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α_1-Adrenergic Responsiveness during Coronary Artery Bypass Surgery: Effect of Preoperative Ejection Fraction

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Elevated catecholamines and β-adrenergic receptor hyporesponsiveness (or desensitization) have been demonstrated in failing human myocardium, but the role of the α-adrenergic receptor remains unclear. The authors tested the hypothesis that α_1-adrenergic responsiveness decreases in patients with impaired ventricular function undergoing coronary artery revascularization. Impaired ventricular function was defined prospectively by left ventricular ejection fraction ≤40% (group I, n = 12), and normal ventricular function by ejection fraction >40% (group II, n = 22). Phenylephrine (Phe) pressor dose-response curves were established prior to anesthesia, during fentanyl anesthesia, and during fentanyl anesthesia plus hypothermic cardiopulmonary bypass at the time of aortic cross-clamp (anes + CPB/AXC). Polynomial regression of the Phe dose response curve estimated the Phe dose required to increase mean arterial blood pressure 20%, designated PD_{20}. Although pre-anesthesia PD_{20} and anes + CPB/AXC PD_{20} values were not affected by ejection fraction, significant differences in PD_{20} ($P < 0.05$) between groups occurred during fentanyl anesthesia (group I = 2.28 ± 1.60 $\mu g \cdot kg^{-1}$, group II 1.57 ± 0.98 $\mu g \cdot kg^{-1}$; mean ± SD). Anes + CPB/AXC was associated with a significant reduction in PD_{20} in both groups compared with pre-anesthesia ($P < 0.01$). Our results suggest impairment of α_1-adrenergic responsiveness occurs during fentanyl anesthesia in patients with ejection fractions ≤40% (evidenced by greater PD_{20} values). Although this impairment may be due to altered Phe pharmacokinetics, these results also support the possible existance of α_1-adrenergic receptor desensitization in this group. Reduction in PD_{20} during anes + CPB/AXC in all patients points to more powerful effects than fentanyl anesthesia alone; such influencing effects may include hemodilution, hypothermia, elevated plasma catecholamines, exclusion of the pulmonary circulation, or altered Phe pharmacokinetics. (Key words: Anesthesia, cardiovascular. Anesthetics, intravenous: fentanyl. Dose-response curves. Heart: ejection fraction. Receptors: alpha-1. Sympathetic nervous system: phenylephrine.)

MANY PATIENTS WITH impaired left ventricular function require coronary artery bypass surgery. Alterations in adrenergic function may add to the complexity of management of these patients. Elevated norepinephrine levels,[1–3] β-adrenergic receptor desensitization,[4] and relative β_2-adrenergic receptor predominance[5,6] have been demonstrated in advanced myocardial disease, but the role of the α-adrenergic receptor remains less clear. Although α-adrenergic receptor desensitization has been described in rabbits,[7] α-adrenergic receptor number appears to stay constant in severely failing human myocardium.[8] An absence of α-adrenergic receptor desensitization has been demonstrated in human platelets during cardiopulmonary bypass (CPB),[9] but platelets have only α_2-adrenergic receptors.[10] Since β-adrenergic receptor desensitization occurs in failing human myocardium and α-receptor desensitization occurs in animals, we tested the hypothesis that α_1-adrenergic responsiveness decreases in patients with coronary artery disease and impaired left ventricular function undergoing coronary artery revascularization compared with patients with normal ventricular function. We also assessed changes in α_1-adrenergic responsiveness during fentanyl anesthesia and cardiopulmonary bypass.

Left ventricular ejection fraction (LVEF), determined at cardiac catheterization, is an easily obtainable preoperative index of cardiac function. Decreased LVEF (less than or equal to 40%) has been correlated with increased morbidity and mortality during cardiac surgery,[11–16] and was used prospectively to define impaired left ventricular function in this study. To our knowledge, this represents the first *in vivo* assessment of α_1-adrenergic responsiveness in patients with impaired ventricular function.

Methods and Materials

STUDY POPULATION

With institutional approval and informed patient consent, 34 patients for elective aortocoronary bypass surgery were studied. Patients with unstable angina, receiving intraaortic balloon counterpulsation, requiring

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intravenous nitroglycerin or inotropic agents, or receiving α-adrenergic blocking medication were excluded from the study. Impaired ventricular function was prospectively defined as LVEF less than or equal to 40% computed by biplane cineangiography of a representative normal cardiac systole during cardiac catheterization within 1 month of surgery. Group I consisted of 12 patients with LVEF less than or equal to 40% (range 20–40%), and group II consisted of 22 patients with LVEF greater than 40% (range 43–68%).

Protocol

Patients were premedicated with intramuscular morphine 0.1 $mg \cdot kg^{-1}$, intramuscular scopolamine 0.2–0.4 mg, and oral diazepam 0.15 $mg \cdot kg^{-1}$ within 2 h of induction of anesthesia. All patients received oxygen at 3 liters per minute *via* nasal cannulae at the time of premedication, which was continued until induction of anesthesia. Intravenous (iv), radial arterial and pulmonary arterial catheters were inserted, and a five-lead electrocardiogram (EKG) was applied. Approximately 1.5 ml 1% lidocaine HCl was used subcutaneously during catheter insertions in all patients. Continuous EKG monitoring with ST segment analysis of leads I, II, and V was accomplished using a Marquette® monitor. Cardiac outputs were measured using the thermodilution method. (−) Phenylephrine HCL (Winthrop Laboratories, New York, NY) was diluted from the clinical liquid preparation to 10 μg per ml in normal saline.

With supine patients resting quietly in an operating room with dimmed lighting, baseline heart rate (HR), mean arterial blood pressure (MAP), central venous pressure (CVP), pulmonary artery diastolic pressure (PAD), pulmonary artery capillary wedge pressure (PCWP) and cardiac output (CO) were measured and blood sampled for plasma catecholamines. A phenylephrine dose response curve was then generated prior to induction of anesthesia (denoted pre-anesthesia) using the bolus technique described below.

To begin the phenylephrine dose response curve, an initial bolus dose of phenylephrine (20 μg) was injected centrally *via* the side-port of an internal jugular vein introducer cannula (Arrow®). The peak MAP occurring in the first 2 min following phenylephrine injection was recorded. HR, PAD, PCWP, and CVP were recorded at peak MAP. Once MAP had returned to baseline, at least 5 min after the first phenylephrine bolus was injected (but longer if necessary), the next bolus dose (40 μg) of phenylephrine was given and hemodynamic parameters recorded as before. Individual bolus doses of phenylephrine were given in the sequence: 20, 40, 80, 120, 160, 200, 240, 280, 320, 360, and 400 μg, allowing MAP to return to baseline between each dose. This sequence of gradually increasing phenylephrine bolus doses continued every 5 min until peak MAP increased 20% above baseline MAP. At this point, the phenylephrine dose-response curve was considered complete. In most patients, MAP increased 20% within the first six bolus doses of phenylephrine; hence, approximately 30 min was required to generate a phenylephrine pressor dose-response curve. Although the primary investigator was not blinded to LVEF, a second blinded investigator confirmed the peak mean blood pressure readings obtained in every patient.

Anesthesia was induced with fentanyl 30 $\mu g \cdot kg^{-1}$ and vecuronium 0.1 $mg \cdot kg^{-1}$ iv, and maintained with a 0.3 $\mu g \cdot kg^{-1} \cdot min^{-1}$ fentanyl infusion. Ten minutes post-intubation and prior to incision, baseline hemodynamics were measured, blood for catecholamine determinations sampled, and then a second phenylephrine dose-response curve (denoted anesthesia) was generated using the bolus dose technique described above.

During cardiopulmonary bypass, after application of the aortic cross-clamp (AXC) and once temperatures stabilized (defined as inflow temperature equal to outflow temperature), baseline hemodynamics were measured and blood for catecholamine determinations sampled; then a third phenylephrine dose-response curve (denoted anes + CPB/AXC) was generated. The fentanyl infusion was continued through aortic cross-clamp and pump flow was held constant throughout the generation of the phenylephrine dose-response curve. Esophageal temperature, rectal temperature, and pump flow (liters per minute) were noted and plasma catecholamines measured as before.

After cardipulmonary bypass, anesthesia was maintained with enflurane as required. Postoperatively patients were taken to the intensive care unit; their tracheas were extubated approximately 6–16 h later. Postoperative EKGs were examined for evidence of myocardial infarction. CPK-MB isoenzymes were not assessed.

Patient Characterisitcs

Specific definitions of medical conditions were used in this study. Hypertension was defined as blood pressure greater than 140/90 mmHg documented on at least three occasions during the current hospital admission, or a history of increased blood pressure requiring medication. Diabetes was considered present if admission blood glucose level was greater than 200 $mg \cdot dl^{-1}$ or if oral hypoglycemic or insulin medication was required. Myocardial infarction was considered to have occurred if there was EKG evidence of an old myocardial infarction or documented episodes of increased CPK-MB isoenzymes without concurrent EKG changes.

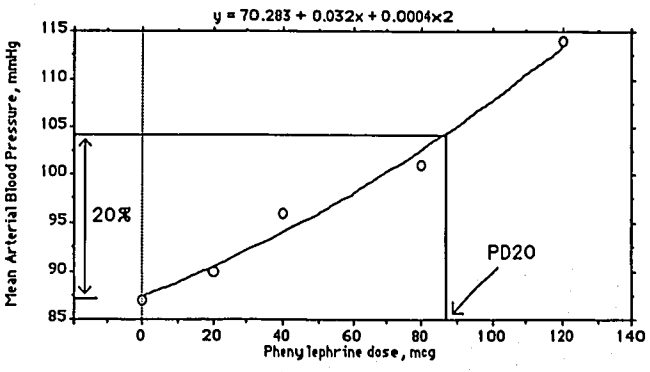

FIG. 1. Second order polynomial regression analysis of phenylephrine pressor dose response curve from a representative patient. Baseline MAP was 87 mmHg, therefore MAP plus 20% = 104.4 mmHg. The phenylephrine pressor dose 20 (PD_{20}) value was 87.0 μg. Since the patient weighed 84.5 kg, the PD_{20} value in $\mu g \cdot kg^{-1}$ = 1.0. This patient had an LVEF of 50%.

Congestive heart failure (CHF) was defined as the presence of at least three of the following: chest roentgenogram evidence of pulmonary edema or four-chamber myocardial enlargement; evidence on physical examination of audible rales, pedal edema, congestive hepatomegally, S_3 gallop, jugular venous distension, or hepato-jugular reflux; increased central venous pressure; increased LVEDP or PCWP unaccompanied by evidence of myocardial ischemia—LVEDP > 18 mmHg during cardiac catheterization or PCWP > 18 mmHg upon insertion of the pulmonary artery catheter on the day of surgery.

Plasma Catecholamine Determinations

Blood samples for plasma catecholamine determinations were collected in 5 ml chilled polypropylene tubes containing anticoagulant (EGTA) and antioxidant (glutathione). After refrigerated centrifugation, the plasma was transferred to plastic storage tubes and stored at −70°C until the time of assay. Plasma catecholamines were thawed, mixed with 10 cc of phosphate buffer (0.1 M, *p*H 7), and separated on a Bio-Rex 70 ion-exchange column. The column was washed with water and then 1 ml sulfuric acid (0.7 M) was added. The catecholamines were eluted with ammonium sulfate (1 M) into tubes containing EDTA/sodium metabisulfite, alumina, and tris buffer (3 M, *p*H 8.5). After microfiltration, 200 microliters of perchloric acid (0.1 M) was added to the solution. The perchlorate-catecholamine solution was injected onto a high-performance liquid chromatography column (stationary phase—C18 column, mobile phase—monochloroacetic acid [0.15 M, *p*H 3] with sodium octyl sulfate) for determination of norepinephrine and epinephrine levels. Plasma catecholamine assay sensitivity was 30 $pg \cdot ml^{-1}$ and the coefficient of variation was 9%.

Data Analysis

The dose of phenylephrine required to increase baseline MAP 20% for a given trial was designated pressor dose 20 (PD_{20}) and was calculated using second order polynominal regression analysis of the phenylephrine dose-response curve. Polynomial regression with or without logarithmic transformation has been shown to be superior to linear regression in analyzing pressor dose-response curves.[17] Figure 1 illustrates second order polynomial regression analysis of a pressor dose-response curve from a representative patient.

The Mann-Whitney U test was used to compare patient characteristics between the two groups. Repeated measures analysis of variance was used to determine significant differences in PD_{20} and plasma catecholamines between groups and time (pre-anesthesia, anesthesia, anes + CPB/AXC). When significant differences occurred using repeated measures analysis of variance, unpaired two-tailed two-sample *t* tests with Bonferroni correction were used to determine the exact *P* value. Covariants (specific patient characteristics) were used with repeated measures analysis of variance to determine the effect of patient characteristics on PD_{20}. Linear regression analysis was used to test for relationships between LVEF and PD_{20}. Statistical significance was declared with a *P* value <0.05.

Phenylephrine Pressor Dose 15 mmHg

By design, PD_{20} represents the amount of phenylephrine required to increase MAP 20%. However, MAP values were lower during anes + CPB/AXC than during other times during the study. To investigate whether changes in PD_{20} during anes + CPB/AXC were introduced as a result of lower MAP during this time period, we retrospectively designated phenylephrine pressor dose 15 mmHg ($PD_{15\ mmHg}$) as the amount of phenylephrine required to increase MAP by an absolute 15 mmHg. As with PD_{20}, $PD_{15\ mmHg}$ was calculated using second order polynomial regression analysis of the phenylephrine dose-response curve. It is important to note that PD_{20} represents the amount of phenylephrine required to increase MAP 20%, whereas $PD_{15\ mmHg}$ represents the amount of phenylephrine required to increase MAP an absolute 15 mmHg.

Results

Patient Outcome

All patients were well sedated upon arrival to the operating room, but were easily aroused and fully responsive to command. No patient complained of chest pain, had ST segment depression or elevation, or had an increase in baseline premature ventricular contrac-

TABLE 1. Patient Characteristics (Mean ± SD)

Characteristic	Group I (LVEF ≤ 40%)	Group II (LVEF > 40%)	P Value*
General:			
Gender—female	3/12	5/22	NS
Race—black	2/12	0/22	NS
Age (years)	60.8 ± 8.9	58.2 ± 8.9	NS
Weight (kg)	75.7 ± 7.8	81.0 ± 12.4	NS
Medical history:			
Ejection fraction (%)	33.9 ± 6.3	54.1 ± 8.0	$P = 0.0001$
Ejection fraction range (%)	20–40	43–68	—
Hypertension	8/12	11/22	NS
Diabetes	1/12	5/22	NS
Myocardial infarction	12/12	10/22	$P = .0008$
Congestive heart failure	5/12	1/22	$P = .006$
Preoperative medication:			
Calcium channel blockers	9/12	17/22	NS
Beta-adrenergic blockers	4/12	16/22	$P = .026$
Diuretics	4/12	2/22	NS
Nitrates	9/12	9/22	NS
Digoxin	3/12	1/22	NS
Laboratory values:			
Hematocrit (%)	38.1 ± 4.0	39.8 ± 4.1	NS
Potassium (mEq·l)	3.8 ± .4	3.9 ± .3	NS
Surgery:			
# Vessels bypassed	3.1 ± .9	3.0 ± 1.2	NS
Temperature during aortic crossclamp (inflow = outflow temperature), °C	24.0 ± 2.7	24.7 ± 3.7	NS

* NS = not significant at the 95% confidence level.

tions (PVCs) during the phenylephrine dose-response study, and no patient had EKG evidence of perioperative myocardial infarction. One patient with normal ventricular function had sustained hypertension after induction of anesthesia, and was, therefore, excluded from the study and given vasodilators with good results. There were no perioperative or postoperative complications attributable to the administration of phenylephrine. One patient with LVEF > 40% did require thoracic re-exploration for post-surgical bleeding. There was no operative mortality.

PATIENT CHARACTERISTICS

Table 1 summarizes patient characteristics from group I (LVEF ≤ 40%) and group II (LVEF > 40%). The two groups were not significantly different except for the following characteristics: history of myocardial infarction ($P = .0008$), history of congestive heart failure ($P = .006$), and history of beta-adrenergic blocking medication ($P = .026$). Of note, all patients in group I had a history of previous myocardial infarction. More patients with a history of congestive heart failure were seen in group I than group II, and fewer patients with impaired ventricular function were receiving beta-adrenergic blocking medication than those with normal ventricular function.

HEMODYNAMICS

Hemodynamic values prior to phenylephrine administration (MAP, HR, CO, CVP, PAD, PCWP, SVR) are shown in table 2 for each group and time period studied. There were no differences in hemodynamic values between groups at any time period, except during pre-anesthesia, when patients in group I had lower MAP than patients in group II ($P < 0.05$). During cardiopulmonary bypass, MAP, CO, and CVP were significantly lower ($P < 0.05$) than during pre-anesthesia in both groups.

PLASMA CATECHOLAMINES

Plasma cathecholamine concentrations are shown in table 3. Large variability in plasma catecholamine concentrations occurred in both groups. There were no significant differences in plasma catecholamine concentrations between groups at any time period. Although epinephrine and norepinephrine concentrations increased during Anes + CPB/AXC in both groups, this increase did not reach statistical significance.

PHENYLEPHRINE PRESSOR DOSE 20 VALUES

PD_{20} values for all patients are shown in figure 2. Pre-anesthesia PD_{20} and anes + CPB/AXC PD_{20} were

TABLE 2. Hemodynamic Values (Mean ± SD)

	Pre-anesthesia				Anesthesia				Anes+ CPB/AXC			
	Group I LVEF ≤ 40%		Group II LVEF > 40%		Group I LVEF ≤ 40%		Group II LVEF > 40%		Group I LVEF ≤ 40%		Group II LVEF > 40%	
MAP (mmHg)	72.8 ± 9.5	*	83.2 ± 7.8		78.1 ± 10.3	-NS-	80.0 ± 12.4		42.4 ± 6.2†‡	-NS-	47.2 ± 16.8†‡	
HR (beats · min^{-1})	56.6 ± 13.0	-NS-	54.9 ± 9.4		52.6 ± 14.8	-NS-	51.3 ± 8.2		—		—	
CO (L · min^{-1})	4.2 ± 0.9	-NS-	4.8 ± 0.9		4.3 ± 1.4	-NS-	4.4 ± 1.7		3.2 ± 0.5†	-NS-	3.3 ± 0.5†‡	
CVP (mm Hg)	7.9 ± 3.1	-NS-	8.4 ± 3.6		8.6 ± 1.6	-NS-	8.3 ± 3.3		3.7 ± 3.1†‡	-NS-	4.2 ± 3.2†‡	
PAD (mm Hg)	13.0 ± 3.8	-NS-	12.4 ± 4.5		12.7 ± 2.6	-NS-	11.9 ± 3.6		—		—	
PCWP (mm Hg)	15.7 ± 4.1	-NS-	14.8 ± 6.3		15.2 ± 3.5	-NS-	12.1 ± 3.9		—		—	
SVR (dyne · sec · cm^{-5})	1180 ± 350	-NS-	1325 ± 315		1397 ± 341	-NS-	1408 ± 397		1009 ± 219	-NS-	1062 ± 596	

NS = not significant at the 95% confidence level between groups. All hemodynamic parameters were measured prior to phenylephrine administration. Cardiac output listed during anes + CPB/AXC represent cardiopulmonary bypass pump flow.

* $P < 0.05$ between groups.
† $P < 0.05$ compared to pre-anesthesia for same patient group.
‡ $P < 0.05$ compared to anesthesia for same patient group.

not affected by LVEF. Hence, similar amounts of phenylephrine were required to achieve a 20% increase in MAP in each group during these time periods. However, during fentanyl anesthesia, significant ($P < 0.05$) differences were noted between groups. Patients with LVEF ≤ 40% required more phenylephrine to increase MAP 20% than did patients with LVEF > 40%. There was also an inverse correlation between LVEF and PD_{20} during fentanyl anesthesia, as shown in figure 3 ($r = 0.42$, $P < 0.03$). During anes + CPB/AXC, PD_{20} was significantly lower ($P < 0.01$) than pre-anesthesia in both groups. Hence, less phenylephrine was required to achieve a 20% increase in MAP during anes + CPB/AXC compared with pre-anesthesia. In addition, PD_{20} values were significantly lower ($P < 0.01$) in group II during fentanyl anesthesia compared with pre-anesthesia. Therefore, less phenylephrine was required during anesthesia than during pre-anesthesia to increase MAP 20% in patients with normal ventricular function.

PHENYLEPHRINE PRESSOR DOSE 15 MMHG

A comparison of PD_{20} and $PD_{15\ mmHg}$ values in both groups is shown in table 4. Although $PD_{15\ mmHg}$ values are higher than PD_{20} values during anes + CPB/AXC, significant ($P < 0.05$, group I; $P < 0.01$, group II) decreases in $PD_{15\ mmHg}$ still occur during anes + CPB/AXC compared to pre-anesthesia. Hence, less phenylephrine was required in both groups during anes + CPB/AXC to increase MAP 15 mmHg compared to pre-anesthesia.

PHENYLEPHRINE PRESSOR DOSE 20 AND PATIENT CHARACTERISTICS

PD_{20} was not correlated with the following patient characteristics during any time period: gender, race, age, weight, body surface area, hypertension, diabetes, myocardial infarction, calcium channel blockers, beta-adrenergic blockers, diuretics, nitrates, digoxin, HR, CO, CVP, PAD, PCWP, SVR, hematocrit, potassium, number of vessels bypassed, or temperature during Anes + CPB/AXC. PD_{20} did not correlate with MAP for a given time period (pre-anesthesia, anesthesia, anes + CPB/AXC). Congestive heart failure was the only patient characteristic that correlated with PD_{20}; this correlation occurred during anesthesia.

Six patients in the study had congestive heart failure. PD_{20} values for patients with CHF are shown in figure 4. As with LVEF < 40%, the presence of CHF significantly ($P < 0.01$) increased PD_{20} during anesthesia compared with patients without CHF. Hence, more phenylephrine was required to increase MAP 20% during anesthesia in patients with CHF compared to patients without CHF. Significantly lower PD_{20} values oc-

TABLE 3. Plasma Catecholamines (pg · ml^{-1}, Mean ± SD)

Time	Epinephrine		Norepinephrine	
	Group I (LVEF ≤ 40%)	Group II (LVEF > 40%)	Group I (LVEF ≤ 40%)	Group II (LVEF > 40%)
Pre-anesthesia	560 ± 846	543 ± 109	633 ± 557	536 ± 366
Anesthesia	316 ± 292	525 ± 526	380 ± 210	586 ± 272
CPB/AXC	612 ± 438	834 ± 906	670 ± 249	855 ± 736

There were no significant differences between groups during any time period.

curred in all patients during anes ± CPB/AXC compared with pre-anesthesia ($P < 0.01$), and in patients without CHF during anesthesia compared to pre-anesthesia ($P < 0.01$). There were no significant differences in plasma catecholamine levels between patients with and without CHF at any time interval (pre-anesthesia, anesthesia, anes + CPB/AXC).

Discussion

Our results demonstrate several important characteristics of α_1-adrenergic function in patients with impaired left ventricular function, defined by decreased LVEF. First, our data suggest that changes in α_1-adrenergic responsiveness (as evidenced by the pressor effects of phenylephrine) do not occur in the awake (pre-anesthesia) state in patients with impaired left ventricular function. However, fentanyl anesthesia appears to be associated with significant differences in α_1-adrenergic responsiveness between the two groups. Also, patients with CHF require more phenylephrine to increase MAP 20% during anesthesia compared to patients without CHF. Finally, significant reductions in PD_{20} values occur in all patients during anes + CPB/AXC. Each of these findings will be discussed following an analysis of intergroup differences and the effect of patient characteristics on PD_{20} values.

PATIENT CHARACTERISTICS

Groups I (LVEF ≤ 40) and group II (LVEF > 40) were well matched except for four characteristics: LVEF, history of myocardial infarction, history of congestive heart failure, and beta-adrenergic blocking medication. LVEF was significantly different because of study design. The remaining characteristics may be seen as markers of impaired ventricular function. All patients in group I had a history of myocardial infarction, as compared to only 45% in group II. In the presence of coronary artery disease, myocardial infarction or ischemia is probably the cause of decreased LVEF in patients with impaired ventricular function. Congestive heart failure was more common in the group with LVEF ≤ 40 as expected. The use of beta-adrenergic antagonists was more frequent in group II, and, presumably, reflects the general medical practice of avoiding beta-adrenergic blockade medication in patients with impaired left ventricular function, despite recent evidence that β-adrenergic blockade may be of benefit in some forms of myocardial failure.[18] One-third of the patients with LVEF ≤ 40% were taking beta-adrenergic blockade medication prior to surgery.

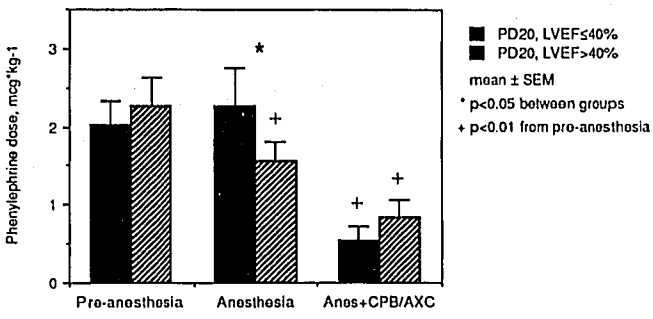

FIG. 2. Comparison of phenylephrine pressor dose 20 (PD_{20}) between group I (LVEF ≤ 40%, n = 12) and group II (LVEF > 40%, n = 22). Significant differences in PD_{20} occur between groups during fentanyl anesthesia ($P < 0.05$). PD_{20} in both groups decreases during anes + CPB/AXC compared to pre-anesthesia ($P < 0.01$) and in group II (LVEF > 40%) during anesthesia compared to pre-anesthesia ($P < 0.01$). Exact PD_{20} values are as follows (LVEF ≤ 40%, LVEF > 40%; μg · kg^{-1} mean ± SD): Preanesthesia—2.0 ± 1.1, 2.3 ± 1.6; anesthesia —2.3 ± 1.6, 1.6 ± 1.0; anes + CPB/AXC—0.6 ± 0.6, 0.9 ± 1.0

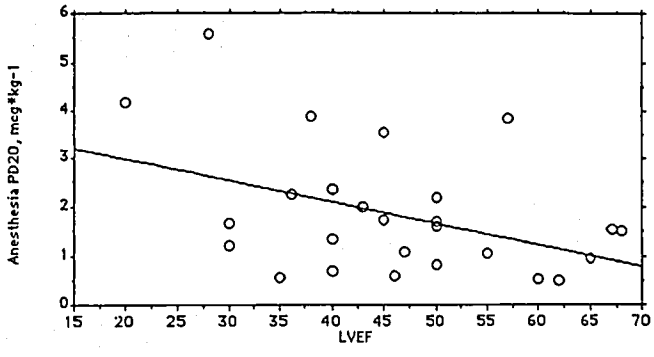

FIG. 3. Inverse correlation between left ventricular ejection fraction (LVEF) and phenylephrine pressor dose 20 (PD_{20}) during fentanyl anesthesia ($r = 0.42$, $P < 0.03$).

TABLE 4. Comparison of Phenylephrine Pressor Dose 20 (PD_{20}) and Phenylephrine Dose 15 mmHg ($PD_{15\ mmHg}$) during CPB/AXC ($\mu g \cdot kg^{-1}$, Mean ± SD)

	PD_{20}		$PD_{15\ mmHg}$	
	Pre-anesthesia	anes+ CPB/AXC	Pre-anesthesia	anes+ CPB/AXC
Group I (LVEF ≤ 40%)	2.04 ± 1.05 †	0.57 ± 0.62	2.03 ± 1.03 *	0.88 ± 0.79
Group II (LVEF > 40%)	2.28 ± 1.63 †	0.84 ± 1.01	2.13 ± 1.55 †	1.35 ± 1.39

* $P < 0.05$. † $P < 0.01$.

Hemodynamic values were similar in both groups except for lower pre-anesthesia MAP values in group I. There was a trend toward lower SVR and CO in group I, but this did not reach statistical significance. Lower MAP and trend toward lower SVR in group I may have enabled CO to remain in the normal range, in spite of the lower ejection fraction present in this group.

PHENYLEPHRINE PRESSOR DOSE RESPONSE CURVES

Phenylephrine, an α_1-adrenergic agonist,[19,20] was administered using a bolus technique during this study. Phenylephrine has previously been administered as a continuous infusion to assess adrenergic responsiveness in various clinical and laboratory settings. Since continuous infusion of pressors to patients with myocardial disease and depressed ejection fraction may increase afterload and potentially increase myocardial wall stress and myocardial oxygen consumption, a shorter duration of peak mean blood pressure effect of phenylephrine is desirable in these patients. For this reason, a bolus technique of phenylephrine administration was developed to assess α_1-adrenergic responsiveness in this study. Pooled PD_{20} values from groups I and II during pre-anesthesia correspond well to measurements of phenylephrine pressor responsiveness in the literature[21–26] made with continuous phenylephrine infusion techniques.

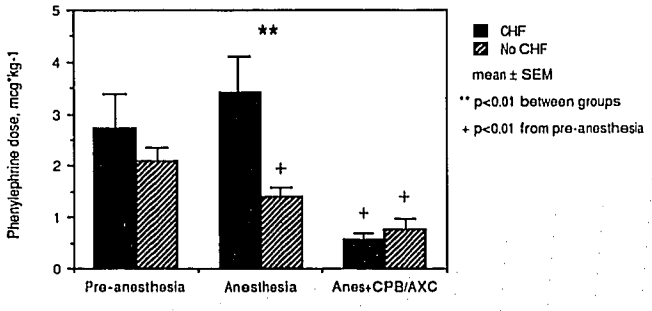

FIG. 4. Comparison of phenylephrine pressor dose 20 (PD_{20}) between patients with congestive heart failure (CHF, n = 6) and patients without CHF (n = 28). Significant differences in PD_{20} occur between groups during fentanyl anesthesia ($P < 0.01$). PD_{20} values in both groups decrease during anes + CPB/AXC compared to pre-anesthesia ($P < 0.01$) and in patients without CHF during anesthesia compared to pre-anesthesia ($P < 0.01$). Exact PD_{20} values are as follows (CHF, no CHF; $\mu g/\cdot kg^{-1}$, mean ± SD): Pre-anesthesia—2.7 ± 1.6, 2.1 ± 1.4; anesthesia—3.4 ± 1.7, 1.4 ± 0.7; anes + CPB/AXC—0.6 ± 0.3, 0.8 ± 1.0.

MAP was chosen as the hemodynamic marker for vascular responsiveness to bolus phenylephrine in this study. Although MAP is a frequently used end-point of pressor responsiveness,[21–26] SVR has also been used to evaluate the effects of phenylephrine infusion in cardiac surgery patients with good ventricular function.[27] Peak MAP occurs simultaneously with peak SVR after bolus phenylephrine administration to cardiac surgery patients when near-continuous CO measurement with esophageal Doppler is employed.[28] However, MAP is a more accurate hemodynamic marker for vascular responsiveness than SVR in the setting of bolus phenylephrine administration when CO is measured using the thermodilution method, as in this study. SVR is related to CO by the equation SVR = (MAP − CVP)/CO. Since it is impossible to predict when the peak vascular response will occur following a bolus dose of phenylephrine, an accurate thermodilution CO measurement (and, hence, SVR calculation) is difficult.

PHENYLEPHRINE PRESSOR DOSE 20 VALUES AND PATIENT CHARACTERISTICS

The absence of a correlation between PD_{20} and any patient characteristic (except CHF) listed in table 1 is of note, since controversy exists regarding the effect of cardiac medications on adrenergic function. For example, beta-adrenoceptor blockade has been implicated as causing unopposed alpha-adrenoceptor tone and enhanced pressor responsiveness to drugs such as phenylephrine.[29] Our study suggests that this does not occur during cardiac surgery. Phenylephrine PD_{20} was not affected by preoperative beta-adrenergic blockade medication in either group, and this is in agreement with the findings of other studies in non-surgical patients.[30]

Calcium channel blockade has been implicated in decreasing α-adrenergic responsiveness.[31,32] Recent studies,[33–37] however, have shown that calcium channel blockade interferes selectively with the α_2-adrenergic

receptor. Our previous study measuring SVR during phenylephrine infusion suggests that α-adrenergic responsiveness is slightly diminished in patients receiving calcium channel blockers compared to unblocked subjects.[27] However, the present study does not demonstrate an effect of calcium channel blocking medication on phenylephrine PD_{20} values.

Cholinergic blockade has been shown to slightly increase pressor responses in humans.[38] In our study, all patients were given scopolamine as part of the routine premedication, so this comparison could not be made. It is interesting to note that hypertension[38,39] and aging[40,41] have been associated with increased circulating catecholamines. Neither of these patient characteristics has been implicated in impaired α_1-adrenergic responsiveness[23,30,42]; PD_{20} was not correlated with age or the presence of hypertension in our study.

Pre-anesthesia Phenylephrine Pressor Dose 20 Values

Our results suggest that changes in α_1-adrenergic responsiveness (as evidenced by the pressor effects of phenylephrine) evaluated in the awake state do not occur in patients with decreased ejection fraction. Adrenergic hyporesponsiveness frequently involves attenuation of responsiveness to pharmacological or hormonal stimulation with time. Specifically, continuous administration of a receptor agonist may decrease responsiveness, or desensitize the receptor to further agonist challenges. α_1-adrenergic hyporesponsiveness or desensitization has been demonstrated *in vitro*,[43,44] in rats with phenochromocytoma (plasma catecholamines increased 50–100-fold),[45] and in rats[46] and rabbits[7] given continuous catecholamine infusions (plasma catecholamines increased 15–20-fold), but has not been categorically documented in humans.[47,48]

Our inability to demonstrate α_1-adrenergic hyporesponsiveness in awake patients with impaired left ventricular function is most likely due to patient selection, and may also be related to similar pre-anesthesia plasma catecholamine values in both groups. Although almost one-half of the patients with LVEF $\leq$ 40% had a history of congestive heart failure, none of these patients had valvular heart disease, all were considered operative candidates, and all were in good medical condition prior to surgery. These criteria may have selected patients with impaired ventricular function that was not as severe as those patients with end-stage CHF reported by Cohn[1] where elevated catecholamine levels were present. Also, by excluding patients receiving intraaortic balloon counterpulsation, intravenous nitroglycerin, or intravenous inotropic support, subjects with overt cardiac failure and with potentially very elevated catecholamines were not studied. Finally, even the most elevated plasma catecholamine values in patients with ventricular failure reported by Cohn[1] were only four to five times normal. Hence, we speculate that plasma catecholamine values in patients with impaired ventricular function may not be increased enough for sufficient time to be associated with clinically evident changes in α_1-adrenergic responsiveness.

Phenylephrine Pressor Dose 20 Values and Anesthesia

Fentanyl anesthesia was associated with a significant difference in PD_{20} in patients with impaired left ventricular function compared to those with normal ventricular function. Essentially, PD_{20} values in group I (LVEF $\leq$ 40) remained similar to pre-anesthesia values, while PD_{20} values in group II (LVEF > 40) decreased significantly during anesthesia compared to pre-anesthesia values. There were no significant hemodynamic or plasma catecholamine changes between time periods pre-anesthesia and anesthesia, or between groups during anesthesia. Since PD_{20} values were higher in patients with impaired ventricular function, decreased α_1-adrenergic responsiveness may have been revealed with anesthesia in this group.

Substantial differences in PD_{20} values also occur during fentanyl anesthesia in patients with CHF compared to patients without CHF. In brief, PD_{20} values in patients with CHF remained similar to pre-anesthesia values, while PD_{20} values in patients without CHF decreased significantly during anesthesia compared with pre-anesthesia. This provides further evidence that α_1-adrenergic responsiveness in patients with impaired ventricular function differs from patients with normal ventricular function during fentanyl anesthesia.

Why is this difference in PD_{20} values between groups only seen during anesthesia? First, it is possible that phenylephrine pharmacokinetics may be altered in patients with LVEF $\leq$ 40% (possibly secondary to differing volumes of distribution between the two groups) during fentanyl anesthesia. This seems unlikely, however, since such a difference should also be seen during pre-anesthesia. Second, clinical variables that may alter α-adrenergic function, such as pain perception, movement, and anxiety, are almost completely eliminated by anesthesia. High-dose fentanyl anesthesia has been shown to prevent increases in plasma catecholamines and blood pressure from potent stimuli, such as intubation and surgery.[49] In fact, although it did not reach statistical significance, there was a trend toward decreased catecholamine levels in patients with LVEF $\leq$ 40% (table 3) during fentanyl anesthesia. Hence, during fentanyl anesthesia, changes in blood pressure or sys-

temic vascular resistance may more accurately reflect α_1-receptor pressor responsiveness to phenylephrine, allowing subtle changes in receptor function, such as hyporesponsiveness, to be revealed.

Decreases in α_1-adrenergic pressor responsiveness may be a beneficial adaptive mechanism in patients with impaired left ventricular function. Decreased responsiveness to endogenous or exogenous vascular α_1-adrenergic agonists may decrease systemic vascular resistance and facilitate forward flow of blood from the impaired left ventricle. However, in the myocardium itself, there is evidence[50-53] that α_1-adrenergic receptors mediate inotropy in rat, cat, and bovine species. This has not been categorically documented in humans,[54] however. Bristow[4,5] has demonstrated a decrease in human myocardial β_1-adrenergic receptors with no change in β_2-adrenergic receptor number in severe heart failure. He has also recently demonstrated[8] that myocardial α_1-adrenergic receptor number stays constant in end-stage ventricles from heart transplant patients. Hence, we can speculate that, while vascular α_1-adrenergic hyporesponsiveness may be beneficial in heart failure, myocardial α_1-adrenergic hyporesponsiveness may be maladaptive in that it may render the patient less sensitive to inotropic support.

Phenylephrine Pressor Dose 20 Values and Anesthesia + Cardiopulmonary Bypass/Aortic Cross-clamp

Highly significant reductions in PD_{20} values were observed during anes + CPB/AXC in both groups. This confirms previous work by Massagee[27] in which 50% less phenylephrine was required to increase SVR during hypothermic cardiopulmonary bypass and aortic cross-clamp compared to awake patients. No significant differences were seen between groups during anes + CPB/AXC. Although MAP was lower during anes + CPB/AXC than pre-anesthesia (table 2), analysis of $PD_{15\ mmHg}$ (table 4) confirms that significant decreases in PD_{20} seen during anes + CPB/AXC are due to more than decreased MAP.

Several important events occur during anes + CPB/AXC that may contribute to lower PD_{20} values and the absence of intergroup differences in PD_{20} that were seen with anesthesia alone. These events include hemodilution, hypothermia, increased plasma catecholamines, addition of the cardiopulmonary bypass circuit volume to intravascular volume, exclusion of the pulmonary circulation, and, possibly, altered phenylephrine or fentanyl pharmacokinetics. Hemodilution has been shown to reduce pressor responsiveness to norepinephrine, but not to phenylephrine in rats.** Hemodilution may partially account for the reduction in PD_{20} seen in our patients. Another important event during CPB is cooling. The alpha-adrenergic effects of hypothermia have been extensively studied in canine saphenous and femoral veins, but not in arteries. Venous vasoconstriction induced by α_1-adrenergic activity is reduced, and that induced by α_2-adrenergic activity is augmented by cooling.[55-57] Hypothermia may also affect arterial vasoconstriction, and may account for decreased PD_{20} during anes + CPB/AXC in this study. Catecholamine release is also impaired in canine saphenous veins with cooling.[58] While catecholamine release is inhibited by cooling in the venous system, circulating plasma catecholamine levels are known to rise overall during CPB.[49] There was a trend toward increased plasma catecholamine levels in all patients during anes + CPB/AXC in our study, but this trend did not reach statistical significance. Of note, plasma catecholamine levels in this study were drawn within 10 min of aortic cross-clamp—relatively early in the bypass period. It has been shown that plasma catecholamine levels continue to rise throughout CPB.[59] Hence, anes + CPB/AXC may occur early enough in CPB to account for a trend of increased catecholamines without a high enough rise to reach significance. During CPB, the volume of the cardiopulmonary bypass circuit is added to the intravascular volume of the patient. This may lead to dilution of medications given intravenously, suggesting more phenylephrine might be required to have the same effect. Our data supports that of Massage[27] in that less phenylephrine is required during anes + CPB/AXC than during a pre-anesthesia or fentanyl anesthesia alone. This suggests that increases in intravascular volume due to the addition of the cardiopulmonary bypass circuit may be offset by other changes in volume of distribution of drugs during hypothermic cardiopulmonary bypass. During CPB, the pulmonary circulation is excluded, potentially changing the volume of distribution of many drugs changes[60] and altering secretion of hormones from this vascular bed. Finally, phenylephrine pharmacokinetics have not been studied during CPB; changes in phenylephrine or fentanyl pharmacokinetics may also contribute to lower PD_{20} values. In essence, any or all of these factors may overwhelm the effect seen between groups during anesthesia alone. Further research is needed to establish which of these events led to the significant reduction in PD_{20}

** Estafanous FB, Sheng Z, Pedrinelli R, Azmy S, Tarizi RC: Hemodilution effects to pressor response to norepinephrine. J Cardiothorac Anesth 1:36-41, 1987.

seen during anes + CPB/AXC in all patients during this study; it is also important to determine if this reduction continues to be present throughout CPB.

Why was less phenylephrine required to increase MAP 20% during anes + CPB/AXC when, during many clinical situations, large amounts of phenylephrine are required to maintain MAP during CPB? In this study, α_1-adrenergic responsiveness was only evaluated during the specific time period of aortic cross-clamp, with stable hypothermic conditions. Changes in temperature, blood viscosity, or catecholamine levels may alter α_1-adrenergic responsiveness during other periods of cardiopulmonary bypass. The effect of cardiopulmonary bypass on α_1-adrenergic function is, thus, a fertile area for continued research.

Overall Patient Safety

Our results suggest that α_1-adrenergic responsiveness can be safely studied using a bolus technique to generate phenylephrine dose response curves in fully monitored cardiac surgery patients. The administration of α-agonists to patients with coronary artery disease may be contraindicated, since α-adrenergic agonism has been implicated in coronary artery vasoconstriction and spasm.[61-63] However, a recent study[64] suggests that infusions of norepinephrine do not cause coronary vasoconstriction until infusion times exceed 10 min. Since the peak blood pressure effect of phenylephrine lasts only seconds using our bolus technique, coronary vasoconstriction should, theoretically, be clinically unimportant. Another recent study[65] suggests that α_1-adrenergic agonists may have an "anti-steal" effect in coronary arteries in the presence of fixed stenoses. There was an absence of angina, ST segment changes, and perioperative myocardial infarction in any of our patients.

In conclusion, these data suggest that α_1-adrenergic responsiveness in awake patients with coronary artery disease is not affected by preoperative ejection fraction. Fentanyl anesthesia is associated with decreased α_1-adrenergic responsiveness in patients with impaired ventricular function compared to patients with normal ventricular function. Finally, these results confirm[27] that less phenylephrine is required during cardiopulmonary bypass and aortic cross-clamp than during the awake state to produce the same pressor effect.

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