

Effect of Phenylephrine Bolus Administration on Global Left Ventricular Function in Patients with Coronary Artery Disease and Patients with Valvular Aortic Stenosis

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Background: Although phenylephrine bolus administration is frequently used to increase coronary perfusion pressure in patients with coronary artery disease or valvular aortic stenosis, there are no data describing its effect on left ventricular function (LVF).

Methods: Twenty patients scheduled for elective coronary artery bypass grafting (group 1) and 18 patients scheduled for elective aortic valve replacement (group 2) entered the study. The effect of phenylephrine was compared with that of norepinephrine in those patients who developed a defined degree of arterial hypotension under general anesthesia. These patients were randomized to receive an initial bolus of either phenylephrine (1 µg/kg) or norepinephrine (0.05 µg/kg) followed by a bolus of the other drug after arterial pressure and heart rate (HR) had returned to baseline. Transesophageal echocardiography was used to evaluate LVF. Arterial pressure, HR, ejection time, and LV diameter, area, and wall thickness were recorded immediately before and for 3 min after bolus administration. Fractional diameter shortening, fractional area change, mean heart rate corrected velocity of circumferential fiber shortening (mVcf_c), and LV meridional end-systolic wall stress (ESWS) were calculated.

Results: Both substances effectively restored arterial pressure in both groups. However, in group 1, phenylephrine administration resulted in a reduction of fractional area change from 0.51 (median) to 0.39 ($P = 0.0007$) and a reduction of mVcf_c from 1.16 to 0.61 circ/s ($P = 0.0001$). End-systolic wall stress increased from 98 to 186 10^3 dyne · cm⁻² ($P = 0.0001$). Administration of norepinephrine to group 1 and administration of

either substance to the group 2 patients did not cause any significant changes of LVF.

Conclusions: The results indicate that phenylephrine given as an intravenous bolus to patients with CAD anesthetized with fentanyl causes a transient impairment of LV global function and that phenylephrine bolus administration is well tolerated in patients with valvular aortic stenosis. (Key words: Anesthesia: cardiac. Heart: coronary artery disease. Monitoring: transesophageal echocardiography. Surgery: coronary artery bypass graft. Sympathetic nervous system: alpha adrenergic agonists.)

PHENYLEPHRINE, an α_1 -adrenergic agonist, is frequently administered as an intravenous bolus to increase arterial pressure during general and regional anesthesia.^{1,2} It is believed to be particularly useful in patients with coronary artery disease (CAD) and in patients with valvular aortic stenosis. In both groups of patients, phenylephrine is preferred over other sympathomimetics because it increases coronary perfusion pressure without chronotropic side effects.^{3,4} Despite its widespread use, there is no information available regarding the influence of phenylephrine bolus administration on left ventricular function in these patients. In particular, the time course of its influence on left ventricular pre- and afterload has not been described.

The aim of the current study was to continuously assess left ventricular function after phenylephrine bolus injection. Transesophageal echocardiography was preferred to other monitoring techniques because it allows evaluation of left ventricular function on a beat-to-beat basis. We assumed it to accurately reflect rapid changes of left ventricular function that could be expected after vasopressor bolus injection. We studied patients with severe coronary artery disease and normal left ventricular global function and patients with valvular aortic stenosis. Only those patients who developed a defined degree of arterial hypotension during general anesthesia were studied. In both groups, we

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compared the effects of phenylephrine with that of norepinephrine, which we hypothesized to be different from that of phenylephrine because of its β -agonist properties.¹

Materials and Methods

Study Population

After approval by the Ethics Committee of our institution and written informed consent, 20 patients scheduled for elective coronary artery bypass grafting (group 1) and 18 patients scheduled for elective aortic valve replacement (group 2) were enrolled in the study.

Exclusion criteria for group 1 were the absence of sinus rhythm, unstable angina pectoris, recent myocardial infarction (<3 months), impaired global left ventricular function (cardiac index < 2.1 L · min⁻¹ · m⁻² or left ventricular end-diastolic pressure > 15 mmHg), and any contraindication to transesophageal echocardiography, such as gastric or esophageal pathology. Of the 20 patients in group 1, six were excluded during the course of the study. Four of the patients were normo- or hypertensive after induction of anesthesia and, thus, did not meet the criterion for vasopressor administration. One of the patients developed atrial fibrillation after induction of general anesthesia and before administration of the vasopressor. One patient was excluded because it was not possible to obtain a cross-sectional left ventricular M-mode registration at maximal left ventricular diameter without including a hypokinetic wall region.

Exclusion criteria for the group 2 patients were the absence of sinus rhythm, the presence of significant coronary stenosis (as assessed from preoperative coronary arteriography), the presence of any significant valvular lesion other than valvular aortic stenosis, and

any contraindication against transesophageal echocardiography. Only those subjects whose left ventricular function was compensated at the time of surgery (NYHA functional class III or better) were included. Of the 18 group 2 subjects, eight were excluded during the course of the study. Six patients did not meet the criterion for vasopressor administration. One patient needed vasopressor support immediately after induction of anesthesia and before the echocardiographic probe had been inserted. In another patient, it was not possible to define the pericardial outline on the echocardiographic recordings and, as a result, left ventricular wall thickness could not be measured. In all, 14 group 1 and 10 group 2 patients were evaluated. The demographic data of both groups, as well as the hemodynamic characteristics obtained during preoperative cardiac catheterization, are presented in table 1.

Protocol

All patients received 2 mg flunitrazepam orally the night before surgery and 1–3 h before induction of anesthesia. Any antihypertensive, antiarrhythmic, or antianginal medication was maintained with the last dose given in the morning before surgery. Anesthesia was induced with 0.01 mg/kg flunitrazepam and 10 μ g/kg fentanyl. Muscle paralysis was obtained with 0.1 mg/kg pancuronium. The trachea was intubated and ventilation controlled artificially with intermittent positive pressure ventilation and inspired N₂O of 50% in oxygen. Minute volume was adjusted to produce normocapnea (PETCO₂ 4.6–6.0 kPa) (Capnometer: Hewlett-Packard® Germany, Böblingen, Germany). Additional doses of flunitrazepam and fentanyl were given when the patients reacted to laryngoscopy with an increase of heart rate or mean arterial pressure by more than 20% of the preinduction values.

Of the 24 patients studied, arterial blood pressure was monitored in 19 *via* a femoral artery catheter;

Table 1. Demographic Data and Hemodynamic Characteristics Obtained during Preoperative Cardiac Catheterization in the Two Groups

	M/F (n/n)	Age (yr)	Weight (kg)	Height (cm)	BSA (m ²)	LVEDP (mmHg)	MPAP (mmHg)	CI (L · min ⁻¹ · m ²)	Δ P (mmHg)
Group 1 (CAD)	12/2	61 (49–69)	75 (63–84)	172 (160–176)	1.86 (1.67–1.97)	9.5 (5–15)	14 (9–29)	3.15 (2.2–3.8)	—
Group 2 (AS)	5/5	62 (52–78)	69 (50–85)	165 (154–175)	1.75 (1.53–2.00)	14.5 (7–34)	21 (13–39)	2.74 (2.1–4.2)	95 (30–123)

Data are median values (with range in parentheses).

BSA = body surface area; LVEDP = left ventricular end-diastolic pressure; MPAP = mean pulmonary artery pressure; CI = cardiac index; Δ P = mean pressure gradient over the aortic valve.

however, in five patients, a radial artery catheter was preferred because of a known occlusive disease of the femoral arteries. A triple-lumen central venous catheter was inserted, as well as a pulmonary artery catheter. A standard seven-lead ECG was monitored. The expiratory CO₂ curve was displayed for documentation of the respiratory phase.

During the induction period and before beginning measurements, the patients received 10 ml/kg of lactated Ringer's solution. The protocol proceeded only when the patients met the criterion for vasopressor administration. This criterion was a mean arterial pressure that was more than 10% less than the lowest reading recorded by the nurses on the surgical ward during the 24 h preceding the operation. Phenylephrine (1 µg/kg) or norepinephrine (0.05 µg/kg) was then injected *via* a central venous catheter in random order, the second substance being administered when arterial pressure and heart rate had returned to baseline levels. Recording of hemodynamic parameters started immediately before injection and was continued for 3 min after administration.

Hemodynamic Measurements and Calculations

After induction of general anesthesia, the transesophageal probe (3400R Varian,[®] 3.5 MHz transducer; DIASONICS[®], Milpitas, CA) was advanced to a position where left ventricular cross-sectional images at mid-papillary muscle level could be obtained.⁵ Two-dimensional and M-mode recordings were displayed, as well as arterial pressure, ECG lead II, and capnographic curve. Care was taken that M-mode recordings were obtained in the maximal left ventricular diameter and did not include wall motion abnormalities. All data were recorded simultaneously on videotape. Evaluation of these data took place off-line on an electronic device (Cardio 200[®]; KONTRON Instruments[®], GmbH., FRG).

The following dimensions were measured from the echocardiographic recordings immediately before and 30, 60, 120, and 180 s after administration of the vasopressor: left ventricular (LV) end-systolic and end-diastolic diameter (ESD, EDD), end-systolic and end-diastolic cross-sectional area (ESA, EDA), and end-systolic and end-diastolic wall thickness (ESWT, EDWT). Left ventricular ejection time (LVET) could not be determined from arterial pressure or carotid pulse curve tracing because some of the group 2 patients did not show a dicrotic notch in their pulse curve because of a minimal incompetence of the aortic valve. Hence, left ventricular ejection time was defined as time from

the peak of the R-wave to the minimal left ventricular dimension. The following parameters were calculated:

Fractional diameter shortening:⁶

$$\text{FDS} = \frac{(\text{EDD} - \text{ESD})}{\text{EDD}} \quad (1)$$

Fractional area change:⁷

$$\text{FAC} = \frac{(\text{EDA} - \text{ESA})}{\text{EDA}} \quad (2)$$

End-systolic meridional wall stress:⁸

$$\text{ESWS} = \frac{1.332 \times \text{SAP} \times \text{ESD}}{4 \times \text{ESWT} \times \left(1 + \frac{\text{ESWT}}{\text{ESD}}\right)} \times [10^3 \times \text{dyne} \times \text{cm}^{-2}] \quad (3)$$

According to the methods of Reichek *et al.*, we included (peak) systolic arterial pressure (SAP) in our calculation of end-systolic wall stress, which has been shown to correlate well with invasively measured wall stress in a variety of clinical conditions.⁸ Because left ventricular pressure cannot be assessed by measuring peripheral artery pressure in subjects with aortic stenosis, wall stress could not be obtained in group 2 patients.

To assess left ventricular systolic performance, we calculated mean velocity of circumferential fiber shortening:⁹

$$\text{mVcf} = \frac{\text{FDS}}{\text{LVET}} \left[\frac{\text{circ}}{\text{s}} \right] \quad (4)$$

Left ventricular ejection time was rate corrected to the heart rate of 60 by division through the square root of the RR-interval (RR).¹⁰ Accordingly, rate-corrected mean velocity of fiber shortening (mVcf_c) was calculated as:

$$\text{mVcf}_c = \text{mVcf} \times \sqrt{\text{RR} - \text{interval}} \left[\frac{\text{circ}}{\text{s}} \right] \quad (5)$$

The evaluation of the echocardiographic recordings was performed off line by two independent investigators who were blinded to the group and to the treatment. Interobserver variability, which had been assessed before the beginning of the study, showed correlation coefficients of $r = 0.996$ (EDD), $r = 0.992$ (ESD), $r = 0.932$ (EDWT), $r = 0.910$ (ESWT), $r = 0.887$ (EDA), and $r = 0.873$ (ESA). The mean difference \pm SD between the two readers was $1.5 \pm 1.2\%$, $1.9 \pm 1.8\%$, $4.1 \pm 3.3\%$, $4.6 \pm 5.1\%$, $5.6 \pm 4.7\%$, and

Table 2. Hemodynamic Data

	Phenylephrine					Norepinephrine				
	0	30 s	60 s	120 s	180 s	0	30 s	60 s	120 s	180 s
MAP (mmHg)										
CAD	71 (65-76)	93 (86-101)	94 (88-100)	87 (78-97)	80 (75-85) ^{††}	73 (67-80)	97 (86-107)	93 (83-103)	84 (74-95)	77 (68-85) ^{††}
AS	69 (60-79)	98 (86-111)	99 (85-114)	96 (83-109)*	82 (69-94) ^{††}	71 (61-80)	92 (79-105)	91 (81-100)	82 (74-91)	73 (64-83) ^{††}
HR (min)										
CAD	55 (49-61)	51 (46-56)	50 (45-54)	50 (45-55)	51 (46-56) ^{††}	54 (49-59)	51 (46-57)	51 (46-56)	52 (46-57)	53 (47-60) ^{††}
AS	58 (54-63)	55 (51-59)	53 (50-58)	53 (49-57)	53 (49-57) ^{††}	55 (49-60)	53 (47-59)	53 (48-58)	53 (47-59)	53 (48-59)
LVEDD (cm)										
CAD	4.9 (4.5-5.3)	4.8 (4.3-5.3)	4.9 (4.5-5.3)	5.1 (4.6-5.6)	5.0 (4.5-5.4)	4.9 (4.4-5.3)	5.1 (4.6-5.5)	5.1 (4.6-5.5)	5.0 (4.6-5.5)	5.2 (4.6-5.7)
AS	4.5 (3.8-5.1)	4.7 (4.2-5.2)	4.6 (4.2-5.0)	4.7 (4.2-5.3)	4.7 (4.2-5.2)	4.6 (4.0-5.1)	4.7 (4.2-5.2)	4.5 (4.0-5.1)	4.6 (4.0-5.3)	4.6 (4.0-5.2)
LVEDS (cm)										
CAD	3.2 (2.9-3.6)	3.8 (3.4-4.2)*	3.8 (3.4-4.2)*	3.7 (3.4-4.1)	3.7 (3.3-4.1) ^{††}	3.1 (2.8-3.4)	3.3 (2.9-3.7)	3.3 (2.9-3.6)	3.3 (3.0-3.7)	3.4 (3.1-3.7)
AS	3.2 (2.7-3.6)	3.2 (2.8-3.7)	3.3 (2.8-3.7)	3.3 (2.9-3.7)	3.3 (2.9-3.8)	3.2 (2.8-3.7)	3.3 (2.9-3.7)	3.2 (2.7-3.7)	3.3 (2.8-3.8)	3.2 (2.8-3.6)
FDS										
CAD	0.34 (0.29-0.38)	0.21 (0.17-0.25)*	0.22 (0.17-0.28)* [†]	0.26 (0.19-0.33)	0.26 (0.20-0.32) ^{††}	0.36 (0.33-0.39) ^{††}	0.34 (0.28-0.40)	0.35 (0.30-0.40)	0.33 (0.29-0.38)	0.33 (0.29-0.37)
AS	0.28 (0.23-0.33)	0.31 (0.24-0.38)	0.29 (0.23-0.36)	0.30 (0.25-0.35)	0.29 (0.24-0.35)	0.29 (0.23-0.35)	0.31 (0.25-0.37)	0.29 (0.24-0.34)	0.29 (0.24-0.35)	0.30 (0.25-0.35)
LVEDA (cm ²)										
CAD	19.6 (16.7-22.5)	22.7 (20.0-25.3)	22.6 (19.6-25.6)	23.5 (20.7-26.3)	22.1 (18.9-25.3) ^{††**}	20.4 (17.8-23.1)	21.8 (18.9-24.7)	21.8 (18.5-25.1)	21.1 (17.9-24.2)	21.7 (18.7-24.7) ^{††}
AS	16.0 (13.1-18.9)	19.2 (15.2-23.2)	18.7 (15.5-21.9)	18.4 (15.9-22.9) [§]	17.0 (15.0-19.0) ^{††}	17.6 (15.2-20.1)	18.8 (15.4-22.2)	18.7 (14.5-22.9)	17.9 (14.3-21.4)	17.0 (13.6-20.4)
LVEDA (cm ²)										
CAD	9.3 (7.6-11.1)	13.4 (10.9-16.0)* [†]	13.4 (10.9-15.8)* [†]	13.2 (11.1-15.4)* [†]	12.4 (9.6-15.2) ^{††§†}	9.7 (8.1-11.3)	10.5 (8.8-12.2)	9.9 (7.9-11.9)	9.5 (7.7-11.3)	9.9 (8.1-11.6)
AS	7.8 (6.2-9.4)	9.0 (6.7-11.2)	8.9 (7.5-10.2)	9.1 (7.2-11.1)	8.1 (7.2-9.1)	8.7 (6.6-10.7)	9.3 (7.4-11.2)	9.1 (6.8-11.4)	8.6 (6.6-10.5)	8.6 (6.4-10.8)
FAC										
CAD	0.53 (0.50-0.56)	0.42 (0.36-0.48)* [†]	0.42 (0.36-0.47)* [†]	0.44 (0.40-0.48)* [†]	0.45 (0.37-0.53) ^{††}	0.52 (0.49-0.56)	0.52 (0.49-0.56)	0.55 (0.51-0.60)	0.55 (0.51-0.60)	0.55 (0.50-0.59)
AS	0.51 (0.48-0.55)	0.53 (0.49-0.58) [§]	0.52 (0.47-0.57)	0.53 (0.49-0.57)	0.52 (0.48-0.56)	0.51 (0.46-0.57)	0.50 (0.45-0.56)	0.52 (0.47-0.57)	0.52 (0.48-0.56)	0.49 (0.43-0.56)
mV _{ec} (cm/s)										
CAD	1.09 (0.93-1.24) [†]	0.63 (0.52-0.74)* [†]	0.69 (0.53-0.85)*	0.76 (0.56-0.96)	0.77 (0.61-0.93) ^{††}	1.16 (1.05-1.27) ^{††}	1.10 (0.91-1.29)	1.11 (0.95-1.27) ^{††}	1.01 (0.86-1.17)	1.01 (0.84-1.19)
AS	0.82 (0.66-0.97)	0.87 (0.67-1.07)	0.82 (0.62-1.03)	0.87 (0.69-1.06)	0.82 (0.66-0.98)	0.84 (0.67-1.00)	0.90 (0.71-1.09)	0.83 (0.68-0.98)	0.82 (0.64-1.00)	0.89 (0.73-1.05)
ESWS										
(10 ⁸ dyne·cm ⁻³)										
CAD	104 (75-134)	231 (138-324) [§]	208 (151-266)*	179 (131-228)	163 (108-219) ^{††}	93 (70-116)	140 (102-177)	129 (92-166)	140 (100-179)	130 (100-160)

Data are mean values (with 95% confidence interval in parentheses).

MAP = mean arterial pressure; HR = heart rate; LVEDD = left ventricular end-diastolic diameter; LVEDS = left ventricular end-systolic diameter; FDS = fractional diameter shortening; LVEDA = left ventricular end-diastolic area; LVESA = left ventricular end-systolic area; FAC = fractional area change; mV_{ec} = mean velocity of circumferential fiber shortening; ESWS = end-systolic wall stress.* *P* < 0.01 versus norepinephrine.† *P* < 0.05 versus AS.‡ *P* < 0.01 versus AS.§ *P* < 0.05 versus norepinephrine.†† *P* < 0.001, significant change.** *P* < 0.05, significant change.

8.7 ± 5.4% for EDD, ESD, EDWT, ESWT, EDA, and ESA, respectively. Only measurements obtained during exhalation were included. The endocardial and pericardial outlines were identified according to the leading-edge method.¹¹ End-diastole was indicated by the peak of the R-wave. End-systole was defined as the smallest systolic endocardial diameter and area, respectively. Wall thickness was measured at the anterior wall of the left ventricle.

Statistical Analysis

Because some of the hemodynamic parameters were not distributed normally, but showed a right- or left-sided skewed distribution, nonparametric tests were selected for statistical analysis. Statistical evaluation included the Friedman test for analyzing the time course of the hemodynamic parameters after the administration of phenylephrine or norepinephrine. The

Wilcoxon signed-rank test was used to compare the two vasopressors given in each group. This comparison was performed before and 30, 60, 120, and 180 s after administration. The two groups of patients were compared using the Mann-Whitney U test. All hemodynamic values obtained in our protocol are presented as arithmetic means (95% confidence interval). The demographic data, as well as the hemodynamic characteristics of the two groups, are presented as medians (minimum, maximum). A value of $P < 0.05$ indicated statistical significance.

Results

Group 1

Hemodynamic data obtained during the course of our measurements in both groups of patients are presented in table 2 and in figure 1A–C. All group 1 patients

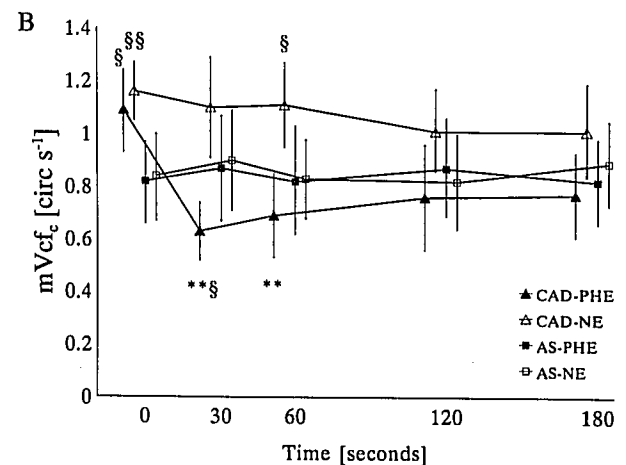
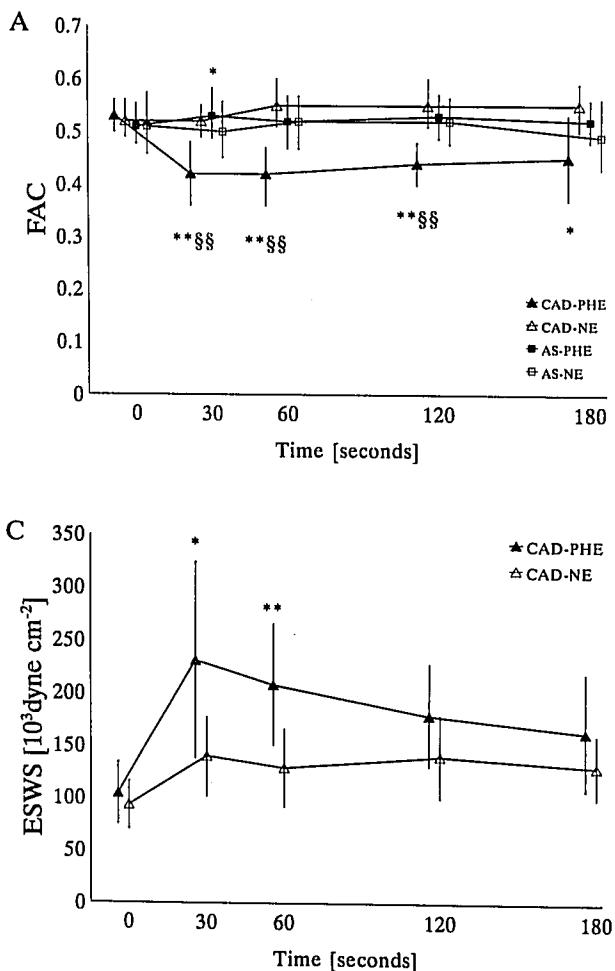


Fig. 1. Fractional area change (FAC) (A), mean heart rate corrected velocity of circumferential fiber shortening (mVcf_c) (B), and left ventricular meridional end-systolic wall stress (ESWS) (C), immediately before (0) and 30, 60, 120, and 180 s after bolus administration of phenylephrine (PHE, filled symbols) or norepinephrine (NE, open symbols). Data on the group 1 patients are symbolized with triangles, and those on the group 2 patients with squares. All data are given as means (95% CI). * and ** indicate $P < 0.05$ and $P < 0.01$, respectively, versus NE; § and §§ indicate $P < 0.05$ and $P < 0.01$, respectively, versus group 2.

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showed significant increases of mean arterial pressure (MAP) that peaked between 20 and 50 s after central venous administration of either vasopressor. In all patients, MAP returned to baseline between 2 and 5 min after injection. There was no difference in the maximal MAP and in the duration of MAP increase following phenylephrine and epinephrine. The heart rate transiently decreased following phenylephrine and norepinephrine ($P = 0.0017$ and $P = 0.0003$, respectively) without significant differences between both agents. The fractional area change was significantly reduced after phenylephrine with a significant difference to norepinephrine 30, 60, 120, and 180 s after administration. This was mainly a result of an increased ESA in response to phenylephrine, whereas norepinephrine caused only insignificant changes. There was a slight increase in EDA after phenylephrine ($P = 0.042$), with no change after norepinephrine; the difference between both vasopressors did not reach the level of significance at any time. There was a significant reduction of $mVcf_c$ in response to phenylephrine ($P = 0.0001$), but not after norepinephrine, the difference between the two being significant 30 and 60 s after injection. End-systolic wall stress was almost doubled in response to phenylephrine ($P = 0.0001$), with no significant change after norepinephrine. There was a significant difference between phenylephrine and norepinephrine 30 and 60 s after administration.

Group 2

In the group 2 patients, both vasopressors similarly increased arterial pressure. However, the effect of phenylephrine appeared to be more sustained compared with norepinephrine, with significant differences of mean arterial pressure 120 and 180 s after administration. There were no significant differences of mean arterial pressure between the two groups of patients with either substance and at any time during our observation period. A significant slowing of the heart rate could be observed in group 2 in response to phenylephrine, equal to that seen in group 1. In contrast, norepinephrine administered to the group 2 patients did not cause any significant changes of heart rate. Fractional area change was not significantly altered after administration of either vasopressor. Thirty, 60, and 120 s after the administration of phenylephrine, there was a significant difference between the groups as a result of a fractional area change reduction in the group 1 subjects. None of the vasopressors caused an alteration of $mVcf_c$ in group 2. Compared with group 1,

however, there was a lower $mVcf_c$ in the group 2 subjects at baseline. This relation was inverted 30 s after administration of phenylephrine as a result of a severely decreased $mVcf_c$ in the group 1 patients ($P < 0.05$). After the administration of norepinephrine, $mVcf_c$ in group 2 remained below the values in group 1 with a significant difference 60 s after injection ($P < 0.05$).

Discussion

Bolus administration of both phenylephrine and norepinephrine effectively restored arterial pressure in patients with coronary artery disease and those with valvular aortic stenosis. However, when phenylephrine was given to the CAD patients, we observed a reduction of fractional area change associated with a severe increase of end-systolic wall stress. This transient impairment of systolic global left-ventricular function was not observed in response to norepinephrine. In the patients with valvular aortic stenosis, neither of the substances appeared to have negative effects on global left ventricular function.

Besides fractional area change, $mVcf_c$ was used to assess LV function. Mean velocity of circumferential fiber shortening was reduced in the CAD patients in response to phenylephrine and was not altered in response to norepinephrine nor, in the aortic stenosis patients, in response to either substance. Because both fractional area change and $mVcf_c$ are known to be dependent on left ventricular afterload,^{10,12} it seems reasonable to assume that the increase of LV wall stress, rather than an altered contractility, caused the impairment of LV function after administration of phenylephrine.

The fact that phenylephrine, but not norepinephrine, administration had negative effects on left ventricular function in the CAD patients is most likely caused by their different affinity to adrenergic receptors. Although both substances predominantly stimulate α -adrenergic receptors, norepinephrine, in contrast to phenylephrine, is known to have relevant β -receptor agonist properties.¹ Phenylephrine given to patients with valvular aortic stenosis did not have any negative influence on ventricular performance, because ventricular afterload in this group of patients is mainly dependent on the pressure gradient across the aortic valve, rather than on the systemic vascular resistance.

There was a cardiac slowing in response to phenylephrine and norepinephrine in the CAD patients that can be assumed to be baroreflex mediated. The decrease of heart rate in the aortic stenosis patients reached the level of significance only after phenylephrine admin-

istration. There is some evidence that baroreceptor reflex function is impaired in subjects with aortic stenosis^{13,14} or heart failure with or without myocardial hypertrophy from another origin.^{15,16} We were not able to confirm this on the basis of our data, because the sensitivity of the baroreflex control of heart rate indicated by the heart rate response to phenylephrine was not different in both groups of patients. A possible explanation could be that general anesthesia, which is well known to have a depressant effect on baroreceptor reflex sensitivity,^{17,18} might have obscured differences between the groups.

At present, there is no report about the effects of vasopressor bolus administration on left ventricular function in patients with myocardial disease. Some information about the hemodynamic consequences of phenylephrine bolus administration have been provided by Schwinn and Reves, who investigated a group of CAD patients using esophageal Doppler technique.¹⁹ They reported changes of MAP, the time course and magnitude of which were similar to our observations. In addition, they found a decrease in cardiac output and an increase in calculated systemic vascular resistance that paralleled the time course of the arterial pressure change.

Our findings are similar to those of Smith *et al.*²⁰ They reported an increase in left ventricular wall stress and a decrease in mVc_f in CAD patients undergoing carotid endarterectomy with general anesthesia who received a phenylephrine infusion to support the arterial pressure intraoperatively. They also found a threefold greater incidence of regional wall motion abnormalities with phenylephrine, compared with a group in which arterial pressure was maintained using a light anesthesia regimen. In our study, we have not attempted to evaluate the echocardiographic data with respect to wall motion abnormalities. No currently used method for describing wall motion abnormalities has ever been validated for conditions in which afterload changes occur "from beat to beat" associated with rapid changes of ventricle size. Therefore, no method seemed applicable to our protocol.

We recognize several limitations of our research. Our findings are, in principle, limited to patients with normal left ventricular global function. We excluded from our study patients with reduced left ventricular function, because we were reluctant to cause acute ventricular decompensation by administering phenylephrine. It is widely believed that α -receptors are not subject to down-regulation in patients with increased

catecholamine plasma concentrations. In contrast, Schwinn *et al.* demonstrated a decreased α_1 -adrenergic responsiveness in patients with CAD and reduced left ventricular function.²¹ As a consequence, it is not possible to conclude from our data the response of subjects with reduced ventricular function to phenylephrine.

We used an intravenous anesthetic technique supplemented by nitrous oxide, and our results do not necessarily apply to other anesthetic techniques. In particular, the use of volatile anesthetics may result in a different hemodynamic response to vasopressor administration.

We studied patients with isolated valvular aortic stenosis. Patients in whom aortic stenosis is accompanied by significant degrees of aortic or mitral incompetence may poorly tolerate increases of afterload.

We administered phenylephrine to patients who were moderately hypotensive after induction of general anesthesia. Patients with severe arterial hypotension may react differently to vasopressor administration, depending on the relation of intravascular volume status, peripheral vascular resistance, and cardiac sympathetic tone.

The alterations of left ventricular function associated with increases of wall stress that we observed in the CAD patients in response to phenylephrine were transient, and it is not known whether they have any influence on clinical outcome. In contrast to sustained increases of wall stress that may lead to myocardial ischemia in CAD patients,²⁰ the effect of a transient increase is not known. It is well documented that such α_1 -agonists as phenylephrine may cause coronary vasoconstriction *via* stimulation of vascular α_1 -adrenergic receptors.^{22,23} Although it is unlikely that therapeutic infusions significantly alter myocardial oxygen supply,^{24,25} the effect of phenylephrine boluses on myocardial oxygen supply/demand ratio is not known.

In conclusion, this study describes the effect of phenylephrine bolus administration on left ventricular function in patients with coronary artery disease and those with valvular aortic stenosis. Phenylephrine, given as intravenous bolus to patients with coronary artery disease, causes a transient increase of left ventricular wall stress associated with an impairment of left ventricular global function. Left ventricular global function remains unaltered after bolus administration of norepinephrine, most likely because of its β -receptor agonistic properties. Administration of either substance to patients with valvular aortic stenosis did not cause any significant change of left ventricular performance.

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