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Influence of Phenylephrine Bolus Administration on Left Ventricular Filling Dynamics in Patients with Coronary Artery Disease and Patients with Valvular Aortic Stenosis

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Background: **Left ventricular diastolic function is known to be impaired in patients with coronary artery disease and patients with valvular aortic stenosis. Phenylephrine is frequently administered as an intravenous bolus in these patients perioperatively to increase coronary perfusion pressure. Although this is common practice, there is no information about the effect of phenylephrine bolus administration on left ventricular filling dynamics.**

Methods: **Twenty patients with coronary artery disease (group 1), 15 patients with valvular aortic stenosis (group 2), and 10 subjects without cardiovascular disease (group 3, control) entered the study. Left ventricular filling was evaluated using transesophageal pulsed Doppler echocardiography before and after phenylephrine injection given to patients whose mean blood pressure has decreased by more than 20% (and was not higher than 90 mmHg). We recorded the transmitral blood flow velocity curve and measured peak early and peak atrial flow velocity, acceleration and deceleration time of the early flow velocity peak, and mitral valve diameter. We calculated the ratio of peak early to peak atrial flow velocity (PE/PA), acceleration and deceleration rate of the early flow peak, and peak filling rate.**

Results: **Phenylephrine effectively restored arterial pressure in all three groups. However, in group 1, phenylephrine administration resulted in a reduction of PE/PA, acceleration rate of the early flow peak, and peak filling rate from 1.25 (mean) to 0.75 ($P < 0.001$), 411 to 276 cm/s^2 ($P < 0.001$), and 439 to 305 ml/s ($P < 0.001$), respectively. In contrast, in group 2, intravenous phenylephrine increased PE/PA, acceleration rate of the early flow peak, and peak filling rate from 0.76 to 0.97 ($P < 0.001$), 365 to 503 cm/s^2 ($P < 0.05$), and 321 to 388 ml/s ($P < 0.01$), respectively. In the control subjects, phenylephrine caused a transient reduction of PE/PA and peak filling rate from 1.71 to 1.39 ($P < 0.001$) and 618 to 524 ml·s^{-1} ($P < 0.001$), respectively.**

Conclusions: **Phenylephrine bolus administration causes an alteration of left ventricular filling in coronary artery disease patients that seems to be more marked than that seen in normal subjects. In patients with aortic stenosis no deleterious effects were observed in response to phenylephrine. (Key words: Anesthesia: cardiac. Heart: left ventricular diastolic function. Monitoring: transesophageal Doppler echocardiography. Surgery: coronary artery bypass graft. Sympathetic nervous system: α-adrenergic agonists.)**

PHENYLEPHRINE, an α_1-adrenergic agonist, is frequently administered as an intravenous bolus to increase arterial pressure during various forms of anesthesia.[1,2] It is believed to be particularly useful in patients with coronary artery disease and in patients with valvular aortic stenosis. In both groups of patients, phenylephrine is preferred over other sympathomimetic agents because it increases coronary perfusion pressure without chronotropic side effects.[3,4] We have recently shown that phenylephrine given as an 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 systolic function, whereas phenylephrine appeared to be well tolerated by the aortic stenosis patients.[5]

It is well known that coronary artery disease as well as myocardial hypertrophy secondary to valvular aortic stenosis may lead to left ventricular diastolic dysfunction.[6–11] Aim of the present investigation was to find out whether phenylephrine bolus administration causes an additional impairment of left ventricular filling and if so, what the time course of this alteration is. Pulsed Doppler echocardiography was used to assess left ventricular filling by measuring the transmitral flow velocity profile.[12,13] Our study population comprised pa-

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Table 1. Demographic Data in All Three Groups and Hemodynamic Characteristics Obtained during Preoperative Cardiac Catheterization in Groups 1 and 2

Group	M/F (n/n)	Age (yr)	Weight (kg)	Height (cm)	BSA (m^2)	Medication (B/N/G/C)	LVEDP (mmHg)	CI ($l \cdot min^{-1} \cdot m^{-2}$)	MPAP (mmHg)	ΔP (mmHg)
1 (CAD)	9/5	61 (50–72)	73 (58–85)	169 (158–188)	1.83 (1.61–2.21)	3/13/2/7	9 (5–14)	3.3 (2.2–4.4)	16 (12–21)	—
2 (AS)	7/4	66 (53–82)	72 (58–92)	169 (154–189)	1.84 (1.57–2.30)	0/3/5/1	14 (8–30)	2.9 (2.0–4.4)	22 (12–35)	87 (50–140)
3 (Control)	8/1	46 (27–59)	77 (66–86)	175 (165–187)	1.88 (1.75–2.11)	0/0/0/0	—	—	—	—

Data are arithmetic mean (minimum, maximum) and absolute numbers (n), respectively.

BSA = body surface area; Medication = preoperative cardiovascular medication (given in number of individuals); B = β-blockers; N = nitrates; G = glycosides; C = calcium antagonists; LVEDP = left ventricular end-diastolic pressure; CI = cardiac index; MPAP = mean pulmonary artery pressure; ΔP = peak pressure gradient over the aortic valve.

tients with coronary artery disease and those with valvular aortic stenosis both with compensated left ventricular function. Only those subjects who developed a defined degree of arterial hypotension during general anesthesia were studied. There is evidence that acute increases in left ventricular afterload may alter the transmitral flow velocity profile in a way similar to that seen in left ventricular diastolic dysfunction.[12,14–16] We therefore included a group of subjects without cardiovascular disease as control group in our protocol.

Materials and Methods

Study Population

After approval by the ethics committee of our institution and written informed consent, 20 patients with coronary artery disease scheduled for elective coronary artery bypass grafting (group 1) and 15 patients with valvular aortic stenosis scheduled for elective valve replacement (group 2) were enrolled in the study. The 10 subjects of the control group (group 3) were ASA physical status 1 and 2 patients without any cardiovascular disease and without contraindication to transesophageal echocardiography scheduled for elective abdominal or orthopedic surgery.

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 $l \cdot min^{-1} \cdot m^{-2}$ or left ventricular end-diastolic pressure > 15 mmHg), and any contraindication to transesophageal echocardiography. Of the 20 patients of group 1, six were excluded during the course of the study. Five of the patients were normo- or hypertensive after induction of anesthesia and, thus, did not meet the criterion for vasopressor administration. In one patient the Doppler sample volume could not be positioned in an acute angle to the transmitral blood flow direction and as a consequence an adequate Doppler flow velocity curve could not be obtained.

Exclusion criteria for the group 2 patients were the absence of sinus rhythm, 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 (New York Heart Association functional class 3 or better) were included. Of the 15 group 2 subjects four were excluded during the course of the study. Two patients did not meet the criterion for vasopressor administration. In another two patients it was not possible to clearly define the margins of the Doppler flow velocity curve because of "noise" artifacts.

One of the 10 control patients was excluded because of a poor quality of the transmitral flow velocity curve. In all, 14 group 1, 11 group 2, and 9 group 3 patients were evaluated. The demographic data in all three groups, as well as the hemodynamic characteristics in groups 1 and 2 obtained during preoperative cardiac catheterization and the preoperative cardiac medication, are presented in table 1.

Protocol

All patients received 1–2 mg flunitrazepam orally the night before surgery and 1–4 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 10 μg/kg flunitrazepam and 10 μg/kg fentanyl. Muscle paralysis was obtained with 0.1 mg/kg pancuronium. The trachea was intubated and ventilation controlled with intermittent positive pressure ventilation and inspired N_2O of 50% in oxygen.

Additional doses of flunitrazepam (up to a total dose of 2 mg) and fentanyl were given when the patients reacted to laryngoscopy with an increase of heart rate or mean arterial pressure.

All patients received a radial artery catheter. A triple-lumen central venous catheter (Deltacath, Becton Dickenson, Sandy, UT) as well as a 7-French pulmonary artery catheter (Baxter Healthcare Corporation, Edwards Critical Care Division, Irvine, CA) was inserted into the right internal jugular vein in all group 1 and 2 patients. None of the group 3 patients received a pulmonary artery catheter. A standard seven lead ECG was monitored throughout the protocol. An Ultramark 9 ultrasound system with a 5 MHz transesophageal transducer (Advanced Technology Laboratory, Inc., Bothell, WA) was used to perform the echocardiographic studies.

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 mean arterial pressure had dropped by at least 20% below the awake baseline value and was not higher than 90 mmHg. Phenylephrine 1 μg/kg was then injected *via* central venous catheter and cubital vein cannula (Group 3), respectively. 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 was advanced to a position behind the left atrium where both mitral leaflets could be outlined.[17] The probe was then angled to visualize the left ventricular cavity with a maximum long axis. The Doppler beam was aligned parallel to presumed mitral inflow and the sample volume was moved to a position between the mitral leaflet tips. The length of the sample volume was 1.5–2 mm and the pulse repetition frequency 5 KHz. Minor adjustments of the transducer position were made to obtain optimal spectral display (highest velocity with least spectral dispersion).

Starting immediately before injection of phenylephrine we continuously measured the following parameters: arterial pressure, heart rate, central venous pressure, pulmonary artery pressure (in groups 1 and 2) and transmitral flow velocity profile. The Doppler signals along with ECG lead II registration were recorded on VHS format videotape (Panasonic Videorecorder, Matsushita Electric Industrial Co., Ltd., Osaka, Japan). The other hemodynamic parameters were recorded by using a strip chart recorder (Siredoc 220, Siemens AG, Erlangen, Germany) at a speed of 25 mm/s. Immediately before injection of phenylephrine (0) and 30, 60, 120, and 180 s after injection thermodilution cardiac output (single cold saline injections) and pulmonary capillary wedge pressure measurements were obtained. At the same points in time the following parameters were calculated by using standard formula[18]: mean arterial pressure, mean pulmonary artery pressure, cardiac index, systemic vascular resistance, pulmonary vascular resistance and left ventricular stroke volume index.

The transmitral flow velocity tracing was analyzed by established methods.[12,13,19–23] In subjects with sinus rhythm the transmitral flow velocity curve is characterized by an initial peak E (maximal early diastolic filling velocity due to rapid passive filling, a subsequent deceleration toward baseline, a period of low velocity diastasis, and a second acceleration–deceleration peak A (maximal atrial filling velocity). We measured peak early and peak atrial velocities. The acceleration and deceleration times were determined as the time interval from the onset of diastolic flow to the early flow peak and the time interval from the early flow peak to the end of the E wave, respectively. From the two-dimensional echocardiogram we measured the diameter of the mitral valve annulus. From these measurements we calculated the ratio of the peak early to the peak atrial velocities (PE/PA),[20] the acceleration rate of the early velocity peak (= peak early velocity/acceleration time),[24] the deceleration rate of the early velocity peak (= peak early velocity/deceleration time),[20] and the peak filling rate (= peak early velocity $\times$ mitral valvular area).[19] The cross-sectional area from the mitral annulus was derived from the annular diameter, assuming a circular geometry such as $\pi(d/2)^2$.

The Doppler tracings were analyzed off-line with an electronic evaluation device (Cardio 200, Kontron Instruments GmbH., Germany) by two independent observers. Quantitative evaluation of the diastolic velocity waveforms were performed 0, 30, 60, 120, and 180 s after phenylephrine injection. For each of these points the waveform with the highest early flow velocity peak was chosen from five consecutive cardiac cycles. The Doppler curves were traced along the outer margins of the gray scale. Inter- and intraobserver reproducibilities in our study were similar to those recently reported for a large group of subjects with sinus rhythm.[22] Interobserver variability in our study showed mean absolute differences (percent precision) of peak early ve-

locity, peak atrial velocity, PE/PA, acceleration of the early velocity peak, and deceleration of the early velocity peak of 3.8%, 4.5%, 6.5%, 6.4% and 7.7%, respectively. Intraobserver variabilities for reader 1 (AWG) and reader 2 (WS) were 3.9% and 5.0%, 4.3% and 3.9%, 3.3% and 5.0%, 7.3% and 8.5%, 6.3% and 5.0% for peak early velocity, peak atrial velocity, PE/PA, acceleration of the early velocity peak, and deceleration of the early velocity peak and the two readers, respectively.

Statistical Analysis

Statistical evaluation of our data was performed using a personal computer based program (StatView IV, Abacus Concepts Inc., Berkeley, CA). Comparisons over time as well as between groups were performed using the two-way analysis of variance for repeated measures. When a significant difference was detected, pairs of means were compared using a *post hoc* Scheffé test. All hemodynamic data obtained in our protocol are presented as arithmetic means (± standard deviation). The demographic data, as well as the hemodynamic characteristics of the two groups are given as arithmetic means (minimum, maximum). A value of $P < 0.05$ indicated statistical significance.

Results

Hemodynamic data obtained during the course of our measurements are presented in table 2 and in figure 1. The patients in all three groups showed a similar blood pressure response to phenylephrine with maximum values reached 30–120 s after injection and with no significant difference in the magnitude of blood pressure increase. There was a slight but significant cardiac slowing in all groups in response to phenylephrine induced pressure increase. The time course of the change of pulmonary artery pressure in the group 1 patients appeared to be similar to that of the arterial pressure. In contrast, in the aortic stenosis patients the increase of mean pulmonary artery pressure was transient and baseline values were reached 180 s after injection. There was a slight but significant increase of pulmonary capillary wedge pressure in both groups whereas central venous pressure remained unchanged throughout the observation period. Systemic vascular resistance strongly increased in both groups, however the effect appeared to be more sustained in the group 1 patients. Similarly the effect of phenylephrine on pulmonary vascular resistance was marked in the coronary artery patients whereas any changes in the group 2 subjects remained insignificant. Cardiac index was not altered in group 2 and was transiently reduced in the group 1 patients ($P < 0.001$). Stroke volume index remained unchanged in either group.

There was an inverse influence of phenylephrine on peak early and peak atrial flow velocity in the group 1 patients with a decrease of peak early and an increase of peak atrial flow velocity that was significant 30, 60, and 120 s after injection. As a result, PE/PA was reduced by 40% in the group 1 patients. This reduction was still significant ($P < 0.001$) at the end of the observation period. The subjects with valvular aortic stenosis obviously showed an impaired left ventricular diastolic function at baseline with an inverse peak early to peak atrial flow velocity relationship. A significant increase of peak early flow velocity compared with baseline ($P < 0.01$) was measured at 120 and 180 s after phenylephrine injection leading to an increase of PE/PA to nearly 1 ($P < 0.001$). Acceleration rate and peak filling rate showed changes similar to the change in PE/PA. At all points of observation deceleration did not change significantly. In the control patients phenylephrine administration resulted in a significant decrease of peak early flow that reached significance 30 and 60 s after injection, whereas peak atrial flow remained unchanged. As a consequence, there was a transient decrease of PE/PA at 30 and 60 s ($P < 0.001$). With a significantly higher baseline value and a maximum decrease in PE/PA of less than 20% of baseline, the values in the control group remained significantly above those in groups 1 and 2 over the whole observation period ($P < 0.001$). Similarly, peak flow rate was transiently reduced by phenylephrine in the control patients ($P < 0.001$) but was higher than that in groups 1 and 2 all the time. Any changes in acceleration rate or deceleration rate in the control subjects remained below the level of significance.

Discussion

Intravenous bolus administration of phenylephrine effectively restored arterial pressure in all three groups of patients. In the patients with coronary artery disease, however, this was associated with an alteration of left ventricular filling as assessed by analyzing the transmitral blood flow velocity waveform. The subjects with valvular aortic stenosis showed an altered left ventricular diastolic function at baseline. The administration

of phenylephrine in this group apparently improved left ventricular filling dynamics. Left ventricular filling in the control patients at baseline was different from that observed in group 1 or group 2 with higher values for peak flow rate and PE/PA. In addition, there was only a transient drop of PE/PA in response to phenylephrine that appeared to be less marked than that observed in the group 1 patients.

In all groups phenylephrine administration caused comparable increases of arterial pressure, and pulmonary artery pressure and systemic vascular resistance were similarly affected in groups 1 and 2. The cardiac slowing that occurred in response to phenylephrine in all groups can be assumed to be baroreflex mediated. The drop of cardiac index and the increase of pulmonary capillary wedge pressure that was observed in the coronary artery patients in response to the sudden increase of left ventricular afterload, are consistent with earlier observations from Schwinn and Reves[25] and from our group.[5] Schwinn and Reves, studying the hemodynamic effects of intravenous phenylephrine bolus injection in patients with coronary artery disease by esophageal Doppler cardiac output measurements, reported changes in systemic vascular resistance and cardiac output[25] similar to those found in the present study. We have compared the cardiac effect of phenylephrine between subjects with valvular aortic stenosis and those with coronary artery disease by esophageal echocardiography.[5] Consistent with the current results we found a decrease of left ventricular area ejection fraction in the coronary artery patients and no indication of an altered left ventricular performance in the aortic stenosis patients.[5]

It is generally accepted that the shape of the transmitral flow velocity curve provides an overall assessment of the left ventricular filling.[13,26-28] However, it is not only altered by myocardial diastolic dysfunction that means by impairment of left ventricular (passive) compliance or (active) relaxation.[29] It also depends on left ventricular loading conditions, heart rate, left ventricular contractility and as most biologic parameters it varies with age.[12,24,30,31] Assuming a constant left ventricular contractility, our data on left ventricular filling have therefore to be interpreted as the result of (1) a change in heart rate, (2) altered left ventricular loading conditions and possibly (3) a change in intrinsic myocardial diastolic properties.

Van Dam *et al.*[30] investigated the influence of heart rate and age on the transmitral flow velocity curve in 215 healthy subjects. They found an increase of PE/PA with lower heart rate. However, this relationship appeared to be age-dependent in a way that it seemed to be relevant in younger individuals whereas in the age group above 50, there was very little influence on the transmitral flow pattern. Although the subjects in the control group were somewhat younger than those in group 1 or 2 it appears unlikely that the minor changes in heart rate that occurred in response to phenylephrine had a major influence on our diastolic function parameters.

There was a slight but significant increase of pulmonary capillary wedge pressure after phenylephrine injection in both groups, which is consistent with an increased left ventricular end-diastolic area reported in our earlier study, both findings indicating an enhancement of left ventricular preload. Stoddard *et al.*[24] studied the influence of alterations in preload on the pattern of the transmitral flow velocity profile in a group of healthy subjects, in patients with coronary artery disease and a group of patients with critical aortic stenosis. Under the condition of an increased preload they found PE/PA unchanged in the normal subjects as well as in the patients with coronary artery disease. In the group of aortic stenosis patients the increase of left ventricular preload, which was associated with an increase in left ventricular filling pressure from 19 to 26 mmHg, resulted in a significant increase in PE/PA. Similarly, Vanoverschelde *et al.*[32] reported PE/PA to be normal in a group of aortic stenosis patients with elevated pulmonary capillary wedge pressure and a highly abnormal left ventricular filling pattern in a group of subjects with aortic stenosis and normal left pulmonary artery wedge pressure. Appleton *et al.*[33] investigated the effect of acute increases of left ventricular preload (ventriculography) on left ventricular filling dynamics in patients with coronary artery disease, idiopathic congestive cardiomyopathy, or restrictive myocardial processes. They reported a normalization of an abnormal transmitral flow pattern in response to ventriculography and speculated that an increase of left atrial pressure might have "masked" a left ventricular relaxation abnormalities. Appleton called this phenomenon "pseudonormalization."[34] As a consequence, the increase of left ventricular preload seen in our patients in response to phenylephrine may have obscured more pronounced alterations of the transmitral flow velocity waveform in the subjects with coronary artery disease. In the group of aortic stenosis patients the phenomenon of "pseudonormalization" may have contributed to the increase in PE/PA that occurred 120 s after phenylephrine injection.

Table 2. Hemodynamic Data

	0 Min	30 Min	60 Min	120 Min	180 Min
HR (beats/min)					
CAD	58 ± 7	56 ± 6*	53 ± 7‡	53 ± 6‡	55 ± 7‡
AS	57 ± 10	56 ± 11	54 ± 10*	54 ± 9†	54 ± 9*
Control	59 ± 13	56 ± 15*	56 ± 13*	56 ± 13*	58 ± 13
SAP (mmHg)					
CAD	94 ± 13	120 ± 17‡	131 ± 17‡	127 ± 21‡	119 ± 18‡
AS	97 ± 13	129 ± 15‡	131 ± 20‡	131 ± 20‡	120 ± 20‡
Control	98 ± 10	118 ± 14‡	121 ± 15‡	115 ± 14†	110 ± 13
DAP (mmHg)					
CAD	54 ± 8	71 ± 10‡	74 ± 9‡	70 ± 10‡	65 ± 9‡
AS	51 ± 8	68 ± 13‡	66 ± 13‡	65 ± 13‡	60 ± 11*
Control	58 ± 9	69 ± 9†	71 ± 9‡	66 ± 8	63 ± 9
MAP (mmHg)					
CAD	67 ± 9	87 ± 12‡	93 ± 12‡	89 ± 13‡	83 ± 11‡
AS	67 ± 10	88 ± 13†	88 ± 14‡	87 ± 15‡	80 ± 13†
Control	71 ± 8	86 ± 10‡	88 ± 10‡	82 ± 9‡	79 ± 9
MPAP (mmHg)					
CAD	13 ± 2	15 ± 3‡	16 ± 3‡	16 ± 2‡	15 ± 2‡
AS	16 ± 3	18 ± 3†	19 ± 3†	18 ± 3*	17 ± 2
CVP (mmHg)					
CAD	6 ± 2	6 ± 2	6 ± 2	6 ± 2	6 ± 2
AS	7 ± 2	7 ± 3	7 ± 3	7 ± 2	7 ± 3
PCWP (mmHg)					
CAD	8 ± 2	10 ± 2†	10 ± 2‡	10 ± 2†	9 ± 2
AS	11 ± 2	12 ± 2*	12 ± 2*	12 ± 2	12 ± 2
PVR ($dyne \cdot s \cdot cm^{-5}$)					
CAD	102 ± 39	131 ± 45	152 ± 53‡	141 ± 49†	145 ± 44†
AS	124 ± 59	161 ± 89	168 ± 64	153 ± 61	148 ± 54
SVR ($dyne \cdot s \cdot cm^{-5}$)					
CAD	1,314 ± 237	1,921 ± 384‡	2,221 ± 460‡	1,966 ± 447‡	1,830 ± 375‡
AS	1,553 ± 283	2,080 ± 449†	2,147 ± 514‡	2,044 ± 628†	1,890 ± 407
CI ($L \cdot min^{-1} \cdot m^2$)					
CAD	2.1 ± 0.3	1.9 ± 0.2	1.8 ± 0.3‡	1.9 ± 0.3	1.9 ± 0.3
AS	1.8 ± 0.4	1.8 ± 0.4	1.7 ± 0.4	1.8 ± 0.4	1.7 ± 0.2
SVI ($ml \cdot beat^{-1} \cdot m^2$)					
CAD	36 ± 5	34 ± 4	34 ± 6	36 ± 5	35 ± 5
AS	31 ± 6	32 ± 6	32 ± 5	34 ± 5	33 ± 5
PE (cm/s)					
CAD	51 ± 11	39 ± 12‡	36 ± 12‡§	40 ± 12‡¶	47 ± 13¶
AS	41 ± 6¶	36 ± 7	38 ± 7	47 ± 11	50 ± 10†
Control	54 ± 7	46 ± 6‡	47 ± 8‡	51 ± 8	54 ± 7
PA (cm/s)					
CAD	41 ± 9	46 ± 10†	47 ± 11‡	47 ± 9‡¶	47 ± 8†¶
AS	55 ± 13**	57 ± 15**	57 ± 15¶	54 ± 13**	52 ± 12**
Control	32 ± 6	34 ± 7	34 ± 7	33 ± 7	32 ± 7
AR_E (cm/s^2)					
CAD	411 ± 118	316 ± 144†	276 ± 135‡§	323 ± 123*§	359 ± 111
AS	365 ± 122	322 ± 97	299 ± 90	426 ± 94	503 ± 178*
Control	483 ± 91	424 ± 68	414 ± 56	442 ± 95	460 ± 73
DR_E (cm/s^2)					
CAD	250 ± 73§	223 ± 83§	202 ± 66§	233 ± 87§	304 ± 127
AS	229 ± 60¶	220 ± 87§	221 ± 98	278 ± 94	255 ± 80
Control	341 ± 68	324 ± 52	302 ± 52	347 ± 52	357 ± 66

(Table continues)

Table 2. Hemodynamic Data *(continued)*

	0 Min	30 Min	60 Min	120 Min	180 Min
PE/PA					
CAD	1.25 ± 0.11**	0.84 ± 0.13‡;**	0.75 ± 0.15‡;**	0.84 ± 0.16‡;**	1.01 ± 0.23‡;**
AS	0.76 ± 0.14**	0.66 ± 0.16**	0.70 ± 0.17**	0.89 ± 0.11*,**	0.97 ± 0.09‡;**
Control	1.71 ± 0.31	1.39 ± 0.25‡	1.39 ± 0.36‡	1.60 ± 0.38	1.73 ± 0.41
PFR (ml/s)					
CAD	439 ± 86**	334 ± 89‡;**	305 ± 89‡;**	341 ± 89‡;**	404 ± 106**
AS	321 ± 79**	284 ± 76**	297 ± 71**	369 ± 79**	388 ± 81†;**
Control	618 ± 85	524 ± 65‡	527 ± 87‡	584 ± 89	616 ± 87

Data are arithmetic means ± SD.

HR = heart rate; CAD = coronary artery disease; AS = valvular aortic stenosis; SAP = systolic arterial pressure; DAP = diastolic arterial pressure; MAP = mean arterial pressure; MPAP = mean pulmonary artery pressure; CVP = central venous pressure; PCWP = pulmonary capillary wedge pressure; PVR = pulmonary vascular resistance; SVR = systemic vascular resistance; CI = cardiac index; SVI = stroke volume index; PE = peak early flow velocity; PA = peak atrial flow velocity; AR_E = acceleration rate of early flow velocity; DR_E = deceleration rate of atrial flow velocity; PE/PA = ratio of peak early to peak atrial flow velocity; PFR = peak filling rate.

* $P < 0.05$ *versus* baseline (0).

† $P < 0.01$ *versus* baseline (0).

‡ $P < 0.001$ *versus* baseline (0).

§ $P < 0.05$ *versus* control.

¶ $P < 0.01$ *versus* control.

** $P < 0.001$ *versus* control.

The predominant hemodynamic effect of phenylephrine is peripheral vasoconstriction and thereby an increase of left ventricular afterload. Several studies have been performed on the influence on acute changes in left ventricular afterload on left ventricular diastolic function in animals,[14,35,36] healthy humans,[15] and cardiac patients.[16] Vandenberg *et al.*[14] studied the effect of a phenylephrine infusion on the transmitral flow velocity pattern dogs of two age groups. Phenylephrine did not alter the transmitral flow velocity pattern in the younger group, whereas in the older animals there was a decrease of the velocity–time integral of the early velocity peak. PE/PA, however, remained unchanged in either group. Colan *et al.*[15] examined the effect of methoxamine infusion on peak rates of left ventricular dimension change and wall thinning as well as their timing in diastole in a group of patients without cardiac disease. They observed a delay of both peak velocities in response to methoxamine without any significant change in their magnitude. In this study there is a significant decrease PE/PA in response to phenylephrine coronary artery disease patients as well as in subjects without cardiac disease. The former, however, started off lower baseline levels and appeared to show a more pronounced and longer lasting depression. Very similar data were reported from Nishimura *et al.*,[16] who examined the effect of a phenylephrine infusion on the mitral inflow profile in ten patients with coronary artery disease. In their study, however, arterial pressure was elevated from normal to hypertensive values, whereas we attempted to normalize a decreased arterial pressure. It is known that patients with coronary artery disease may show an altered left ventricular diastolic function even in the absence of acute myocardial ischemia.[7,8] This may be the main reason for the different mitral flow velocity pattern at baseline in groups 1 and 3. Furthermore, it has been well documented that acute ischemia may alter left ventricular relaxation as well as passive compliance.[37,‖] In principle, we cannot exclude that myocardial ischemia, that could have occurred in response to phenylephrine induced increase of left ventricular wall stress, may have contributed to the alteration of left ventricular filling in the group 1 patients. However, in view of the normal electrocardiogram and considering the duration and magnitude of arterial pressure increase the presence of myocardial ischemia appears unlikely. In patients with severe aortic stenosis left ventricular afterload is mainly determined by the pressure gradient across the aortic valve

‖ Van Wezel HB, Koolen JJ, Visser CA, Schuurhuis A: Ischemia induced systolic and diastolic dysfunction in anesthetized patients undergoing percutaneous transluminal coronary angioplasty (abstract). J Cardiothorac Anesth 3(suppl 1):39, 1989.

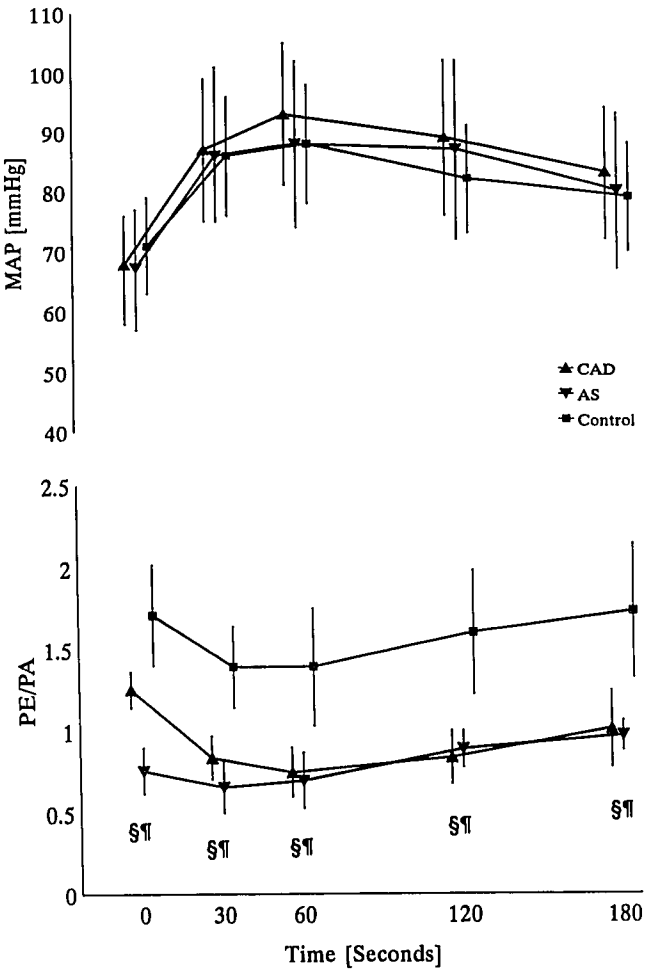

Fig. 1. Mean arterial pressure (MAP) and peak early to peak atrial flow velocity ratio (PE/PA) immediately before (0) and 30, 60, 120, and 180 s after intravenous phenylephrine administration in groups 1 (CAD), 2 (AS) and 3 (control). §Significant difference of CAD, $P < 0.001$ *versus* control. ¶Significant difference of AS, $P < 0.001$ *versus* control.

and to a lesser degree by the arterial pressure. The influence of phenylephrine induced changes in left ventricular afterload may therefore be assumed to be of minor importance in this group of patients.

We recognize some limitations in our methods. 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 left ventricular decompensation by administering phenylephrine. Although congestive heart failure is known to be frequently associated with impairment of left ventricular filling, little is known about the influence of acute changes in left ventricular afterload in this group of patients.[19,38]

We used multiple Doppler echocardiographic indices, because there is no single parameter which sufficiently describes left ventricular filling characteristics.[27,29,39] However the parameters used in this study have been validated against standard techniques and are well established.[12,13,19–21] Despite a major research interest in understanding diastolic function for the past decade, diastole is still not completely understood.[27] In particular, the interrelation of diastolic and systolic events awaits further clarification.[29,39] As a consequence, it is very difficult to interpret our data on systolic left ventricular function in relation to our findings on left ventricular filling. Pulsed Doppler measurements themselves are not flawless.[39] Positioning of the Doppler sample volume can alter the shape of the transmitral flow velocity profile. In addition, there usually is some variation of the various Doppler echocardiographic parameters over one respiratory cycle,[39] which again may be due to changes of the sample volume in relation to the heart or secondary to changes of the transmitral flow itself.

The individuals in the control group were considerably younger than those in groups 1 and 2 (mean age 46 *vs.* 61 and 66 yr, respectively). Although it is recognized that most of the echocardiographic parameters of left ventricular diastolic function are age dependent[14,30,31] there is some indication that this follows an exponential relationship with minor age dependence in the higher-age groups.[30] Bahl *et al.*[40] investigated the influence of age on a number of commonly used Doppler echocardiographic parameters. They found no significant difference for any of the parameters between a "middle-age" (41–50 yr) and a "higher-age" (61–75 yr) group.[40]

In conclusion, this study elucidates the effects of phenylephrine bolus administration on left ventricular filling dynamics in patients with coronary artery disease, with valvular aortic stenosis and without cardiac disease. Phenylephrine given as an intravenous bolus to patients with coronary artery disease caused an alteration of left ventricular filling seen as a reversal of PE/PA. Compared with a group of subjects without cardiovascular disease, the patients with coronary artery disease showed lower baseline values of PE/PA. In addition, the alteration caused by phenylephrine administration appeared to be more pronounced in the coronary artery disease patients. In the patients with and without coronary artery disease the most likely mech-

anism of the alteration of the transmitral flow velocity profile were phenylephrine-induced changes in left ventricular loading, with no indication of changes in myocardial intrinsic diastolic properties. Administration of phenylephrine to subjects with valvular aortic stenosis caused an improvement of left ventricular filling dynamics, which was impaired at baseline, possibly on the basis of an increased left atrial pressure.

References

1. Weiner N: Norepinephine, epinephrine, and sympathomimetic amines, The Pharmacological Basis of Therapeutics. 6th edition. Edited by Goodman LS, Gilman A. New York, Macmillan, 1980, pp 138–175

2. Stoelting RK: Sympathomimetics, Pharmacology and Physiology in Anesthetic Practice. Philadelphia, JB Lippincott, 1987, pp 251–268

3. O'Connor JP, Wynands JE: Anesthesia for myocardial revascularisation, Cardiac Anesthesia. Edited by Kaplan JA. New York, Grune & Stratton, 1987, pp 551–588

4. Jackson JM, Thomas SJ: Valvular heart disease, Cardiac Anesthesia. Edited by Kaplan JA. Grune & Stratton, 1987, pp 589–633

5. Goertz AW, Lindner KH, Seefelder C, Schirmer U, Beyer M, Georgieff M: Effect of phenylephrine bolus administration on global left ventricular function in patients with coronary artery disease and patients with valvular aortic stenosis. ANESTHESIOLOGY 78:834–841, 1993

6. Gibson DG, Prewitt TA, Brown DJ: Analysis of left ventricular wall movement during isovolumic relaxation and its relation to coronary artery disease. Br Heart J 39:1010–1019, 1976

7. Bonow RO, Bacharach SL, Green MV, Kent KM, Lipson DR, Leon MB, Epstein SE: Impaired left ventricular diastolic filling in patients with coronary artery disease: Assessment with radionuclide angiography. Circulation 64:315–323, 1981

8. Kuecherer HF, Ruffmann K, Schaefer E, Kuebler W: Doppler echocardiographic assessment of left ventricular filling dynamics in patients with coronary heart disease and normal systolic function. Eur Heart J 9:649–656, 1988

9. Hanrath P, Mathey DG, Siegert R, Bleifeld W: Left ventricular relaxation and filling pattern in different forms of left ventricular hypertrophy: An echocardiographic study. Am J Cardiol 45:15–23, 1980

10. Fifer MA, Borow KM, Colan SD, Lorell BH: Early diastolic left ventricular function in children and adults with aortic stenosis. J Am Coll Cardiol 5:1147–1154, 1985

11. Murakami T, Hess OM, Gage JE, Grimm J, Krayenbuehl HP: Diastolic filling dynamics in patients with aortic stenosis. Circulation 73:1162–1174, 1986

12. DeMaria AN, Wisenbaugh TW, Smith MD, Harrison MR, Berg MR: Doppler echocardiographic evaluation of diastolic dysfunction. Circulation 84(suppl I):I-288–I-295, 1991

13. Thomas JD, Weyman AE: Echocardiographic doppler evaluation of left ventricular diastolic function: Physics and physiology. Circulation 84:977–990, 1991

14. Vandenberg BF, Kieslo RA, Fox-Eastham K, Tomanek RJ, Kerber RE: Effect of age on diastolic left ventricular filling at rest and during inotropic stimulation and acute systemic hypertension: experimental studies in conscious beagles. Am Heart J 120:73–81, 1990

15. Colan SD, Borow KM, Neumann A: Effects of loading conditions and contractile state (methoxamine and dobutamine) on left ventricular early diastolic function in normal subjects. Am J Cardiol 55: 790–796, 1985

16. Nishimura RA, Abel MD, Housmans PR, Warnes CA, Tajik AJ: Mitral flow velocity curves as a function of different loading conditions: Evaluation by intraoperative transesophageal Doppler echocardiography. J Am Soc Echo 2:79–87, 1989

17. Schlüter M, Hinrichs A, Thier W, Kremer P, Schröder S, Cahalan MK, Hanrath P, Siglow V: Transesophageal two-dimensional echocardiography: Comparison of ultrasonic and anatomic sections. Am J Cardiol 53:1173–1178, 1984

18. Niemer M: Herz und Kreislauf, Datenbuch Intensivmedizin. Edited by Niemer M, Nemes C, Lundsgaard-Hansen P, Blauhut B. Stuttgart, Gustav Fischer Verlag, 1992, pp 366–727

19. Rokey R, Kuo LC, Zoghbi WA, Limacher MC, Quinones MA: Determination of parameters of left ventricular diastolic filling with pulsed doppler echocardiography: Comparison with cineangiography. Circulation 71:543–550, 1985

20. Spirito P, Maron BJ, Bonow RO: Noninvasive assessment of left ventricular diastolic function: Comparative analysis of doppler echocardiographic and radionuclide angiographic techniques. J Am Coll Cardiol 7:518–526, 1986

21. Pearson AC, Goodgold H, Labovitz AJ, Ratcliff J: Comparison of pulsed doppler echocardiography and radionuclide angiography in the assessment of left ventricular filling. Am J Cardiol 61:446–454, 1988

22. Galderisi M, Benjamin EJ, Evens JC, D'Agostino RB, Fuller DL, Lehman B, Wolf PA, Levy D: Intra- and interobserver reproducibility of Doppler-assessed indexes of left ventricular diastolic function in a population-based study (the Framingham Heart Study). Am J Cardiol 70:1341–1346, 1992

23. Spirito P, Maron J, Verter I, Merrill JS: Reproducibility of Doppler echocardiographic measurements of left ventricular diastolic function. Eur Heart J 9:879–886, 1988

24. Stoddard MF, Pearson AC, Kern MJ, Ratcliff J, Mrosek DG, Labovitz AJ: Influence of alterations in preload on the pattern of left ventricular diastolic filling as assessed by Doppler echocardiography in humans. Circulation 79:1226–1236, 1989

25. Schwinn DA, Reves JG: Time course and hemodynamic effects of alpha-1-adrenergic bolus administration in anesthetized patients with myocardial disease. Anesth Analg 68:571–578, 1989

26. Abel MD, Nishimura RA: The intraoperative use of pulsed-wave Doppler echocardiography, Intraoperative Use of Echocardiography. Edited by DeBruijn NP, Clements FM. Philadelphia, JB Lippincott, 1991, pp 183–210

27. Nishimura RA, Housmans PR, Hatle LK, Tajik AJ: Assessment of diastolic function of the heart: Background and current applications of doppler echocardiography: I. Physiologic and pathophysiologic features. Mayo Clin Proc 64:71–81, 1989

28. Nishimura RA, Abel MD, Hatle LK, Tajik AJ: Assessment of diastolic function of the heart: Background and current applications of doppler echocardiography: II. Clinical studies. Mayo Clin Proc 64:181–204, 1989

29. Plotnik GD: Changes in diastolic function: Difficult to measure, harder to interpret. Am Heart J 118:637–641, 1989

30. Van Dam I, Fast J, De Boo T, Hopman J, Van Oort A, Heringa A, Alsters J, Van Der Werf T, Daniels O: Normal diastolic filling patterns of the left ventricle. Eur Heart J 9:165–171, 1988

31. Kuecherer H, Ruffmann K, Kuebler W: Effect of aging on doppler echocardiographic filling parameters in normal subjects and in patients with coronary artery disease. Clin Cardiol 11:303–306, 1988

32. Vanoverschelde JLJ, Essamri B, Michel X, Hanet C, Cosyns JR, Detry JMR, Wijns W: Hemodynamic and volume correlates of left ventricular diastolic relaxation and filling in patients with aortic stenosis. J Am Coll Cardiol 20:831–821, 1992

33. Appleton CP, Hatle LK, Popp RL: Relation of transmitral flow velocity patterns to left ventricular diastolic function: New insights from a combined hemodynamic and Doppler echocardiographic study. J Am Coll Cardiol 12:426–440, 1988

34. Appleton CP: Doppler assessment of left ventricular diastolic function: The refinements continue. J Am Coll Cardiol 21:1697–1700, 1993

35. Ishida Y, Meisner JS, Tsujioka K, Gallo JI, Yoran C, Frater RWM, Yellin EL: Left ventricular filling dynamics: Influence of left ventricular relaxation and left atrial pressure. Circulation 74:187–196, 1986

36. Cheng CP, Freeman GL, Santamore WP, Constantinescu MS, Little WC: Effect of loading conditions, contractile state, and heart rate on early diastolic left ventricular filling in conscious dogs. Circ Res 66:814–823, 1990

37. Bowman LK, Cleman MK, Cabin HS, Zaret BL, Jaffe CC: Dynamics of early and late left ventricular filling determined by doppler two-dimensional echocardiography during percutaneous transluminal coronary angioplasty. Am J Cardiol 61:541–545, 1988

38. David D, Lang RM, Neumann A, Sareli P, Marcus R, Spencer KT, Borow KM: Comparison of doppler indexes of left ventricular diastolic function with simultaneous high fidelity left atrial and ventricular pressures in ideopathic dilated cardiomyopathy. Am J Cardiol 64:1173–1179, 1989

39. Shapiro SM, Bersohn MM, Laks MM: In search of the holy grail: The study of diastolic ventricular function by the use of Doppler echocardiography. J Am Coll Cardiol 17:1517–1519, 1991

40. Bahl VK, Dave TH, Sundaram KR, Shrivastava S: Pulsed Doppler echocardiographic indices of left ventricular diastolic function in normal subjects. Clin Cardiol 15:504–512, 1992