Anesthesiology
74:1035–1043, 1991

Cardiovascular Effects of Low-dose Epinephrine Infusions in Relation to the Extent of Preoperative β-Adrenoceptor Blockade

Jörg Tarnow, M.D., Rainer Karl Müller, M.D.†*

The relationship between the extent of preoperative β-adrenoceptor blockade and the hemodynamic properties of epinephrine was investigated in patients scheduled for elective myocardial revascularization during the immediate preoperative period under steady-state hemodynamic and anesthetic conditions. Twenty patients had been treated with β-adrenoceptor blocking drugs for at least 3 weeks before the study; 11 unblocked patients served as control group. The extent of clinical β-adrenoceptor blockade was quantified using the isoproterenol sensitivity test. The dose of isoproterenol required to increase heart rate by 25 beats per min was defined as the chronotropic dose 25 (CD_{25}), representing the degree of β-adrenoceptor blockade. Geometric mean CD_{25} per 70 kg was 3.0 μg in the control group and 21.8 μg in the patients receiving β-adrenoceptor blocking drugs. The authors found a significant inverse relationship between CD_{25} values and changes in cardiac index in response to three epinephrine infusion rates (0.01, 0.02, and 0.04 $\mu g \cdot kg^{-1} \cdot min^{-1}$), the correlation coefficients being −0.71, −0.81, and −0.86, respectively. Compared to unblocked patients, almost no change, or even a decrease, of the cardiac index was observed at greater degrees of clinical β-adrenoceptor blockade, particularly in patients receiving nonselective blockers. Moreover, there was a significant linear correlation (r = 0.76–0.86) between CD_{25} values and the effects of epinephrine on systemic vascular resistance index (SVRI); *i.e.*, SVRI significantly decreased in control patients but markedly increased in patients with high degrees of preoperative β-adrenoceptor blockade. This unmasked vasoconstrictive response to low doses of epinephrine was observed despite the fact that the majority of our patients had received cardioselective adrenergic blocking drugs. We also found a significant positive relationship between CD_{25} values and the effect of epinephrine on mean arterial pressure, whereas correlations between the degree of β-blockade and heart rate responses to epinephrine were inverse. The authors conclude that these results could have important clinical implications for the use of epinephrine during the prebypass period in patients who are receiving chronic β-blocker therapy and require inotropic support. (Key words: Sympathetic nervous system: β-adrenergic receptor blockade. Sympathetic nervous system, catecholamines: epinephrine; isoproterenol.)

CARDIAC SURGICAL patients may temporarily need the perioperative use of cardioactive drugs. Despite the availability of newer sympathomimetic amines epinephrine continues to be a frequently used cardiac stimulant. When used at low-dose infusion rates epinephrine also possesses a pronounced β_2-receptor vasodilator action leading to a decrease in systemic vascular resistance.[1] Both inotropic support and peripheral vasodilation are considered desirable in patients who develop acute perioperative heart failure.

If such a patient has been preoperatively treated with β-adrenoceptor blocking agents (as have the majority of patients undergoing coronary artery bypass grafting), requires inotropic support, and receives low doses of epinephrine, the expected improvement in cardiovascular dynamics may be attenuated, abolished, or even converted into a predominantly α-adrenergic effect. We presumed that unfavorable interactions between β-receptor blocking drugs and epinephrine depend on the degree of the preexisting β-adrenergic blockade.

Since there were no previous data on the cardiovascular effects of epinephrine in relation to the extent of β-adrenergic blockade, we undertook a clinical study to quantitatively define such an interaction during the immediate preoperative period under steady-state hemodynamic and anesthetic conditions. Although inotropic support is more often needed following cessation of cardiopulmonary bypass, this period appeared to be unsuitable because of its potential for unstable and uncontrolled baseline conditions.

Materials and Methods

Patient Population

Thirty-one patients with chronic, stable angina pectoris scheduled for elective myocardial revascularization were studied. Patients with unstable angina pectoris, left main coronary artery stenosis, myocardial infarction within the preceding 3 months, conduction block, or arrhythmias were excluded from the study. No patient had valvular heart disease or clinical evidence of cardiac failure. Global left ventricular function at rest was normal (left ventricular end-diastolic pressure < 18 mmHg and ejection fraction > 0.5) in all patients. Written informed consent was obtained from each patient, and the study protocol was approved by the local Ethics Committee.

Twenty patients (39–72 yr of age, mean age 52 yr), had been treated with β-adrenoceptor blocking drugs for at least 3 weeks before the study. Thirteen patients were receiving metoprolol (25–200 mg/day), and three were receiving bisoprolol (2.5–10 mg/day). Four patients were receiving nonselective β-adrenergic blockers (two patients

* Professor of Anesthesiology and Chairman, Department of Anesthesiology, Heinrich-Heine-University Düsseldorf, Germany.

† Staff Anesthesiologist, Department of Anesthesiology and Intensive Care Medicine, UKRV, Free University Berlin, Germany.

Received from the Department of Anesthesiology, Heinrich-Heine-University, Düsseldorf, Germany. Accepted for publication February 26, 1991.

Address reprint requests to Dr. Tarnow: Department of Anesthesiology, Heinrich-Heine-University, Moorenstr. 5, D-4000 Düsseldorf 1, Germany.

mepindolol 1.25 and 5 mg/day, one patient pindolol 10 mg/day, and one patient sotalol 160 mg/day). All patients received the last dose of their usual β-blocking drug within 2 h prior to the study. No other cardiac medications (nitrates or calcium-channel-blocking drugs) were given within the 20 h before the study began. Twelve of these 20 patients had a history of myocardial infarction; 8 had regional wall motion abnormalities; and 7 were hypertensive.

A control group consisted of 11 patients (40–64 yr, mean 54 yr) who were not taking β-adrenergic blocking drugs. Four control group patients were hypertensive; 6 had a history of myocardial infarction; and 6 demonstrated regional wall motion abnormalities at the time of diagnostic left ventricular angiography.

Hemodynamic Assessment

All patients received oral flunitrazepam 2 mg 90 min before the study, which was performed in a specially equipped unit adjacent to the operating room. Upon arrival, ECG leads were attached, after which peripheral intravenous cannulas, a radial artery catheter, and a central venous catheter were inserted. A 7-Fr Swan-Ganz thermodilution flow-directed catheter was introduced into the pulmonary circulation *via* the right internal jugular vein. Arterial pressure, central venous pressure, pulmonary artery pressure, and pulmonary artery occlusion pressure were measured using calibrated transducers (Bentley Trantec® 800). The zero level was established at the midchest with the patient in the supine position. All pressures, the ECG (leads V5 and II), and heart rate were continuously recorded on an eight-channel recorder (Gould 2800S). Cardiac output was measured in triplicate by thermodilution (Edwards 9520 cardiac output computer) with an on-line temperature probe. Ten milliliters of ice-cold normal saline were injected at end-expiration, and the temperature curve was monitored on an Edwards 9812 recorder. Arterial and mixed venous blood samples were taken to determine blood gases, hemoglobin, and oxygen saturations (IL 1302 blood gas analyzer and IL CO-Oximeter 282). Cardiac index, arterial − mixed venous oxygen content difference, and systemic vascular resistance index (SVRI) were computed using standard formulas.

Induction of anesthesia was achieved with thiopental (3 mg/kg), fentanyl (1.5 μg/kg), and pancuronium (0.1 mg/kg). Anesthesia was maintained in all cases with isoflurane (0.6% end-tidal, Beckman analyzer), nitrous oxide (50%), and oxygen (50%). Ventilation was controlled (Engström ventilator ER 300) to maintain normocapnia, which was continuously monitored by measurement of end-tidal CO_2 concentration (Datex CD 101) and by intermittent blood gas analyses. To achieve stable hemodynamic baseline conditions, we waited for at least 20 min after tracheal intubation before the study began.

Assessment of β-Adrenoceptor Blockade

The extent of β-adrenergic blockade was quantified using the isoproterenol sensitivity test.[2–5] The peak increase in heart rate, from a stable resting value for each patient, was measured in response to five graded intravenous bolus injections of isoproterenol sulfate. The heart rate was computed electronically using an R-wave triggered instantaneous rate-meter (Hellige). Isoproterenol was made up under sterile conditions in concentrations of 1, 10, and 100 μg/ml. The initial isoproterenol dose was 0.4 μg in the patients not pretreated with β-adrenergic blocking drugs and 1.0 μg in the patients receiving β-adrenergic blocking drugs. The dose was then progressively increased until the heart rate had increased by 25 beats per min. The maximum increase of heart rate was recorded for each sequential injection of isoproterenol. Heart rate was allowed to return to baseline (± 1 beat per min) before an additional injection. Log dose–response curves were constructed using normalized (per 70 kg body weight) isoproterenol doses. The dose of isoproterenol required to increase heart rate by 25 beats per min was defined as the chronotropic dose 25 (CD_{25}), representing the degree of β-adrenergic blockade. To assess the intrapatient reproducibility of the heart rate response to isoproterenol, the CD_{25} was repeated after 90 min in ten of the β-blocked patients.

Epinephrine Study Protocol

Following the isoproterenol sensitivity test, baseline measurements at stable anesthetic and hemodynamic conditions were performed. Epinephrine was then administered by an infusion pump in graded doses of 0.01, 0.02, and 0.04 $\mu g \cdot kg^{-1} \cdot min^{-1}$ intravenously for periods of 10 min each. Hemodynamic measurements were made at the end of each infusion rate, including determinations of the arterial − mixed venous oxygen content difference. The entire study lasted 90–110 min. Surgery was started after the study was completed.

Statistical Analysis

Results are presented as single observations and as means ± 1 standard deviation (SD), if not otherwise indicated. The relation between the degree of β-blockade and hemodynamic effects of epinephrine was analyzed by linear regression using the least-squares method after logarithmic transformation of the CD_{25} per 70 kg values. Comparisons within and between the two patient groups were performed by the Wilcoxon signed-rank test and

the Mann-Whitney U-test, respectively. A probability (P) value of ≤ 0.05 was considered significant.

Results

Figure 1 shows the averaged (mean ± SD) dose–response curves for the control group and for the patients receiving β-adrenergic blocking drugs. There was a parallel shift to the right of the isoproterenol dose–response curve in the β-blocked patients. Individual CD_{25} per 70 kg values demonstrate a wide intersubject variability as expressed in the range of CD_{25} values determined in each group, but the overlap between blocked and unblocked patients was minimal. The geometric mean CD_{25} per 70 kg was 3.0 μg isoproterenol (95% confidence limits [CL] 2.1–4.3 μg) in the control group and 21.8 μg isoproterenol (95% CL 12.3–38.7 μg) in the patients receiving β-adrenergic blocking drugs ($P \leq 0.01$), representing a dose ratio of 7.3. The highest CD_{25} values (as high as 364 μg/70 kg) were observed in patients pretreated with nonselective β-adrenergic blockers, whereas the three patients receiving the highly selective β_1-antagonist bisoprolol had a lesser degree of β-blockade (isoproterenol CD_{25} values of 5.7, 6.1, and 8.1 μg per 70 kg, respectively).

The intrapatient reproducibility of the heart rate response to the CD_{25} was good. After a time interval of 90 min, this isoproterenol dose increased heart rate by 25.9 ± 1.8 beats per min (mean ± SD). No significant correlation was found between CD_{25} and age, sex, resting heart rate, or blood pressure.

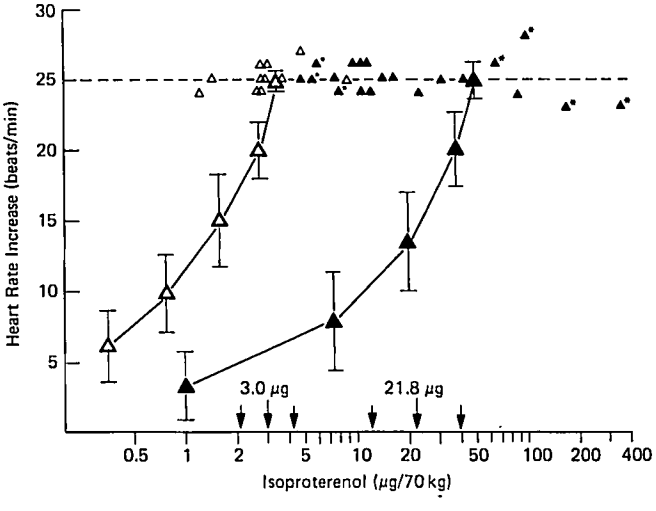

FIG. 1. Isoproterenol log dose-response curves for the control group (open triangles) and for patients receiving β-adrenoceptor blocking drugs (filled triangles). Mean values ± SD and the individual distribution of the isoproterenol doses that induced a heart rate increase of 25 beats per min (CD_{25} per 70 kg) are shown. Arrows indicate the geometric mean of the isoproterenol CD_{25} per 70-kg values and the 95% confidence intervals of the mean. Points denote patients who had been treated with the highly selective β_1-antagonist bisoprolol; asterisks indicate patients who were receiving nonselective β-blocking drugs.

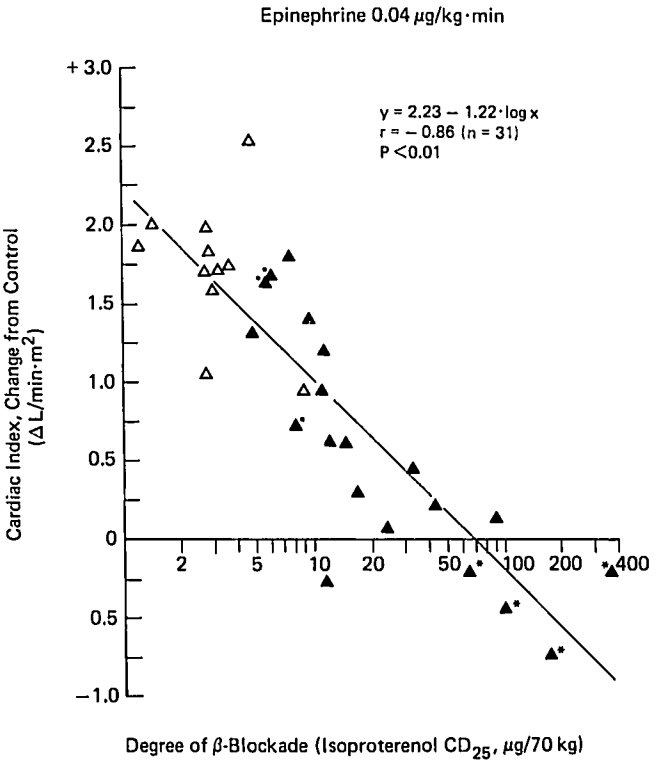

FIG. 2. Relationship between the degree of β-adrenoceptor blockade (expressed as isoproterenol CD_{25} per 70 kg) and the effects of epinephrine 0.04 $\mu g \cdot kg^{-1} \cdot min^{-1}$ on cardiac index in patients with (filled triangles) and without (open triangles) preoperative β-adrenoceptor blocker therapy. Points denote patients who had been treated with the highly selective β_1-antagonist bisoprolol; asterisks indicate patients who were receiving nonselective β-blocking drugs.

There was a significant decrease of both systolic and diastolic arterial pressures by 15–20 mmHg in response to the isoproterenol CD_{25} in control patients and in the patients receiving cardioselective β-blockers. By contrast, no change in either systolic or diastolic pressure was observed in patients receiving nonselective β-adrenergic blocking drugs. Transient arrhythmias occurred in three of the 31 patients. Transient ST-segment depression occurred in two patients (one in the control group and one pretreated with β-blocking drugs). The peak heart rates observed in response to the isoproterenol CD_{25} were less than 110 beats per min and persisted for less than 30 s. The duration of the ECG changes did not exceed 1 min and required no therapy.

Figure 2 demonstrates the relation between the degree of β-adrenoceptor blockade (expressed as isoproterenol CD_{25} per 70 kg) and the effect of epinephrine 0.04 $\mu g \cdot kg^{-1} \cdot min^{-1}$ on cardiac index. Baseline cardiac index values were 2.07 ± 0.69 $l \cdot min^{-1} \cdot m^{-2}$ in the control patients and 1.95 ± 0.51 $l \cdot min^{-1} \cdot m^{-2}$ in the patients pre-

treated with β-adrenergic blockers (no significant difference). There was a significant inverse relationship between log CD_{25} per 70 kg values and changes in cardiac index in response to epinephrine: the correlation coefficient was −0.86. Compared to unblocked patients, the effect of epinephrine on cardiac index was attenuated with increasing CD_{25} values in the patients pretreated with β-adrenergic blocking drugs. No increase, or even a decrease, of the cardiac index was observed in patients with higher degrees of nonselective β-adrenoceptor blockade. Similar relationships were found for the three different epinephrine doses used in this study (fig. 3). Doubling the infusion rate resulted in upward and rightward displacement of the relationship between the degree of β-adrenoceptor blockade and the effect on pump function. Failure to increase cardiac index (where the regression lines crossed the x-axis) was shifted toward higher CD_{25} values when the epinephrine dose was increased.

The relationship between the extent of β-adrenoceptor blockade and the effects of epinephrine 0.04 $\mu g \cdot kg^{-1} \cdot min^{-1}$ on SVRI is shown in figure 4. We found a significant linear correlation (r = 0.86) between the two variables. At low CD_{25} values (unblocked patients), moderate to considerable decreases in SVRI occurred, whereas with higher CD_{25} values in the pretreated group, SVRI increased. This unmasked vasoconstrictive effect of epinephrine was particularly observed in patients who had received nonselective adrenergic blocking drugs. The peripheral vascular effects of epinephrine were also dose-dependent. Increasing infusion rates caused greater decreases in systemic vascular resistance in patients with low CD_{25} values (fig. 5) but caused more pronounced vasoconstriction in patients with higher degrees of β-blockade. The relationship between CD_{25} values and the changes in mean arterial pressure observed during the infusion of epinephrine (fig. 6 and 7) was significant and dose-dependent (r = 0.59–0.76). Control group patients showed a significant increase in systolic blood pressure at either unchanged or decreased diastolic pressures, whereas both systolic and diastolic pressures increased in patients who had higher degrees of β-adrenoceptor blockade or who had been treated with nonselective blockers. Epinephrine induced dose-dependent increases in heart rate in most of the nonblocked control patients (fig. 8). In contrast, heart rate decreased at higher levels of β-blockade, particularly in patients who had received nonselective blockers. This inverse relationship was significant for each of the three infusion rates studied: the correlation coefficients were −0.65, −0.71, and −0.74, respectively (fig.

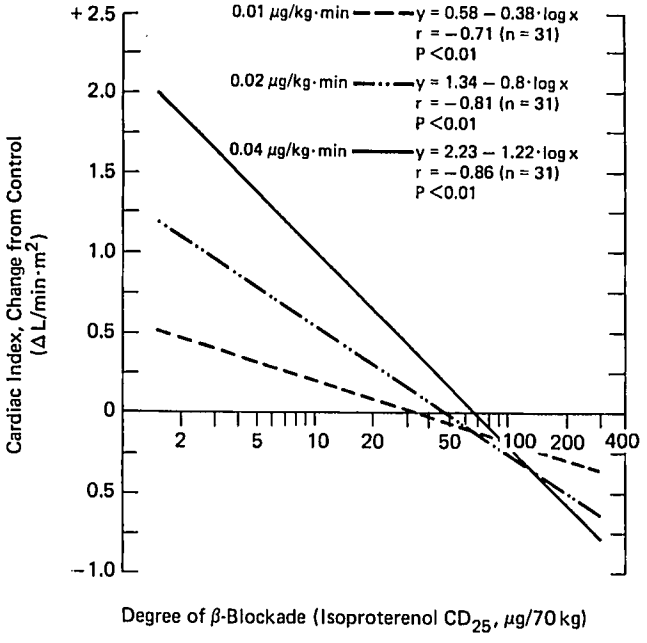

FIG. 3. Relationship between the degree of β-adrenoceptor blockade and the effects of three different doses of epinephrine on cardiac index.

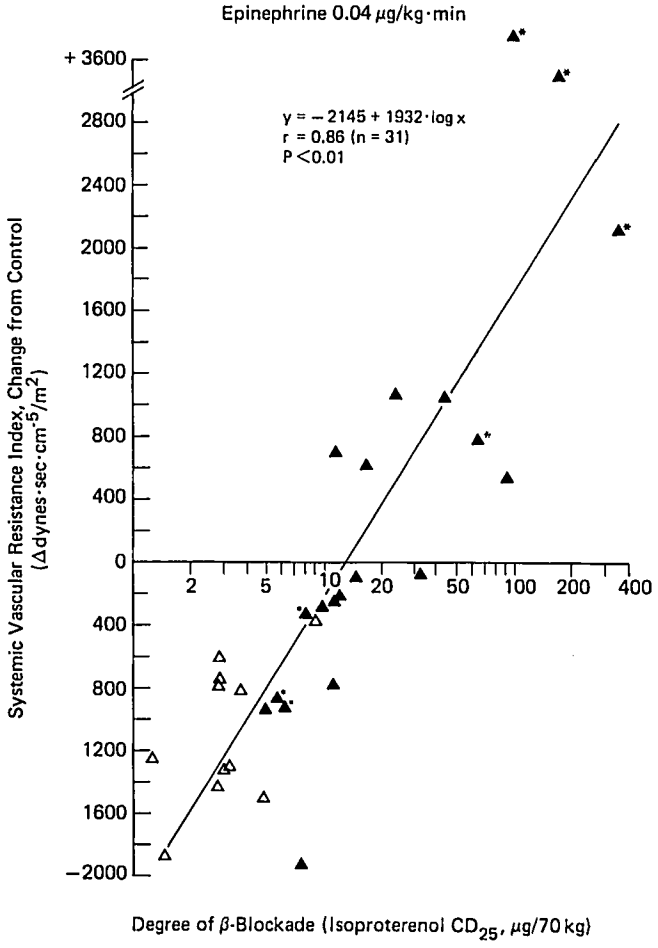

FIG. 4. Relationship between the degree of β-adrenoceptor blockade and the effect of epinephrine 0.04 $\mu g \cdot kg^{-1} \cdot min^{-1}$ on systemic vascular resistance index in patients with and without preoperative β-adrenoceptor blocker therapy. Symbols are as in figure 2.

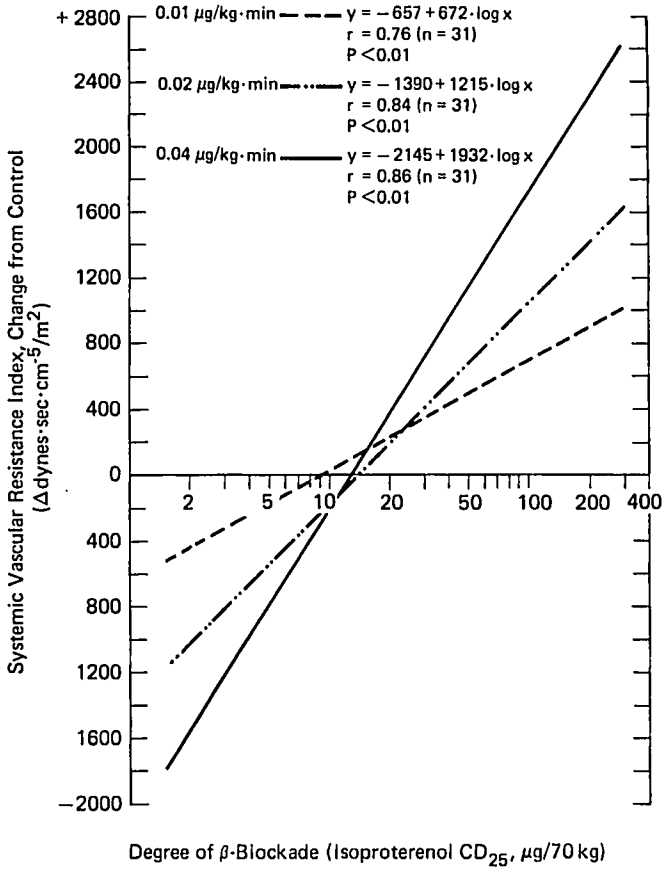

FIG. 5. Relationship between the degree of β-adrenoceptor blockade and the effects of three different doses of epinephrine on systemic vascular resistance index.

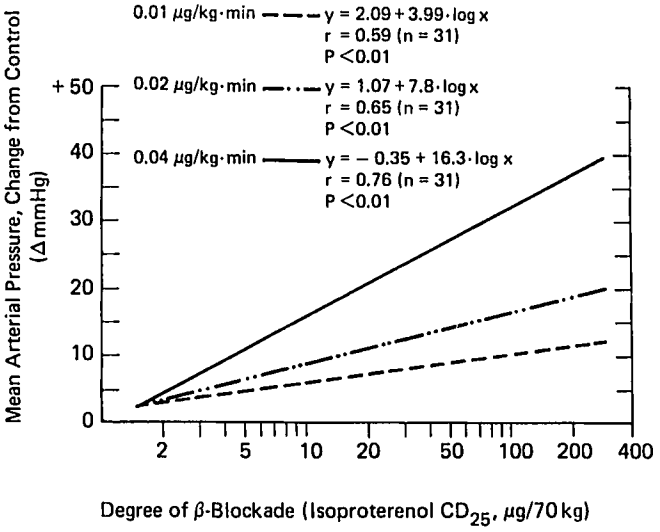

FIG. 7. Relationship between the degree of β-adrenoceptor blockade and the effects of three different doses of epinephrine on mean arterial pressure.

9). The reported hemodynamic changes as plotted against the degree of β-adrenergic blockade showed substantial biologic variability, particularly within the lower ranges of CD_{25} values (< 20 μg per 70 kg). Accordingly, there is some dispersion about the regression lines for the three doses of epinephrine.

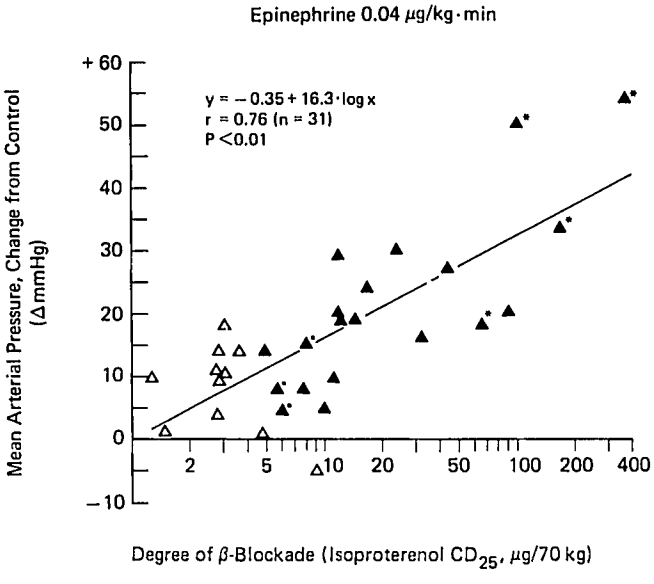

FIG. 6. Relationship between the degree of β-adrenoceptor blockade and the effects of epinephrine 0.04 $\mu g \cdot kg^{-1} \cdot min^{-1}$ on mean arterial pressure in patients with and without preoperative β-adrenoceptor blocker therapy. Symbols are as in figure 2.

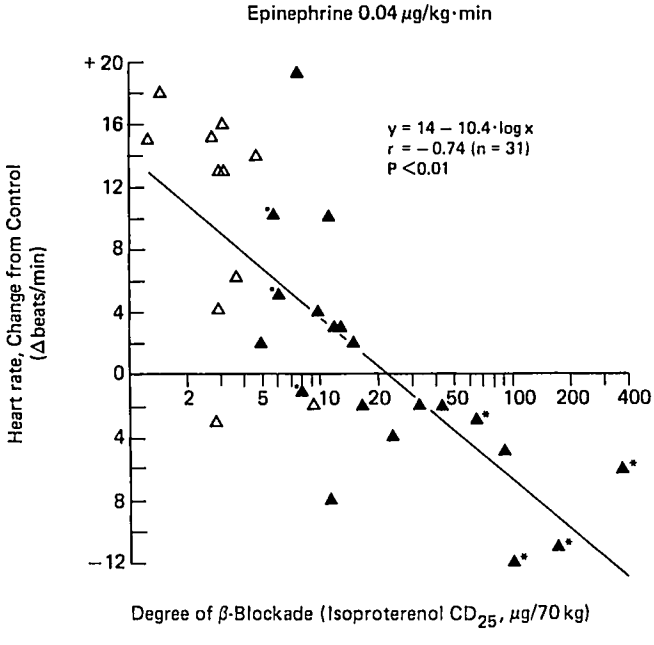

FIG. 8. Relationship between the degree of β-adrenoceptor blockade and the effect of epinephrine 0.04 $\mu g \cdot kg^{-1} \cdot min^{-1}$ on heart rate in patients with and without preoperative β-adrenoceptor blocker therapy. Symbols are as in figure 2.

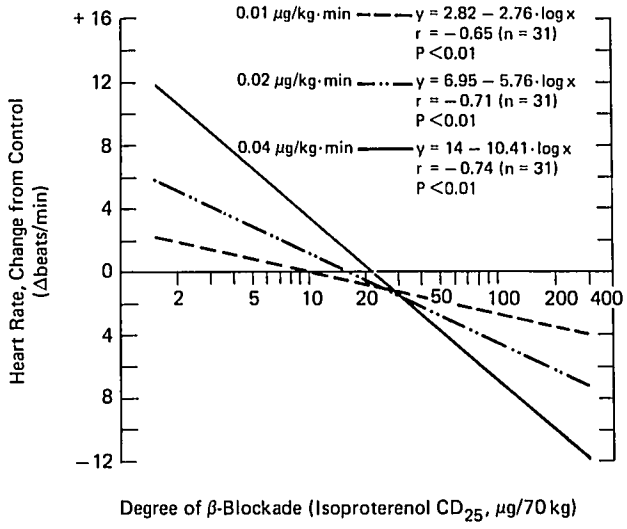

FIG. 9. Relationship between the degree of β-adrenoceptor blockade and the effects of three different doses of epinephrine on heart rate.

Intra- and intergroup comparisons of the hemodynamic variables are summarized in table 1. Except for the lower systolic arterial blood pressure in the patient group receiving preoperative β-adrenoceptor blocker therapy, mean baseline values revealed no differences. Intergroup comparisons for each of the epinephrine doses, however, indicated significantly different changes in cardiac index, systemic vascular resistance, arterial blood pressure, heart rate, and arterial − mixed venous oxygen content difference. Left ventricular filling pressures (pulmonary artery occlusion pressure) remained within the normal range in both groups. Transient electrocardiographic signs of myocardial ischemia (V5 ST-segment depression ≥ 0.1 mV) were observed in four patients during the last minute of the epinephrine 0.04 $\mu g \cdot kg^{-1} \cdot min^{-1}$ infusion rate (three control group patients and one patient with preoperative β-blocker therapy). These changes promptly disappeared when the infusion was stopped. No arrhythmias were noted, and no patient required therapy. There was no postoperative myocardial infarction among the patients included in this study.

Discussion

Among the various techniques available to quantitate the state of β-adrenoceptor blockade in humans,[4] the only one suitable for use during general anesthesia and surgery is the isoproterenol sensitivity test,[5,6] which has been shown to be simple, safe, and highly reproducible, thus allowing a functional assessment of the extent of β-adrenoceptor blockade.[2-5] The validity of this approach as a pharmacodynamic tool has also been proven by the strong correlation between isoproterenol CD_{25} and plasma concentrations of β-adrenoceptor blockers.[6] However, the heart rate response to isoproterenol is not only influenced by the extent of β-blockade in the heart and the patient's age[2,5,7]; it may also depend on variations in reflex responses to its hypotensive property and hence on the type of β-adrenergic blocking agent,[8,9] without necessarily meaning a different degree of β-adrenoceptor sensitivity. We did not find a correlation between age and isoproterenol CD_{25} within our control group of patients, which could be because we examined a relatively narrow age range. In contrast to data obtained in awake patients,[8,9] Dagnino and Prys-Roberts[5] found little difference between isoproterenol CD_{25} values of elderly patients receiving general anesthesia treated with cardioselective or nonselective β-blockers. This observation was made despite the fact that isoproterenol caused a significant decrease in blood pressure only in patients receiving selective β-blockers. Since general anesthesia significantly depresses baroreflex activity in humans,[10] the contribution of vagal withdrawal to the heart rate response to isoproterenol consequent to the decrease in blood pressure probably is negligible under these conditions.

Recently published *in vivo* studies have demonstrated that not only is the stimulation of cardiac β_1-receptors coupled to positive chronotropic responses, but also that β_2-receptors may play a major functional role in the chronotropic (and inotropic) activity of the healthy human heart.[11-13] Since nonfailing human ventricular myocardium and atrial tissue contain a relatively high proportion of β_2-receptors (20–30%),[14-16] it is not surprising that the highest isoproterenol CD_{25} values were observed in patients receiving nonselective (β_1 and β_2) blocking drugs, whereas low degrees of functional β-blockade were found in the three patients pretreated with the highly β_1-selective blocker bisoprolol. In fact, it has been shown that the ratio of β_1/β_2-blocking activity of bisoprolol is 147, far exceeding that of other "cardioselective" drugs such as metoprolol or the nonselective antagonist propranolol with β_1/β_2-blocking ratios of 1.6 and 0.2, respectively.[17] Accordingly, the extent of clinical β-adrenoceptor blockade not only depends on the individual dosage, the duration of therapy, and on whether a patient receives a nonselective or a selective blocker, but also is determined by the degree of selectivity of the latter. It should be noted, however, that the low degree of β-adrenoceptor blockade following bisoprolol pretreatment was observed in only three patients and might have been the result of inadequate β_1-blockade rather than of high selectivity, although these patients had received clinically effective antianginal doses for more than 3 weeks.

The geometric mean isoproterenol CD_{25} values in the two patient groups were almost identical with those obtained in our previous study performed under the same conditions.[18] Although there are no other comparable figures in the literature on isoproterenol CD_{25} values in

TABLE 1. Cardiovascular Effects of Epinephrine in Patients with and without β-Adrenoceptor Blocker Therapy

Variable	Group 1 (n = 11) No β-Adrenoceptor Blockade				Group 2 (n = 20) Preoperative β-Blocker Therapy			
		Epinephrine (μg·kg⁻¹·min⁻¹)				Epinephrine (μg·kg⁻¹·min⁻¹)		
	Control	0.01	0.02	0.04	Control	0.01	0.02	0.04
Cardiac index	2.07 ± 0.69 (l·min⁻¹·m⁻²)	26*	56* (% change)	92*	1.95 ± 0.51 (l·min·m⁻²)	1†	12† (% change)	31*†
Systemic vascular resistance index	2624 ± 595 (dynes·s·cm⁻⁵·m⁻²)	−17*	−31* (% change)	−40*	2,533 ± 569 (dynes·s·cm⁻⁵/m⁻²)	13*†	15*† (% change)	26*†
Mean arterial pressure	72 ± 7 (mmHg)	5*	7* (% change)	12*	67 ± 7 (mmHg)	12*†	19*† (% change)	32*†
Systolic arterial pressure	100 ± 8 (mmHg)	7*	12* (% change)	23*	90 ± 10† (mmHg)	13*†	20*† (% change)	39*†
Diastolic arterial pressure	57 ± 6 (mmHg)	0	−2 (% change)	−2	52 ± 6 (mmHg)	12*†	16*† (% change)	27*†
Heart rate	65 ± 10 (beats per min)	3*	8* (% change)	15*	61 ± 8 (beats/min)	−2*†	−2*† (% change)	1†
Left ventricular filling pressure	8.6 ± 2.6 (mmHg)	1.0*	1.5* (Δ mmHg)	2.0*	9.5 ± 3.2 (mmHg)	1.1*	2.2* (Δ mmHg)	3.6
Arterial–mixed venous O_2 content difference	3.54 ± 0.85 (ml/dl)	−0.7*	−0.9* (Δ ml/dl)	−1.6*	3.54 ± 0.67 (ml/dl)	0.1†	−0.3† (Δ ml/dl)	−0.8*†

* $P \leq .05$ (*vs.* control).

patients undergoing coronary artery bypass surgery, our data and patient characteristics appear to be typical of those of the average patient with ischemic heart disease and normal global left ventricular function.

In the absence of preoperative β-adrenergic blocking drugs, effects of low-dose infusions of epinephrine were primarily those of β_1- and β_2-adrenoceptor stimulation of the heart and the peripheral vascular beds; *i.e.*, cardiac output markedly increased and systemic vascular resistance significantly decreased, resulting in a slightly increased mean arterial pressure. These potentially beneficial hemodynamic changes are in agreement with those in the literature.[1,19] However, the epinephrine doses used in this study are low compared to those usually required in the treatment of heart failure. The low drug doses may have had such a marked effect in the non-β-blocked patients merely by serving to oppose some of the depressant effects of the anesthetic combination on myocardial function and circulating catecholamine levels.

Studies in conscious hypertensive patients have demonstrated that propranolol (as opposed to metoprolol) pretreatment was associated with a marked pressure response when epinephrine was infused at rates of 0.5–8.0 μg/min.[20,21] However, cardiac output was not measured, no control group without β-blockade was included, and the degree of β-adrenergic blockade was not ascertained.

Since our study also involves a quantitative analysis of the extent of clinical β-adrenoceptor blockade, it is the first to allow a direct assessment of its relation to the associated hemodynamic profile of epinephrine. Our major finding is that epinephrine may not be effective for short-term inotropic support of surgical patients with greater degrees of β-blockade. Preoperative treatment with clinically effective doses of the highly selective blocker bisoprolol only slightly blunted the increase in cardiac index (and heart rate). This effect might have been the result either of the use of relatively low doses of bisoprolol or of bisoprolol's inability to block β_2-adrenoceptors, which are partially involved in the positive inotropic (and chronotropic) effects of epinephrine. In contrast, after nonselective blockade epinephrine caused a decrease in cardiac index and heart rate (presumably due to baroreflex mediation), whereas intermediate responses were observed in the 13 patients receiving metoprolol. These results do not contradict *in vitro* findings,[14] indicating that 1) the inotropic and chronotropic response to epinephrine is mediated *via* β_1- and β_2-adrenoceptors; 2) the selectivity of metoprolol for β_1-receptors is only relative and does not spare β_2-receptors at higher doses; and 3) there do not appear to be any significant α-receptor-mediated inotropic responses. The latter conclusion is supported by the observation that epinephrine no longer increased the left ventricular pressure–volume ratio (an index of myocardial contractility) after propranolol pretreatment.[12] On

the other hand, higher degrees of preoperative β-blockade (in particular nonselective blockade) unmasked the intrinsic vascular α-adrenergic properties of epinephrine, resulting in a marked pressor response with associated increases in systemic vascular resistance, thus making epinephrine act like a pure α-agonist. It is unlikely, therefore, that the use of higher doses of epinephrine would have increased cardiac index under these circumstances. Nevertheless, reliance on arterial blood pressure alone may give misleading information with regard to the mechanism of the blood pressure response unless cardiac output is being measured.

We cannot exclude the possibility that the anesthetic technique (*e.g.*, isoflurane) has exaggerated the difference between the effects of epinephrine on cardiac output and systemic vascular resistance in the two patient groups as a result of increased plasma levels of the β-adrenergic blocking drugs. Such an effect has been demonstrated for propranolol during halothane anesthesia in dogs.[22]

Our results could have important clinical implications for the use of epinephrine during the prebypass period in patients undergoing coronary artery bypass surgery who are receiving β-adrenoceptor blocking drugs for control of angina pectoris, hypertension, or arrhythmias. Although a critical time for many of these patients is the period immediately following cessation of cardiopulmonary bypass during which inotropic drugs are commonly (often uncritically) used, this period is a unique situation with obvious potential for unstable and uncontrolled baseline conditions due to bleeding and/or rapid spontaneous changing in ventricular function and peripheral vascular resistance. Since results of any study conducted during this time must be interpreted with caution, the current investigation was performed during the immediate preoperative period under steady-state hemodynamic and anesthetic conditions. It should be stressed, however, that none of our patients was in urgent need of inotropic support. Although cardiac output was low mainly because of a reduced total body oxygen demand in response to anesthesia, muscle relaxation, and mechanical ventilation, other hemodynamic features of acute cardiac failure, such as increased arterial − mixed venous oxygen content difference, elevated left ventricular filling pressure, and high systemic vascular resistance, were not present. Another difference between our study protocol and the most common time of use of inotropic agents is that the plasma levels of β-adrenoceptor blocking drugs and hence the probable degree of β-blockade may be lower after bypass.[23] On the other hand, since β-adrenoceptor down-regulation with preservation of α-adrenoceptor function is a cardinal manifestation of heart failure, the pressor component of even low doses of epinephrine may become more pronounced under these conditions.[24] However, the molecular basis of the pharmacology of epinephrine in patients with heart failure is difficult to predict, because restored β-receptor sensitivity associated with long-term β-adrenoceptor blockade may improve the hemodynamic response to catecholamines and because the role of the α-adrenoceptor in supporting cardiac function may also be enhanced.[15,24,25] Additional studies should therefore be performed in patients receiving β-adrenoceptor blocking drugs who develop congestive heart failure after cardiac surgery, since sympathomimetic amines may well act differently in those situations.

The authors thank Mrs. Kookja Kim, Mrs. Elke Knothe, and Mrs. Gertrud Heymann for technical assistance and Mrs. Anna Manowski for secretarial assistance.

References

1. Weiner A: Norepinephrine, epinephrine, and the sympathomimetic amines, The Pharmacological Basis of Therapeutics. Edited by Goodman Gilman A, Goodman LS, Rall TW, Murad F. New York, MacMillan, 1985, pp 145–180
2. Cleaveland RC, Rangno RE, Shand DG: A standardized isoproterenol sensitivity test: The effects of sinus arrhythmia, atropine, and propranolol. Arch Intern Med 130:47–52, 1972
3. George CF, Conolly ME, Fenyvesi T, Briant R, Dollery CT: Intravenously administered isoproterenol sulfate dose-response curves in man. Arch Intern Med 130:361–364, 1972
4. McDevitt DG: The assessment of β-adrenoceptor blocking drugs in man. Br J Clin Pharmacol 4:413–425, 1977
5. Dagnino J, Prys-Roberts C: Assessment of β-adrenoceptor blockade during anesthesia in humans: Use of isoproterenol dose-response curves. Anesth Analg 64:305–311, 1985
6. Prys-Roberts C, Dagnino J: Pharmacodynamic and kinetic profiles of beta-adrenoceptor antagonists administered by continuous intravenous infusion, Quantitation, Modelling and Control in Anesthesia. Edited by Stoeckel H. Stuttgart, New York, Thieme, 1985, pp 129–133
7. Vestal RE, Wood AJ, Shand DG: Reduced β-adrenoceptor sensitivity in the elderly. Clin Pharmacol Ther 26:181–186, 1979
8. Perucca E, Pickles H, Richens A: Effect of atenolol, metoprolol, and propranolol on isoproterenol induced tremor and tachycardia in normal subjects. Clin Pharmacol Ther 29:425–433, 1981
9. Arnold JM, McDevitt DG: Heart rate and blood pressure responses to intravenous boluses of isoprenaline in the presence of propranolol, practolol and atropine. Br J Clin Pharmacol 16:175–184, 1983
10. Bristow JD, Prys-Roberts C, Fisher A, Piekering TG, Sleight P: Effects of anesthesia on baroreflex control of heart rate in man. ANESTHESIOLOGY 31:422–428, 1969
11. Strauss MH, Reeves RA, Smith DL, Leenen FH: The role of cardiac β_1 receptors in the hemodynamic response to a β_2-agonist. Clin Pharmacol Ther 40:108–115, 1986
12. Leenen FH, Chan YK, Smith DL, Reeves RA: Epinephrine and left ventricular function in man: Effects of beta-1 vs non-selective blockade. Clin Pharmacol Ther 43:519–528, 1988
13. Levine MA, Leenen FH: Role of β_1-receptors and vagal tone in cardiac inotropic and chronotropic responses to a β_2-agonist in humans. Circulation 79:107–115, 1989
14. Kaumann AJ, Lemoine H: β_2-adrenoceptor-mediated positive inotropic effect of adrenaline in human ventricular myocardium. Quantitative discrepancies with binding and adenylate cyclase stimulation. Naunyn Schmiedebergs Arch Pharmacol 335:403–411, 1987

15. Michel MC, Pingsmann A, Beckeringh JJ, Zerkowski HR, Doetsch N, Brodde OE: Selective regulation of β_1- and β_2-adrenoceptors in the human heart by chronic β-adrenoceptor antagonist treatment. Br J Pharmacol 94:685–692, 1988
16. Bristow MR, Hershberger RE, Port JD, Gilbert EM, Sandoval A, Rasmussen R, Cates AE, Feldman AM: β-adrenergic pathways in nonfailing and failing human ventricular myocardium. Circulation 82(suppl I):I-12–I-25, 1990
17. Schliep HJ, Harting J: β1-selectivity of bisoprolol, a new β-adrenoceptor antagonist, in anesthetized dogs and guinea pigs. J Cardiovasc Pharmacol 6:1156–1160, 1984
18. Tarnow J, Komar K: Altered hemodynamic response to dobutamine in relation to the degree of preoperative β-adrenoceptor blockade. ANESTHESIOLOGY 68:912–919, 1988
19. Gattiker R, Schmid E: Haemodynamic effects of dopamine, epinephrine and orciprenaline in patients early after cardiac surgery. Intensive Care Med 4:55–61, 1978
20. van Herwaarden CL, Binkhorst RA, Fennis JF, van't Laar A: Haemodynamic effects of adrenaline during treatment of hypertensive patients with propranolol and metoprolol. Eur J Clin Pharmacol 12:397–402, 1977
21. Houben H, Thien T, van't Laar A: Effect of low-dose epinephrine infusion on hemodynamics after selective and non-selective β-blockade in hypertension. Clin Pharmacol Ther 31:685–690, 1982
22. Gordon L, Wood AJJ, Koshakji RP, Wilkinson GR, Dupont WD, Wood M: Acute effects of halothane anesthesia on arterial and venous concentrations of propranolol in the dog. ANESTHESIOLOGY 67:225–230, 1987
23. Sill JC, Nugent M, Moyer TP, Torres LE, Schaff HV, Tinker JH: Influence of propranolol plasma levels on hemodynamics during coronary artery bypass surgery. ANESTHESIOLOGY 60:455–463, 1984
24. Hayes JS, Bowling N: Role of the alpha agonist activity of dobutamine in mediating cardiac output: Effects of prolonged isoproterenol infusion. J Pharmacol Exp Ther 241:861–869, 1987
25. Heilbrunn SM, Shah P, Bristow MR, Valantine HA, Ginsburg R, Fowler MB: Increased β-receptor density and improved hemodynamic response to catecholamine stimulation during long-term metoprolol therapy in heart failure from dilated cardiomyopathy. Circulation 79:483–490, 1989