetes this may be explained by autonomic neuropathy (16). In subjects with long-standing hypertension, reduced baroreflex sensitivity might contribute to this phenomenon.

In senescent subjects with a previous myocardial infarction, angina and smoking a reduced or unchanged heart rate response to dobutamine was observed despite a diminished increase in systolic blood pressure during the test in the elderly, indicating that there was indeed a reduced sensitivity in the elderly subjects in the four subgroups. The mechanism of this finding in the absence of acute ischemia during the dobutamine stress echocardiography test remains obscure.

Pharmacokinetic data. Pharmacokinetic data on dobutamine in humans are scant. The pharmacokinetic model of dobutamine is that of a first-order derivate, indicated by the linear plasma correlation between infusion rate and concentration (17,18). These previous studies investigated dobutamine infusions between 2.5 and 10 μg/kg per min, in contrast to the present study in which the maximal dose was 40 μg/kg per min. However, pharmacokinetic changes in dobutamine in the elderly, as a possible explanation for our findings, are in our view unlikely because in a study of 34 subjects we found no-age related differences in plasma dobutamine concentrations during infusions.

Conclusions. Sensitivity for dobutamine-induced tachycardia is not reduced in the elderly unless there is evidence of ischemic heart disease. Moreover, an increased sensitivity was found even in "healthy" elderly subjects.

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