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Effects of Dobutamine on Hemodynamics and Left Ventricular Performance after Cardiopulmonary Bypass in Cardiac Surgical Patients

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Background: **Dobutamine is commonly used to improve ventricular performance after cardiopulmonary bypass. The authors determined the effect of dobutamine on hemodynamics and left ventricular performance immediately after cardiopulmonary bypass in patients undergoing coronary artery bypass graft surgery.**

Methods: **One hundred patients received sequential 3-min infusions of dobutamine at 0–40 $\mu g \cdot kg^{-1} \cdot min^{-1}$ immediately after cardiopulmonary bypass. Ten additional patients who received no dobutamine served as controls. Hemodynamics and left ventricular performance (fractional area change by transesophageal echocardiography, stroke volume index, and thermodilution cardiac index) were measured. Mixed-effects modeling accounted for repeated-measures data and interindividual differences and allowed for potential effects of covariates.**

Results: **Heart rate increased in a dose-dependent manner. The slope of HR *versus* dobutamine dose was steeper in individuals in whom peak dobutamine dose was not reached compared with that in the remaining individuals; slope decreased 2.71 ± 0.68% per year of age. Dobutamine affected blood pressure minimally, but slightly decreased pulmonary capillary wedge pressure and central venous pressure. Systemic vascular resistance initially increased with dobutamine ≤ 10 $\mu g \cdot kg^{-1} \cdot min^{-1}$ and remained constant with larger doses. Dobutamine produced a dose-dependent increase in left ventricular performance, primarily by increasing heart rate, because stroke volume index decreased with dobutamine dose.**

Conclusion: **Our results suggest that the response to graded dobutamine infusion in the post–cardiopulmonary bypass period differs from that previously reported. After cardiopulmonary bypass, the dominant mechanism by which dobutamine improves left ventricular performance is by increasing heart rate. Dobutamine affects blood pressure minimally. (Key words: Aortocoronary bypass; heart.)**

SINCE its introduction into clinical practice in 1978, the synthetic catecholamine dobutamine has been used in a number of different clinical settings. As a positive inotrope, dobutamine has been used in patients who require temporary support of failing myocardium, as an intermediate bridge for patients who are awaiting cardiac transplantation, and as an adjunct in cardiac surgery for patients who require inotropic support to be successfully separated from cardiopulmonary bypass (CPB).

Many previous clinical studies evaluated dobutamine in limited intravenous dose ranges, typically no higher than 10–15 $\mu g \cdot kg^{-1} \cdot min^{-1}$.[1–3] Most of these studies included only a small number of patients[2–4] and involved

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cardiac surgery patients in the postoperative period (in the intensive care unit), often hours after these patients had separated from CPB. After undergoing CPB, early reperfusion begins a period of relative hemodynamic instability in which small and rapid changes in ventricular loading, myocardial perfusion pressure, and the endogenous inotropic state can change global ventricular performance markedly. In addition, the early reperfusion period is characterized by a high incidence of regional or global ventricular dysfunction.[5] As a result, the response to dobutamine during this early reperfusion period may differ substantially from that observed in the intensive care unit. Therefore, a systematic approach to evaluating the pharmacologic effects of such inotropes in this critical period is necessary.

As part of a larger study examining myocardial viability after CPB using dobutamine stress echocardiography, we had the opportunity to evaluate the pharmacologic effects of a broad dosing range of dobutamine (up to 40 $\mu g \cdot kg^{-1} \cdot min^{-1}$) on hemodynamics and left ventricular performance in the early post-CPB period in patients undergoing coronary artery bypass graft (CABG) surgery. The present study aimed to extend the dose-response range and to evaluate left ventricular performance by transesophageal echocardiography (TEE) to yield new information to guide optimal dobutamine dosing strategies in such patients.

Methods

Study Population

After the study was approved by the institutional human research committees and informed consent obtained, 121 patients scheduled for CABG surgery at the San Francisco Veterans Affairs Medical Center, University of California-San Francisco/Mount Zion Medical Center, or Kaiser Permanente Medical Center between April 1993 and January 1996 were enrolled. Patients who met the following criteria were excluded: (1) combined CABG-valvular surgery; (2) emergent surgery, including those in cardiogenic shock; (3) need of preoperative inotropic support; (4) history of an adverse reaction to dobutamine; or (5) history of esophageal disease, precluding the insertion of the transesophageal echocardiographic probe.

Intraoperative Management

Standard monitors for patients undergoing CABG surgery were used. These included five-lead electrocardiography, radial and pulmonary arterial catheters, and TEE. Systolic pressure, diastolic pressure, mean arterial pressure (MAP), pulmonary artery pressure, and heart rate (HR) were measured continuously (average, every 60 s) on entry into the operating room and stored in a lap-top computer (Toshiba T1200 XE; Toshiba Corporation, Tokyo, Japan). Systemic and pulmonary vascular resistance (SVR and PVR), cardiac index (CI), and stroke volume index (SVI) were calculated from measured variables using standard equations.

The anesthetic regimen for both the non-CPB and CPB periods was standardized to a combination of sufentanil, midazolam, and isoflurane as needed. CPB was conducted using a membrane oxygenator with hemodilution and moderate systemic hypothermia (minimum temperature reached during CPB was 30 ± 2°C). Multidose cold crystalloid cardioplegia was used for myocardial protection during CPB. Distal anastomoses were usually performed first during continuous aortic cross-clamping, followed by proximal vein grafting during partial aortic occlusion.

Transesophageal Echocardiography

After induction of general anesthesia, short-axis (midpapillary) views of the left ventricle were obtained with a Hewlett-Packard 1500/Omniplane TEE package (Andover, MA). During the collection of dobutamine dose-response hemodynamic data, TEE cardiac images were stored continuously on S-VHS videotape for off-line analysis.

Using a Freeland Cardiology Workstation (Boulder, CO), left ventricular end systolic area (ESA) and end diastolic area (EDA) were measured off-line.[6] One investigator who was blinded to the clinical course of the patients performed all of the quantitative measurements. The measured intraobserver variability between replicate estimates was 4 ± 4% (SD). Fractional area change (FAC), a two-dimensional estimate of ejection fraction, was calculated as:

$$FAC = (EDA - ESA)/EDA \times 100\% \quad (1)$$

Echocardiographic data for each predefined measurement point were measured in duplicate and averaged.

Dobutamine Dose Response

At completion of CABG surgery, patients were separated from CPB using standard techniques of gradually reducing pump flow and increasing ventricular preload. Baseline hemodynamic data and TEE images were ob-

tained within 10 min of cessation of CPB, before protamine administration. After baseline measurements were obtained, dobutamine was infused at 5, 10, 20, 30 and 40 $\mu g \cdot kg^{-1} \cdot min^{-1}$ into the central circulation in consecutive graded steps for a duration of 3 min at each dose.[7] Hemodynamic and echocardiographic data were obtained at the end of each infusion period during end expiration.

For patients with MAP < 50 mmHg and decreased FAC as observed on TEE while being separated from CPB, dobutamine was infused at 5 $\mu g \cdot kg^{-1} \cdot min^{-1}$ shortly before CPB ended. For 21 patients who received dobutamine for separation from CPB, the initial hemodynamic measurements were measured at the lowest dobutamine dose after separation from CPB before the dose escalation study and were considered as the baseline values.

Dobutamine infusion was stopped before reaching the maximum dose of 40 $\mu g \cdot kg^{-1} \cdot min^{-1}$ if patients developed hypotension (systolic blood pressure < 80 mmHg), hypertension (systolic blood pressure > 200 mmHg or diastolic blood pressure > 100 mmHg), tachycardia (> 85% of predicted maximum HR by age), ventricular arrhythmias, ST-segment depression or elevation (≥0.1 mV), or development of new or worsening regional wall motion abnormalities as determined by continuous echocardiographic monitoring.[5] These criteria for stopping dobutamine were monitored by one physician investigator who was present during the entire study. During the infusion, no surgical interventions or manipulations were allowed.

Controls

To separate the effects of escalating dobutamine infusion from those caused by time-dependent changes, we studied an additional 10 patients undergoing CABG surgery who did not receive dobutamine infusion. All 10 patients had identical study measurements performed in the same manner as those who received dobutamine.

Statistical Analysis

We assumed that the relationship between dobutamine infusion rate and each of the effects measured (*e.g.*, HR) could be described by a linear or a nonlinear relationship. For each effect measure, we fit a linear model and then evaluated the quality of fit visually (by plotting residual differences between observed and predicted values) to assess whether a nonlinear model was necessary. Because the quantity of data was small and because some individuals had missing data (*e.g.*, a result of *a priori* hemodynamic limits), we used mixed-effect modeling (NONMEM Version V, level 1.0L4[8]). With this approach, data for all subjects were analyzed simultaneously, accounting for the repeated-measures nature of the data and interindividual differences, and allowing for the effects of covariates such as age and gender.

The basic linear model is represented by the equation:

$$\text{Dependent variable} = \text{Intercept} + \text{Slope} \cdot \text{Dobutamine} + \text{Error} \quad (2)$$

where Dobutamine is the dose in $\mu g \cdot kg^{-1} \cdot min^{-1}$, and Error is the residual difference between the observed and predicted dependent variable. To account for interindividual variability, we assumed that there was a "typical value" for slope (*i.e.*, the value that best described the sample, equivalent to the mean or median value in a traditional two-stage analysis) and that each patient had a value for their intercept that related to the typical value as follows:

$$\text{Slope(individual)} = \text{Slope(population)} + \text{Eta(1)} \quad (3)$$

where Eta(1) is a normally distributed variable with a mean of 0.0 and a variance of omega[2] estimated in the analysis. Similarly, individual values for intercept were assumed to have a mean value equal to the typical value and to be normally distributed. We assumed that measurement error (variance) between the observed and measured values was homoscedastic (*i.e.*, the error in measurement of HR was the same at a HR of 50 *vs.* 100 beats/min).

Dependent variables tested were HR, MAP, pulmonary capillary wedge pressure (PCWP), central venous pressure (CVP), SVR, PVR, CI, ESA, EDA, FAC, and SVI. After each population fit was complete, we used NONMEM's *post hoc* step to obtain Bayesian (individual) estimates of the parameters for each individual. These Bayesian estimates were plotted against covariates, and a smoother (a local linear regression) was used to determine whether covariates should be introduced into the model (see Results for an example). Covariates examined were age, weight, height, gender, cardiac risk factors, coronary anatomy, preoperative ejection fraction, preoperative use of β blockade, requirement of dobutamine for separation from bypass, and whether peak dobutamine dose was reached. If a covariate was introduced to the model (*i.e.*, adding a new parameter), the objective function

Table 1. Patient Demographics

Mean age (yr)	65 ± 10 (SD)
Gender (males/females)	77%/23%
Anginal pattern	26% (stable)
	74% (unstable)
History of hypertension	59%
History of myocardial infarction	36%
Preoperative β blockade	49%
Mean preoperative ejection fraction (%)	
(range 20–87)	52 ± 15 (SD)
Number of stenosed vessels	
1	3%
2	13%
≥3	84%
Left main	20%
Prebypass hemodynamics	
HR (bpm)	68 ± 15
MAP (mmHg)	95 ± 16
CI ($l \cdot min^{-1} \cdot m^{-2}$)	2.31 ± 0.48
SVR ($dyne \cdot s/cm^{-5} \cdot m^{-2}$)	1,674 ± 562
SVI ($l \cdot min^{-1} \cdot m^{-2}$ per beat)	30 ± 2
PCWP (mmHg)	15 ± 4

Dobutamine Dosing Group ($\mu g \cdot kg^{-1} \cdot min^{-1}$)	Number of Patients
0–10	8
0–20	18
0–30	19
0–40	34
5 only	2
5–10	4
5–20	5
5–30	2
5–40	3
10–30	2
10–40	3
Total	100

HR = heart rate; MAP = mean arterial pressure; CI = cardiac index; SVR = systemic vascular resistance; SVI = stroke volume index; PCWP = pulmonary capillary wedge pressure.

(−2 log likelihood, equivalent to residual sum of squares in traditional linear regression analysis) for the two models was compared using the likelihood ratio test.[9] An improvement (decrease) of 3.84 units in the objective function ($P < 0.05$) was considered statistically significant. Unless stated otherwise, all data are shown as mean ± SD or SE where appropriate.

For the 10 control patients, the hemodynamic and echocardiographic measurements at baseline and 3, 6, 9, 12, and 15 min after baseline were compared using one-way analysis of variance. $P < 0.05$ was considered statistically significant.

Results

Of 121 patients enrolled, 10 served as controls, and 100 received dobutamine in the immediate post-CPB period. Eleven patients were excluded from the study before dobutamine infusion for various technical and medical reasons.‡‡ Of 100 patients who received dobutamine, 34 completed the entire dobutamine dosing protocol from 0 to 40 $\mu g \cdot kg^{-1} \cdot min^{-1}$. Twenty-one patients required 5 or 10 $\mu g \cdot kg^{-1} \cdot min^{-1}$ dobutamine to separate from CPB (see table 1 for distribution of patients within dosing groups). Four patients who required epicardial pacing for bradycardia or heart block before dobutamine infusion were excluded from the analysis. Of the 79 patients who did not require dobutamine to separate from CPB, 45 did not reach the peak dose because they exceeded predetermined hemodynamic criteria (table 2).

Heart Rate

Heart rate increased in a dose-dependent manner (fig. 1). Covariate plots from the basic model for the effect of dobutamine on HR suggested that slope of this response differed between individuals for whom peak dobutamine dose was not reached and those remaining. Permitting a different slope for these two groups improved the quality of the fit of the model to the data (the objective function decreased 22.785 units; $P < 0.0001$; fig. 2). Covariate plots now suggested that the slope of the HR response to dobutamine decreased with age. This was evaluated by allowing slope to vary with age according to the following equation:

Table 2. Reasons for Not Reaching Peak Dose

Reason	Number of Patients
Tachycardia	18
Ventricular ectopy	5
Hypertension	10
Hypotension	2
ST-segment changes	4
Regional wall motion abnormalities	2
Tachycardia and hypertension	1
Surgical	1
Tachycardia and ST-segment changes	1
Ventricular ectopy and hypertension	1

‡‡ Two had inadequate echocardiographic images, five had either unstable circulation or ventricular ectopy before weaning from CPB, one had persistent ST elevation, one involved study equipment malfunction, one had aortic trauma, and one was on intra-aortic balloon counter-pulsation.

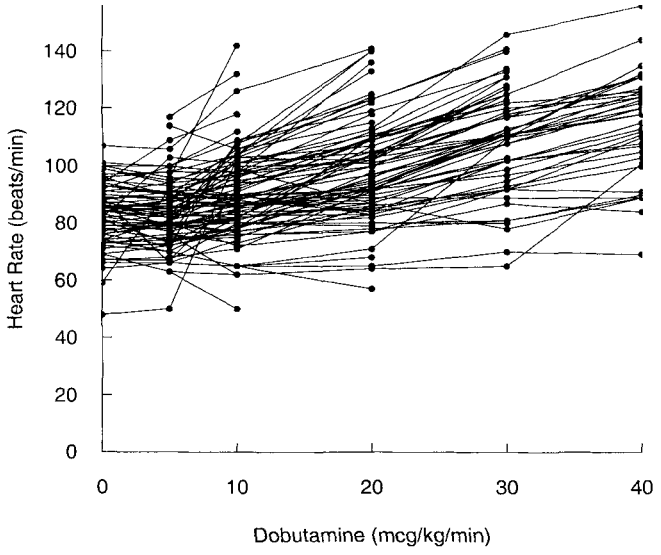

Fig. 1. Dose–response relationship for increasing doses of dobutamine on heart rate for each patient is shown.

$$\text{SLOPE} = \text{TVSLP} \cdot [1 + (\text{AGE} - 65) \cdot \text{FACT1}] \quad (4)$$

where TVSLP is the typical value for slope in either of the groups, age is reported in years, 65 is approximately the median value for age in this sample (this value was incorporated into the analysis so that the estimate for TVSLP applies to the typical, *i.e.*, median, individual) and FACT1 is the effect of age as estimated in the analysis. The objective function for this model improved 11.392 units ($P < 0.001$) compared with that in the model in which slope did not vary with age. HR increased an average of 0.684 ± 0.061 beats/min per $\mu g \cdot kg^{-1} \cdot min^{-1}$ dobutamine in the group that received the peak dobutamine dose and 1.45 ± 0.139 beats/min per $\mu g \cdot kg^{-1} \cdot min^{-1}$ dobutamine in the group that did not receive the peak dobutamine dose. For both groups, the slope of the HR *versus* dobutamine dose response decreased 2.71 ± 0.68% per year of age compared with the value at age 65 yr. Baseline HR (intercept) is shown in table 3.

Mean Arterial Pressure

A model in which MAP varied with dobutamine dose was tested. Because covariate plots suggested that slopes for different individuals centered around zero, we evaluated a model in which the typical value for slope was fixed to 0.0. The objective function for this model increased only 2.286 units ($P > 0.10$), indicating that slope did not differ statistically from 0, *i.e.*, that dobutamine did not increase MAP.

Filling Pressures

Both PCWP (fig. 3) and CVP decreased with increasing doses of dobutamine. Slopes and intercepts for both parameters are shown in table 3.

Systemic Vascular Resistance

The basic model suggested that baseline SVR varied with weight. This was incorporated into the model as:

$$\text{INTER} = \text{THETA}(1) \cdot [1 + (\text{WT} - 80) \cdot \text{FACT1}] \quad (5)$$

where INTER is the baseline SVR for an individual of a given weight, THETA(1) is the "typical value" for the population, WT is weight in kilograms, 80 is the median value for weight in the population, and FACT1 is estimated in the analysis. Compared with the previous

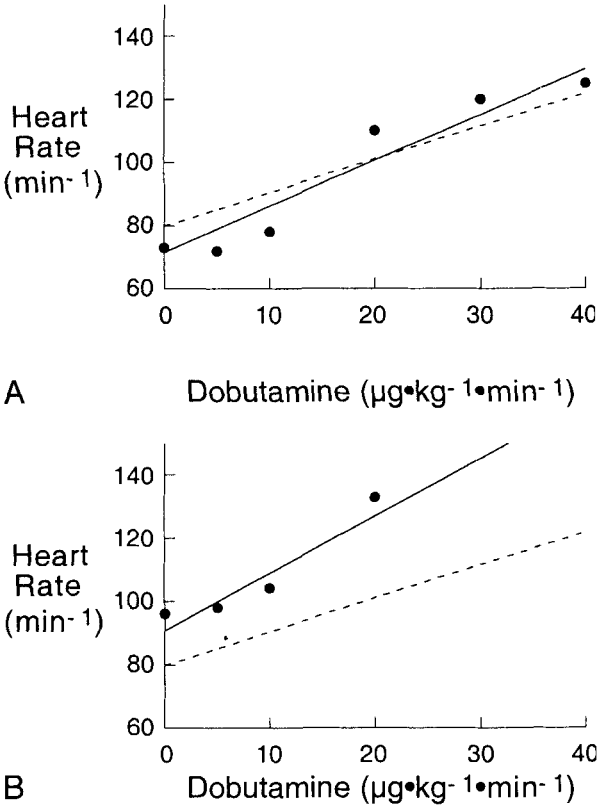

Fig. 2. Heart rate response to dobutamine is shown for two patients. The *solid line* is the population fit to the data for all subjects. The *dashed line* is the *post hoc* data, *i.e.*, the fit to that individual alone. (*A*) The subject shown received all doses of dobutamine; (*B*) the subject did not receive doses > 20 $\mu g \cdot kg^{-1} \cdot min^{-1}$. The mixed-effects analysis demonstrated that the slope of the heart rate–dobutamine relationship was steeper for subjects who did not receive the largest doses of dobutamine.

Table 3. Slopes and Intercepts for Parameters Measured

Parameter	Slope	Baseline Intercept
HR (beats/min)	[0.684 ± 0.061] · [1 − 0.0271 · (age-65)] (group who reached peak dose)	79.7 ± 1.1
	[1.45 ± 0.139] · [1 − 0.0271 · (age-65)] (group who did not reach peak dose)	79.7 ± 1.1
MAP (mmHg)	0.00	73.5 ± 1.0
PCWP (mmHg)	−0.083 ± 0.013	14.8 ± 0.5
CVP (mmHg)	−0.049 ± 0.009	12.4 ± 0.4
SVR (dyne · s/cm^{-5} · m^{-2})	12.9 ± 3.76 (≤ 9.62 μg · kg^{-1} · min^{-1})	1020 ± 37.6
	−0.009 ± 0.0014 (>9.62 μg · kg^{-1} · min^{-1})	
PVR (dyne · s/cm^{-5} · m^{-2})	0.00	129 ± 6.36
CI (l · min^{-1} · m^{-2})	0.019 ± 0.003	2.91 ± 0.077
SVI (l · min^{-1} · m^{-2} per beat)	−0.142 ± 0.028	36.5 ± 0.92
EDA (cm^2)	−0.046 ± 0.016	17.3 ± 1.19
ESA (cm^2)	−0.041 ± 0.011	8.30 ± 0.97
FAC (%)	0.119 ± 0.038	61.6 ± 1.39

Data are mean ± SE. A positive slope indicates the parameter increases with dobutamine and a negative slope, decreases with dobutamine. All non-zero values for slope are statistically different from zero ($P < 0.05$).

HR = heart rate; MAP = mean arterial pressure; PCWP = pulmonary capillary wedge pressure; CVP = central venous pressure; SVR = systemic vascular resistance; PVR = pulmonary vascular resistance; CI = cardiac index; SVI = stroke volume index; EDA = end diastolic area; ESA = end systolic area; FAC = fractional area change.

model, the objective function improved 23.564 units ($P < 0.001$).

Because plots of SVR *versus* dose suggested that slope of the SVR response might differ as a nonlinear function of dobutamine dose, we permitted slope to differ above and below a cutoff dose; the cutoff dose was estimated in the analysis. The objective function for this model improved 10.940 units compared with the basic model ($P < 0.001$). At doses up to 9.62 μg · kg^{-1} · min^{-1}, dobutamine increased SVR 12.9 dyne · s/cm^{-5} · m^{-2} per μg · kg^{-1} · min^{-1} dobutamine; at higher doses, dobutamine had minimal effect on SVR, as evidenced by the small, albeit statistically significant, decrease of 0.009 dyne · s/cm^{-5} · m^{-2} per μg · kg^{-1} · min^{-1} dobutamine (fig. 4).

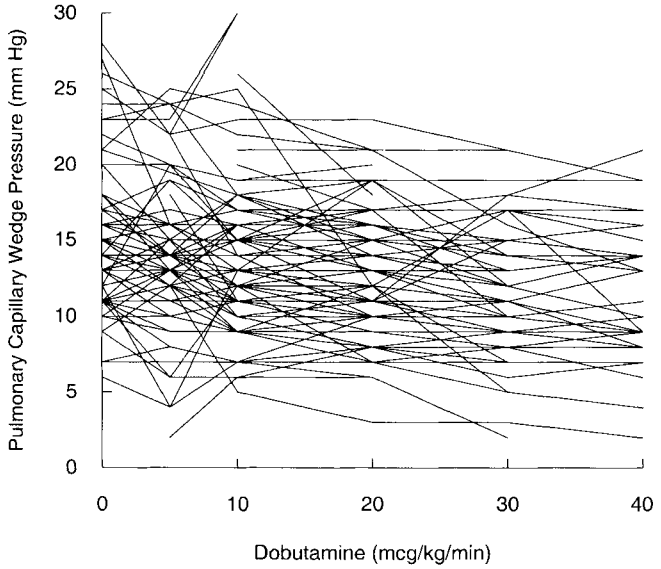

Fig. 3. Dose–response relationship for increasing doses of dobutamine on pulmonary capillary wedge pressure for each patient is shown.

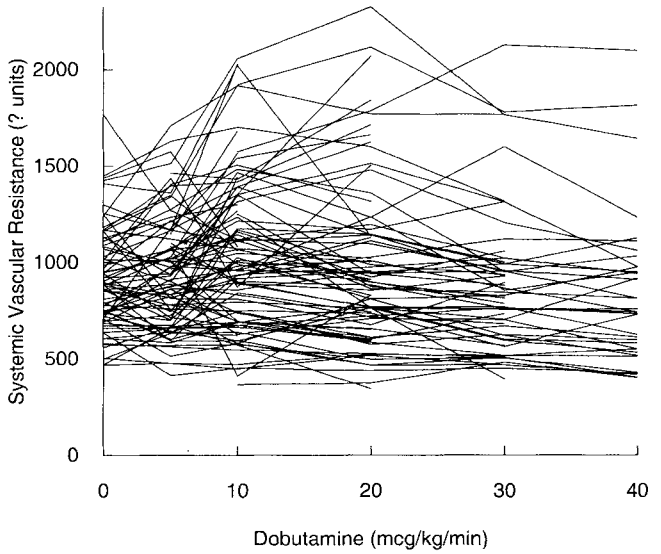

Fig. 4. Dose–response relationship for increasing doses of dobutamine on systemic vascular resistance for each patient is shown.

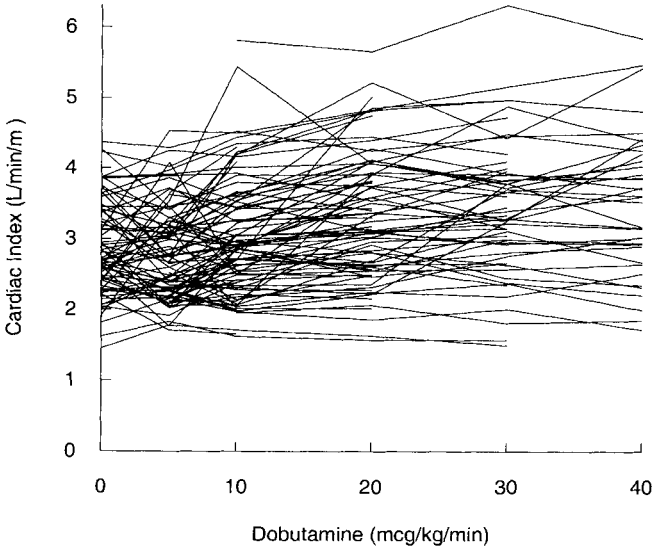

Fig. 5. Dose–response relationship for increasing doses of dobutamine on cardiac index for each patient is shown.

Pulmonary Vascular Resistance

The basic model suggested that PVR decreased with dobutamine. Because the SE for the slope was larger than the typical value, we tested a model in which the typical value for slope was fixed to 0.0 (*i.e.*, no effect of dobutamine on PVR). The objective function for this model increased only 4.007 units ($P = 0.05$), indicating that slope did not differ significantly from 0.0.

Cardiac Index

The basic model indicated that CI increased with dobutamine dose. Covariate plots suggested that women had a lower baseline CI than men. Incorporating this into the model by permitting different parameters for men *versus* women improved the objective function 12.032 units ($P < 0.001$). To evaluate whether the slope varied with dose, as suggested by residual plots, we tested a model in which doses larger than a cutoff value were associated with a slope different from that with smaller doses; the cutoff was estimated in the analysis. The objective function for this model only improved 1.836 units ($P > 0.15$) compared with the previous model. Therefore, CI increased with dobutamine dose, but the slope of the increase did not vary with dose (fig. 5).

Stroke Volume Index

The basic model indicated that SVI decreased with dobutamine dose. Covariate plots suggested that the baseline value varied with gender. Permitting different values for the intercept for each gender improved the objective function 11.495 units ($P < 0.001$). To evaluate whether the change in stroke volume index is a function of the baseline value before dobutamine infusion, we plotted the change in SVI with 5 $\mu g \cdot kg^{-1} \cdot min^{-1}$ dobutamine as a function of the baseline SVI (before dobutamine infusion; fig. 6). Using linear regression analysis, patients with a baseline value of SVI < 34 $l \cdot min^{-1} \cdot m^{-2}$ per beat demonstrated an increase in SVI with 5 $\mu g \cdot kg^{-1} \cdot min^{-1}$ dobutamine, whereas patients with a baseline SVI > 34 $l \cdot min^{-1} \cdot m^{-2}$ per beat demonstrated a decrease. The linear regression equation is calculated as:

$$Y = 10.67 - 0.316*X;\ R^2 = 0.141\ (P = 0.001) \quad (6)$$

Left Ventricular Dimensions

The basic model showed that both EDA and ESA decreased with dobutamine dose. Covariate plots suggested that the baseline values for both parameters varied with gender. For EDA, permitting different values for the intercept for each gender improved the objective function 10.97 units ($P < 0.05$). For ESA, permitting different values for the intercept for each gender improved the objective function 14.8 units ($P < 0.05$). Incorporating the effects of gender, final models showed that both EDA and ESA decreased with dobutamine (table 3). When slope was fixed to 0.0, the objective function for EDA increased 8.31 units ($P < 0.05$), indicating

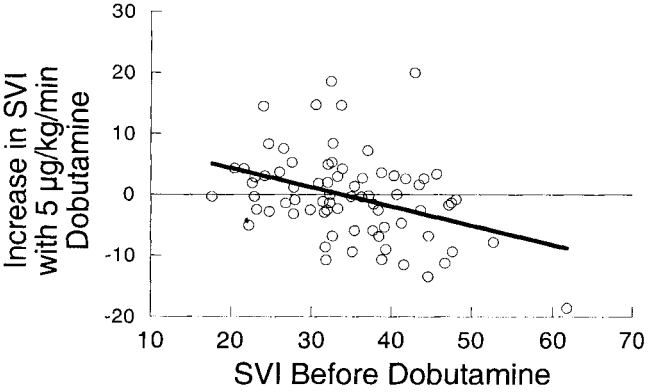

Fig. 6. The increase in stroke volume index (SVI; $l \cdot min^{-1} \cdot m^{-2}$ per beat) from the baseline state (*i.e.*, before dobuatmine) to the value at 5 $\mu g \cdot kg^{-1} \cdot min^{-1}$ dobutamine is plotted against the baseline value. Only patients with observations at both times are displayed. The *thick line*, determined by analysis of linear regression, demonstrates that patients with a baseline value of SVI < 34 $l \cdot min^{-1} \cdot m^{-2}$ per beat respond with an increase in SVI with 5 $\mu g \cdot kg^{-1} \cdot min^{-1}$ dobutamine, whereas patients with a baseline SVI > 34 $l \cdot min^{-1} \cdot m^{-2}$ per beat demonstrate a decrease.

Table 4. Hemodynamic and Echocardiographic Data for 10 Control Patients

Parameter	Baseline	3 min	6 min	9 min	12 min	15 min
HR (beats/min)	90 ± 7	87 ± 7	89 ± 12	88 ± 13	88 ± 14	87 ± 14
MAP (mmHg)	75 ± 13	72 ± 11	70 ± 11	70 ± 13	66 ± 17	70 ± 13
PCWP (mmHg)	15 ± 3	14 ± 3	13 ± 4	14 ± 4	13 ± 5	13 ± 3
CVP (mmHg)	12 ± 2	11 ± 2	11 ± 2	12 ± 3	12 ± 3	12 ± 3
SVR (dyne · sec/cm^{-5} · m^{-2})	898 ± 455	1013 ± 519	957 ± 298	921 ± 386	866 ± 295	996 ± 333
PVR (dyne · sec/cm^{-5} · m^{-2})	101 ± 24	104 ± 55	113 ± 38	100 ± 37	111 ± 34	96 ± 45
CI (l · min^{-1} · m^{-2})	3.1 ± 0.41	2.9 ± 0.55	2.7 ± 0.53	3.0 ± 0.75	2.7 ± 0.60	2.7 ± 0.67
SVI (l · min^{-1} · m^{-2} per beat)	35 ± 5	33 ± 6	31 ± 5	35 ± 11	31 ± 7	31 ± 8
EDA (cm^2)	11.4 ± 3.4	11.2 ± 4.2	10.9 ± 3.0	10.4 ± 3.9	9.8 ± 9.8	10.4 ± 3.4
ESA (cm^2)	4.3 ± 2.1	4.3 ± 2.4	4.2 ± 2.5	3.8 ± 2.8	3.7 ± 2.1	4.0 ± 2.2
FAC (%)	64 ± 12	63 ± 12	63 ± 16	66 ± 14	65 ± 12	62 ± 14

Data are mean ± SD.

HR = heart rate; MAP = mean arterial pressure; PCWP = pulmonary capillary wedge pressure; CVP = central venous pressure; SVR = systemic vascular resistance; PVR = pulmonary vascular resistance; CI = cardiac index; SVI = stroke volume index; EDA = end diastolic area; ESA = end systolic area; FAC = fractional area change.

that slope differed from 0.0. As for ESA, when the slope was fixed to 0.0, the objective function increased 17.11 units ($P < 0.05$), indicating that the slope also differed from 0.0.

Fractional Area Change

The basic model had a slope of 0.119 ± 0.038% per $\mu g \cdot kg^{-1} \cdot min^{-1}$ dobutamine. When the slope was fixed to 0.0, the objective function increased 10.079 units ($P < 0.002$), indicating that the slope differed from 0.0.

Finally, none of the other covariates examined, including cardiac risk factors, coronary anatomy, preoperative ejection fraction, preoperative use of β blockade, requirement of dobutamine for separation from CPB, and whether peak dobutamine dose was reached, had significant impact on the observed hemodynamic responses.

Control measurements of HR, MAP, PCWP, CVP, SVR, PVR, CI, SVI, EDA, ESA, and FAC remained constant over the study period (table 4).

All patients were examined daily while in the hospital. Of the 100 patients studied, one developed new Q waves on postoperative 12-lead electrocardiogram accompanied by CPK-MB enzymes elevation of >50 U on postoperative day 1 consistent with perioperative myocardial infarction. Two patients developed focal neurologic deficits on postoperative days 1 and 2, respectively, consistent with postoperative cerebrovascular accidents. Two additional patients were taken to the operating room for exploration of high mediastinal output.

Discussion

The primary purpose of the present study was to evaluate the complete dose–response relationship of dobutamine in the early post-CPB period in patients undergoing CABG surgery. Our results demonstrate that after CPB, the dominant mechanism by which dobutamine improves ventricular performance is by a dose-dependent increase in HR, because SVI actually decreased with increasing dobutamine dosing. Dobutamine has little effect on blood pressure, increases SVR at lower doses, and decreases PVR minimally.

Comparison with Previous Studies

Our results differ from those of previous reports, suggesting that dobutamine increases contractility without producing marked changes in HR or peripheral vascular resistance, a property superior to other available inotropes.[10] In the present study, dobutamine showed substantial chronotropic effects throughout the dose range tested—HR increased as much as 36% over baseline values at peak dose. The lack of marked HR effects in other studies[1] is likely a result of the lower dose range of dobutamine examined compared with that in the current study. Recently, the marked positive chronotropic effects of higher doses of dobutamine have served as the basis of pharmacologic stress testing of potentially ischemic myocardium.[11] The escalating dobutamine dosing regimen used in the present study is identical to that in standard dobutamine stress echocardiography protocols, in which the peak dobutamine dose used is 40 $\mu g \cdot kg^{-1} \cdot min^{-1}$.[12] A recent study that used dobutamine stress echocardiography in anesthetized patients to detect inducible ischemia demonstrated HR increases similar to those presented here.[13] Another explanation of why dobutamine acts primarily as a chronotropic agent in increasing cardiac performance in our study is that the autonomic nervous system plays an important

role in modulating the cardiovascular effects of dobutamine.[14] In fact, dobutamine has been shown to produce greater HR response in anesthetized and vagotomized dogs[15,16] similar to our observed response in this group of anesthetized subjects. In the anesthetized state, the direct chronotropic effects mediated by β-adrenergic receptors were not attenuated by baroreceptor reflexes to the same extent as in the conscious state.[17,18] Our study results are consistent with previous research demonstrating that the baroreflex-mediated HR responses of adult humans are depressed by general anesthesia.[19-21]

We found that at dobutamine doses $\leq$ 10 $\mu g \cdot kg^{-1} \cdot min^{-1}$, SVR actually increases, and at larger doses, there is no clinically significant change in SVR. This finding differs from earlier work that demonstrated that the primary effect of dobutamine at doses of 2–15 $\mu g \cdot kg^{-1} \cdot min^{-1}$ is to increase cardiac output by enhancing left ventricular contractility and by decreasing SVR.[22] At the vascular level, dobutamine produces a β_2-mediated vasodilating effect, which appears to be balanced by an α_1-mediated vasoconstricting effect produced by dobutamine. At the initiation of dobutamine infusion in our study, baseline values for both SVR and PVR were low in our patients, coinciding with active rewarming that occurred during the completion of CPB. These loading conditions differ substantially from those in previous studies in the intensive care unit,[4] often many hours after cessation of CPB, when both SVR and PVR are substantially higher. The initial increase in SVR associated with dobutamine infusion in our study is likely mediated by stimulation of α_1-adrenoreceptors by dobutamine. Because vascular tone is already low during the early post-CPB period, the potential incremental effect of dobutamine on β_2-adrenoreceptors may have been minimal at lower doses in our study. Furthermore, the peripheral vascular effects of dobutamine are also modulated by the autonomic nervous system. Our patients response to dobutamine is similar to that observed in dogs pretreated with a ganglionic blocker in that low-dose dobutamine produced a pressor response secondary to the increased cardiac output,[14] whereas in conscious untreated dogs, dobutamine decreased total vascular resistance. An alternate explanation is that the enhanced α-adrenergic response of SVR to small doses of dobutamine may be related to β-receptor downregulation or desensitization after CPB.[23]

We found that dobutamine had little effect on systemic blood pressure, similar to that reported in other studies.[2,3] However, the effect of dobutamine on blood pressure can vary.[1] Factors other than the anesthetized state that can affect the cardiovascular response to dobutamine include the additional effects of dobutamine on cardiac preload. In our study, both PCWP and CVP decreased with higher doses of dobutamine.

Clinical Implications

Our investigation is one of the first to study a relatively large group of patients undergoing CABG surgery using a complete dose range of dobutamine infusion during the critical early reperfusion period. We demonstrated that the increase in left ventricular performance, as measured by CI and FAC, is dose-dependent. However, higher doses of dobutamine infusion were accompanied with substantial increases in HR. Although not directly measured, the marked chronotropic effects at higher dobutamine doses likely are accompanied by a marked increase in myocardial oxygen consumption, while providing a relatively small increase in cardiac performance. Furthermore, we demonstrated that low-dose dobutamine infusion affects left ventricular SVI differently as a function of the baseline SVI. SVI increases in patients with a lower baseline SVI, whereas it actually decreases with low-dose dobutamine infusion in those with a higher baseline SVI. These results suggest that using prophylactic inotropic infusion to separate from CPB regardless of cardiac performance may actually be detrimental to some patients.

Our study also demonstrates that age is an important modifier in the HR response to dobutamine. This observation is consistent with other studies in elderly humans, demonstrating the age-associated reduction in adrenergic modulation of cardiovascular function, possibly secondary to age-associated reductions in the postsynaptic responses of the cardiovascular system to β-adrenergic receptor stimulation.[24] As a result, when assessing the chronotropic *versus* inotropic effects of dobutamine, both the activity of the autonomic nervous system and the age of the patient should be considered. The decreased HR response with age demonstrated in our study suggests that the undesirable HR increase with escalating dobutamine infusion may be more marked in younger patients.

In contrast, our study demonstrates that the hemodynamic responses and changes in left ventricular performance resulting from dobutamine infusion are not modified by factors commonly thought to influence the response to inotropic stimulation, including the patient's preoperative ejection fraction, preoperative use of β blockade, and requirement of dobutamine for separation

from bypass. For 21 of our patients who received dobutamine during separation from CPB, we did not obtain baseline measurements before dobutamine was infused. Because of the concern that these patients differed from the remaining patients, all analyses examined whether the slope or intercept of the physiologic response differed between the two groups. The analyses did not identify that the responses to dobutamine were different between these two groups.

Limitations

First, the design of our study—an escalating dose regimen—allows for time to confound the results. By its very nature, the immediate post-CPB period is dynamic, and changes in hemodynamics, loading conditions, and cardiac performance occur rapidly. Therefore, intrinsic cardiac function may have improved or worsened during the time necessary to complete our protocol. The 10 patients who served as controls demonstrated that the observed improvement in intrinsic cardiac performance was a result of dobutamine rather than time-related changes.

Second, we followed the standard dobutamine stress echocardiography protocol, in which each dose was infused for a period of 3 min. The rationale for this time interval is that dobutamine has a half-life of 2 min.[10] Although maximal effects may be achieved with longer dosing intervals, increasing the doses rapidly, as was performed in our study, is common clinical practice. It could be argued that if maximal effects were to be achieved with longer dosing intervals, our results likely underestimated the observed effects of dobutamine, emphasizing the importance of our current findings.

Third, PCWP, CVP, and EDA decreased with higher doses of dobutamine. If preload could be held constant, the improvement in cardiac function may be more evident.

Fourth, we used mixed-effects modeling for our analysis. Another approach that we initially considered was a repeated-measured analysis of variance. However, that approach stratifies groups by dobutamine dose but does not account for missing data. A two-stage analysis in which values for each individual are analyzed by linear regression, followed by averaging the resulting slopes and intercepts, also is flawed: certain individuals had few data points (and none had more than six). Uncertainty about the estimates for these individuals may be large, yet they would contribute to this approach equally compared with an individual in whom the quality of data was better.

Summary

Immediately after CPB, the dominant mechanism by which dobutamine improves cardiac performance is through a dose-dependent increase in HR. Dobutamine has little effect on blood pressure, decreases PVR minimally, and increases SVR only at lower doses. The autonomic nervous system and the age of the patient both seem to modulate the cardiovascular response to dobutamine.

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