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Length-dependent Regulation of Left Ventricular Function in Coronary Surgery Patients

Stefan G. De Hert, M.D., Thierry C. Gillebert, M.D.,† Pieter W. Ten Broecke, M.D.,‡ Adriaan C. Moulijn, M.D.§*

Background: **Load-dependent impairment of left ventricular (LV) function was observed after leg elevation in a subgroup of coronary surgery patients. The present study investigated underlying mechanisms by comparing hemodynamic effects of an increase in LV systolic pressures with leg elevation to effects of a similar increase in systolic pressures with phenylephrine.**

Methods: **The study was performed in patients undergoing elective coronary surgery prior to cardiopulmonary bypass. High-fidelity LV pressure tracings (n = 25) and conductance LV volume data (n = 10) were obtained consecutively during leg elevation and after phenylephrine administration (5 μg/kg).**

Results: **Leg elevation resulted in a homogeneous increase in end-diastolic volume. The change in stroke volume (SV), stroke work (SW) and dP/dt_{max} was variable, with an increase in some patients but no change or a decrease in other patients. For a matched increase in systolic pressures, phenylephrine increased SW and dP/dt_{max} in all patients with no change in SV. Load dependence of relaxation (slope R of the τ–end-systolic pressure relation) was inversely related for changes in SV, SW, and dP/dt_{max} with leg elevation but not with phenylephrine.**

Conclusions: **The different effects of leg elevation and phenylephrine suggest that the observed decrease in SV, SW, and dP/dt_{max} with leg elevation in some patients could not be attributed to an impaired contractile response to increased systolic LV pressures. Instead, load-dependent impairment of LV function after leg elevation appeared related to a deficient length-dependent regulation of myocardial function. (Key words: Afterload; cardiac surgery; contraction; preload; relaxation; ventricular function.)**

IMPAIRED left ventricular (LV) function may manifest as decreased ability of the heart to respond adequately to additional cardiac load. In the perioperative period, the ability of the heart to deal with additional load can be assessed by analysis of the effects of leg elevation on parameters of systolic and diastolic function. In a previous perioperative study on coronary surgery patients, we demonstrated that a postural change induced by leg elevation identified a subgroup of patients who developed load dependent impairment of LV function. These patients responded to leg elevation with a decrease in stroke volume (SV) and dP/dt_{max}, an enhanced load dependence of LV pressure (LVP) fall and a marked increase in LV end-diastolic pressure (EDP).[1] The underlying cause for the impairment of LV function in response to leg elevation in these patients remained to be investigated. Different possible underlying mechanisms should be considered. Baseline parameters of systolic and diastolic function did not predict the response to leg elevation.[1] Impairment of LV function to leg elevation might result from the inability of the heart to deal with an additional increase in systolic pressure due to exhaustion of normal afterload reserve.[2,3] An alternative hypothesis might be the occurrence of deficient length-dependent activation of myocardial function with exhaustion of preload reserve.[4,5]

The present study investigated these possible mechanisms by comparing hemodynamic effects of leg elevation to effects of a bolus injection of phenylephrine with a dose titrated to match systolic pressures obtained with leg elevation. While leg elevation increased venous return resulting in volume loading, phenylephrine induced a more selective increase in afterload.

Methods

The study was performed on patients scheduled for elective coronary bypass surgery with an ejection fraction of more than 40% and with a LVEDP of less than 15 mmHg on preoperative hemodynamic evaluation. The study was approved by the Institutional Ethical Committee and written informed consent was obtained. Patients

* Associate Professor, Department of Anesthesiology.

† Associate Professor, Department of Cardiology.

‡ Staff Member, Department of Anesthesiology.

§ Professor, Head of the Department of Cardiac Surgery.

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Address reprint requests to Dr. De Hert: Department of Anesthesiology, University Hospital Antwerp, Wilrijkstraat 10, B-2650 Edegem, Belgium. Address for electronic mail: sdehert@uia.ac.be

undergoing repeat coronary surgery, concurrent valve repair, or aneurysm resection were excluded.

Preoperative cardiac medication, including β-blocking agents, calcium channel blocking agents, ACE inhibitors, and nitrates were continued until the morning of surgery. Premedication consisted of intramuscular glycopyrolate 2 μg/kg, droperidol 30 μg/kg and fentanyl 1 μg/kg. In the operating room patients received routine monitoring including 5-lead electrocardiogram, radial and pulmonary artery catheters, pulse oximetry, capnography, and blood and urine bladder temperature monitoring. Anesthesia was induced with fentanyl 20 μg/kg, diazepam 0.1 mg/kg, and pancuronium bromide 0.1 mg/kg. An additional dose of 30 μg/kg fentanyl was administered before sternotomy. Standard median sternotomy and pericardiotomy were performed. The aorta was cannulated and epicardial pacemaker wires were attached to the right atrium and right ventricle. Then the experimental protocol was started.

Experimental Protocol

In 15 patients, a sterilized, prezeroed electronic micromanometer (MTCP3Fc catheter, Dräger Medical Electronics, Best, The Netherlands; frequency response = 100 KHz) was positioned in the LV cavity through the apical dimple. The catheter was connected to a Hewlett Packard monitor (HP78342A, Brussels, Belgium). The output signals of the pressure transducer system were digitally recorded together with the electrocardiographic signals at 1-ms intervals (Codas, DataQ, Akron, OH). Zero and gain setting of the tip manometer were checked against a high-fidelity pressure gauge (Druck Limited, Leicester, United Kingdom) after removal. In 10 additional patients, combined pressure and volume data obtained by the conductance method were included. In these patients a combined micromanometer-transducer-conductance catheter (F6, CardioDynamics, Zoetermeer, The Netherlands) was inserted before the start of surgery *via* the femoral artery into the left ventricle for measurement of LV pressures and volumes. The correct position of the conductance catheter was verified by the inspection of the LVP waveform and the segmental conductance signals. The conductance catheter was connected to a Leycom Sigma-5DF signal conditioner processor (CardioDynamics, Zoetermeer, The Netherlands) to measure LV volumes. The conductance catheter method is based on the measurement of the time-varying electrical conductances of five segments of blood in the left ventricle, which are proportional to the intraventricular volume of each of these segments.[6,7] Blood resistivity was measured before each set of recordings by injecting 5 ml of blood in a special cuvette, connected to the signal conditioner processor. Blood resistivity was automatically assessed. Measurement of the total electrical conductance, is not confined to the blood inside the left ventricle but also includes the conductance of the myocardium and the surrounding structures. This parallel conductance (Vc) creates an offset, which has to be subtracted from the total conductance. Parallel conductance was determined by injecting 5 ml hypertonic (8%) saline into the pulmonary artery and acquiring data during the saline injection. Calculation of Vc was performed with the dedicated package CONDUCT-PC (Cardiodynamics, Zoetermeer, The Netherlands). This algorithm indicates the best Vc values. Conductance measurements were included only when sample correlation coefficient reached a value more than 0.95 in all five segments. Conductance catheter SV was calibrated by thermodilution SV volume, determined by thermodilution cardiac output measurement (Vigilance Monitor, model VGS2; Baxter, Irvine, CA). Preliminary experiments indicated that in this phase of the surgical procedure (before cardiopulmonary bypass) variability of measurement of SV with thermodilution was less than 4% with the thermodilution method and less than 6% with the conductance method. The ratio (α) of SV (conductance) on SV (thermodilution) was entered together with the Vc value for the five segments in the software package when analyzing the conductance data for the different runs. The CONDUCT-PC software package was used for acquisition and analysis of conductance catheter data.

The heart was paced for the duration of the protocol at a fixed rate of 90 beats/min in atrioventricular sequential mode with an atrioventricular interval of 150 ms. Measurements were obtained with the ventilation suspended at end-expiration. Measurements consisted of high-speed recordings of digitized electrocardiographic and LVP and volume tracings. These hemodynamic data were recorded during consecutive heartbeats with a progressive increase of systolic and diastolic LVP. Effects of leg elevation were compared with effects of an intravenous bolus administration of low-dose phenylephrine (5 μg/kg). First the caudal part of the surgical table was tilted by 45° resulting in elevation of the legs. After recording the data, the surgical table was returned to horizontal and a stabilization period of 10 min was allowed. Then phenylephrine was administered.

For comparing the two experimental conditions, consecutive heart beats with phenylephrine were selected, with systolic pressures matched with those obtained

with leg elevation. EDP was timed at the peak of the R-wave on ECG. The effects on LV load and function were evaluated by the changes in EDP, peak LVP, LVP at dP/dt_{min} (end-systolic pressure [ESP]), and dP/dt_{max}. Effects on rate of LVP fall were evaluated by the time constant τ of isovolumic relaxation. τ was calculated based on the monoexponential model with nonzero asymptote using LVP values from dP/dt_{min} to a cut-off value of 10 mmHg above EDP.[8,9] The following equation was used: $P(t) = P_0 \cdot e^{-t/\tau} + P_\infty$,[8,10,11] where P_∞ is a nonzero asymptote, P_0 is an amplitude constant, t is time, and τ is the time constant.

It was recently suggested that load dependence of ventricular relaxation would rely on an artifact due to the inadequacy of the monoexponential model for describing pressure decay.[12] Using the logistic model with the formula $P(t) = P_A / (1 + e^{t/\tau}) + P_B$, less load dependence of LV relaxation was observed.[13] In this equation P_B is a nonzero asymptote, P_A is an amplitude constant, t is time, and τ is the time constant. To address this issue, both methods of fitting were used for calculation of τ.

Time constant τ (calculated by both methods) was linearly fit to the corresponding ESP and the slope R (ms/mmHg) of this relation was calculated. R quantified changes in τ induced by the change of ESP during acute load manipulation and described afterload dependence of LVP decrease.[14] This dependence was assessed using both methods of analysis of LVP decay. The reported values of τ in the figures and table represent the monoexponential method of fitting.

End-diastolic volume (EDV), end-systolic volume (ESV), SV, stroke work (SW), and preload-recruitable stroke work (PRSW) were analyzed in 10 patients. Consecutive end-systolic pressure and volume data were fit by linear least squares analysis to the following equation: $P = Ees(V - V0)$, where P is LV pressure, Ees is the slope of the systolic pressure-volume relationship, V is LV systolic volume, and V0 is the volume intercept of the systolic pressure-volume relationship. Sample correlation coefficient of the end-systolic pressure-volume relationship yielded values of $r > 0.94$ in all patients. The effects on afterload were assessed by analysis of end-systolic pressure (ESP) and arterial elastance (Ea). Ea was calculated as the ratio ESP/SV.

Statistical Analysis

A two-way analysis of variance test assessed the effects of leg elevation and phenylephrine administration. Posttest analysis was performed using the Bonferroni-Dunn correction. The interaction analysis evaluated whether the effects of phenylephrine were different from the effects of leg elevation. Relations between hemodynamic parameters were described using linear regression analysis computing Pearson's correlation coefficient. Data were reported as mean ± SD. Statistical significance was accepted at $P < 0.05$.

Table 1. Preoperative and Intraoperative Data

	Value
Preoperative data	
Male/female	18/7
Age (yr)	67 ± 8
Length (cm)	174 ± 9
Weight (kg)	79 ± 10
BSA (m^2)	1.9 ± 0.4
Diabetes	3
Hypertension	15
Previous MI	8
Medication	
Nitrates	14
β-blocking drugs	20
Ca channel blocking drugs	10
ACE inhibitors	10
Intraoperative data	
No. of grafts	4 ± 1
Aortic cross-clamp time (min)	45 ± 12
CPB time (min)	74 ± 16

Data are mean ± SD.

BSA = body surface area; MI = myocardial infarction; ACE = angiotensin-converting enzyme; CPB = cardiopulmonary bypass.

Results

Clinical preoperative and intraoperative data from the patients included are summarized in table 1. Hemodynamic changes with leg elevation or with phenylephrine were not related to any of the reported clinical data. A representative example of the effects of leg elevation and phenylephrine on pressure-volume loops is illustrated in figure 1. It appears that leg elevation and phenylephrine had clearly distinct effects. For a similar increase in systolic pressures, leg elevation increased EDP, EDV, and ESV whereas the effects of phenylephrine on these parameters were more limited.

Pooled hemodynamic data are summarized in table 2. Baseline data before leg elevation and phenylephrine administration were similar. Both interventions increased peak LVP and ESP to the same extent. EDP increased with leg elevation from 8 ± 3 to 13 ± 6 mmHg but did not significantly change with phenylephrine. With leg elevation, an increase in EDV was observed in all patients. This increase was similar in the different

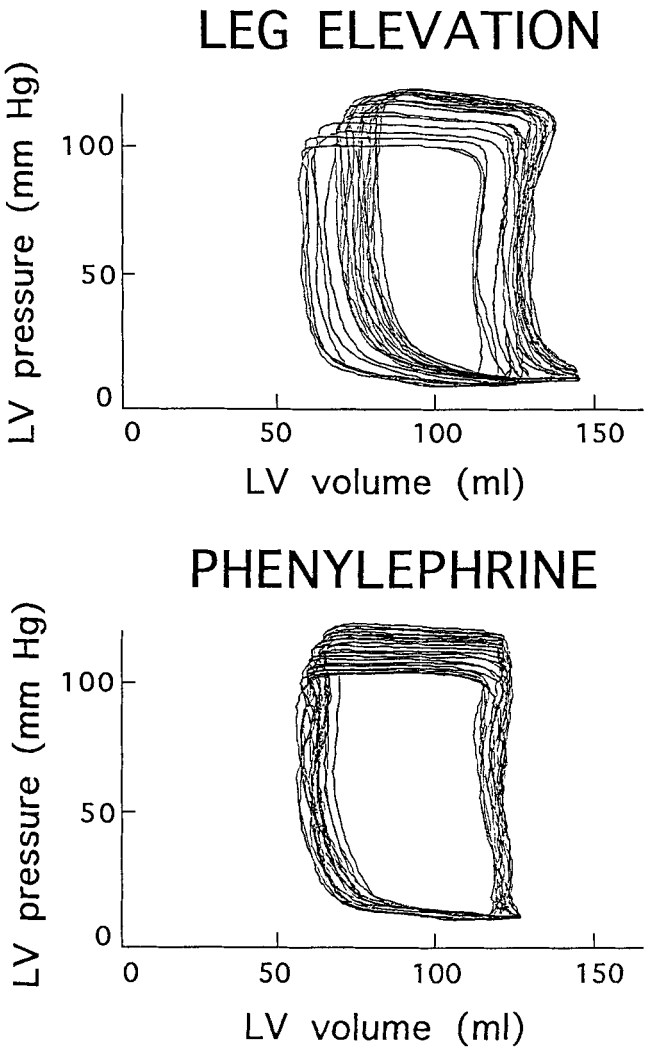

Fig. 1. Representative example of the effects of leg elevation (*upper panel*) and phenylephrine (*lower panel*) in one patient. On each panel, pressure–volume loops of consecutive heart beats are displayed. Increase in systolic pressures was similar with leg elevation and phenylephrine. With leg elevation this increase in systolic pressures was associated with an increase in end-diastolic volume and end-systolic volume, whereas with phenylephrine the changes in ventricular volumes were limited. LV = left ventricular.

patients and corresponded to 9 ± 3% of the baseline EDV. When looking at mean values, ESV increased with leg elevation, whereas SV remained unchanged. With phenylephrine injection, ventricular volumes hardly changed. Accordingly, the slope of the end-systolic pressure–volume relationship was higher with phenylephrine administration than with leg elevation. Ea increased with leg elevation and with phenylephrine. The dP/dt_{max} slightly increased with phenylephrine but not with leg elevation. Time constant τ increased with leg elevation and remained unaltered with phenylephrine.

The response of SV to leg elevation was variable. For a similar increase in EDV, SV and SW increased in four patients, remained unchanged in two patients, and decreased in the remaining four patients (fig. 2, upper and middle panels). A wide variability was also observed in changes of dP/dt_{max} with individual changes ranging from −95 to 150 mm Hg/s (fig. 2, lower panel). After phenylephrine injection, SV remained unchanged, and a homogeneous increase in SW and dP/dt_{max} was observed.

The effects of leg elevation on myocardial relaxation were evaluated by analysis of R. The inset of figure 3 illustrates R. R is the slope of the relation between τ and ESP measured in consecutive beats during pressure increase. A positive value means that τ increases with increased ESP (open squares), whereas a negative value means that τ decreases with increased ESP (filled dots). With leg elevation, there was a wide variability and individual values ranged from −0.347 to 1.53 ms/mmHg. This means that LVP decrease accelerated in some patients but remained unchanged or even slowed in other patients. After phenylephrine administration, individual values ranged from −0.36 to 0.18 ms/mmHg, indicating that with phenylephrine, LVP decrease remained unchanged or even accelerated.

With leg elevation, parameters of contraction and relaxation were coupled. A close relationship was observed between changes in SV and individual R values ($r = 0.85$; $P < 0.001$; fig. 3, upper panel). Accordingly, in the presence of a homogeneous increase in EDV, a close relationship was also observed between changes in ESV and individual R values ($r = 0.79$; $P < 0.001$). Similarly, a close relationship was observed between changes in SW with leg elevation and individual values of R ($r = 0.83$; $P < 0.001$). Changes in SW with leg elevation represent PRSW. PRSW increased in some patients but remained unchanged or even decreased in other patients. The effects of leg elevation on PRSW paralleled the effects on SV and on dP/dt_{max}. A close relationship was found between changes in dP/dt_{max} with leg elevation and individual values of R ($r = 0.88$; $P < 0.001$; fig. 3, lower panel). Patients who developed a decrease in SV (and a major increase in ESV), in PRSW, and in dP/dt_{max} with leg elevation also manifested a marked slowing of LVP decrease, indicating more important load dependence of LVP decrease. This variability among patients was not observed with phenylephrine. Phenylephrine

Table 2. Hemodynamic Effects of Leg Elevation and Phenylephrine

		Baseline	Test	Between Group Difference (*P*)
(n = 25)				
LVP (mmHg)	Leg elevation	95 ± 8	109 ± 8*	
	PE	98 ± 10	111 ± 10*	NS
EDP (mmHg)	Leg elevation	8 ± 3	13 ± 6*	
	PE	9 ± 3	10 ± 3	<0.001
dP/dt_{max} (mmHg/s)	Leg elevation	1,011 ± 105	1,026 ± 126	
	PE	1,021 ± 131	1,090 ± 149*	NS
ESP (mmHg)	Leg elevation	62 ± 6	71 ± 6*	
	PE	63 ± 8	74 ± 8*	NS
Tau (ms)	Leg elevation	62 ± 8	67 ± 7*	
	PE	61 ± 8	59 ± 9	<0.001
R (ms/mmHg)	Leg elevation	0.42 ± 0.47		
	PE	(−)0.17 ± 0.18		<0.001
(n = 10)				
EDV (ml)	Leg elevation	128 ± 11	143 ± 10*	
	PE	126 ± 10	130 ± 12	<0.001
ESV (ml)	Leg elevation	66 ± 11	82 ± 9*	
	PE	64 ± 11	69 ± 7	<0.001
Stroke volume (ml)	Leg elevation	61 ± 10	61 ± 10	
	PE	60 ± 11	62 ± 11	NS
Stroke work (mmHg/ml)	Leg elevation	5,265 ± 433	5,656 ± 523	
	PE	5,305 ± 522	6,140 ± 498	<0.001
Ea (mmHg/ml)	Leg elevation	1.0 ± 0.2	1.2 ± 0.2*	
	PE	1.0 ± 0.2	1.2 ± 0.2*	NS
Ees (ml/mmHg)	Leg elevation	1.6 ± 0.5		
	PE	2.9 ± 0.6		0.009

Data are mean ± SD.

LV = left ventricular; P = pressure; ED = end-diastolic; ES = end-systolic; V = volume; R = afterload dependence of LVP fall; Ea = arterial elastance; Ees = slope of the end-systolic pressure–volume relation; PE = phenylephrine; NS = not significant.

*$P < 0.05$.

resulted in no change in SV, a homogeneous increase in SW and dP/dt_{max} and no load dependence of LVP fall.

With leg elevation, load dependence of LVP fall was coupled with the magnitude of changes in EDP (fig. 4). A close relationship was observed between the individual values of R and changes in EDP with leg elevation ($r = 0.86$; $P < 0.001$). Patients with marked load dependence of LVP decrease (important slowing of LVP decrease with increase in ESP) were also the patients who developed a marked increase in EDP. Conversely, patients with low load dependence of LVP decrease had only a minor increase in EDP. This phenomenon was not observed with phenylephrine ($r = 0.03$; $P = 0.27$). Phenylephrine administration did not alter or slightly accelerated LVP decrease and did not affect EDP.

Identical results were obtained when LVP decay was analyzed using the logistic model of fitting. τ increased with leg elevation from 45 ± 6 to 51 ± 8 ms ($P < 0.001$) but decreased with phenylephrine from 47 ± 5 to 45 ± 6 ms ($P < 0.001$). With leg elevation there was a wide variability in R, and individual values ranged from −0.43 to 1.86 ms/mmHg. After phenylephrine administration, individual values ranged from −0.57 to 0.09 ms/mmHg. A close relationship was found between changes in EDP and individual values of R ($r = 0.89$; $P < 0.001$) with leg elevation but not with phenylephrine ($r = 0.03$; $P = 0.17$).

Discussion

Leg elevation identified a subgroup of patients who developed load-dependent impairment of LV function. These patients responded to the increase in cardiac load with a decrease in SV, SW, and dP/dt_{max}, an enhanced load dependence of LVP decrease, and a marked increase in LVEDP. Leg elevation represents a complex hemodynamic intervention during which systolic and diastolic LV pressures and volumes increase and that affects venous return and LV afterload. It was therefore suggested that impairment of LV function with increased cardiac load might be related to the occurrence of ex-

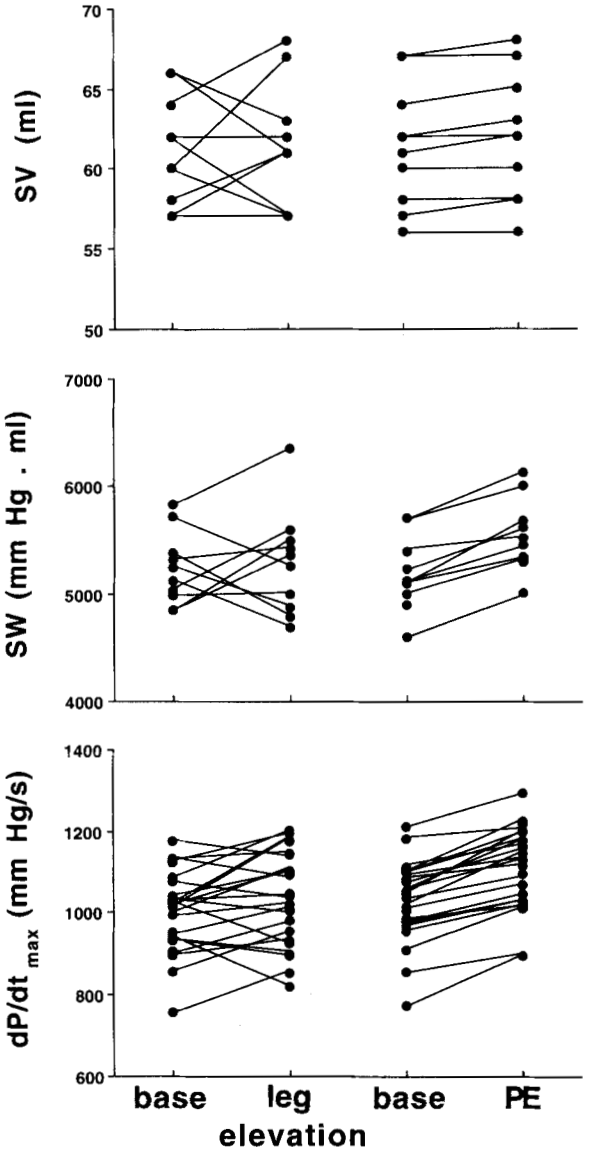

Fig. 2. Effects of leg elevation and phenylephrine (PE) on stroke volume (SV; *upper panel*), stroke work (SW; *middle panel*), and dP/dt_{max} (*lower panel*). For a similar increase in systolic pressure, a different response in SV, SW, and dP/dt_{max} was observed with leg elevation and phenylephrine. With leg elevation, SV, SW, and dP/dt_{max} increased in some patients, remained unchanged in others, whereas in the remaining patients, SV, SW, and dP/dt_{max} decreased. With phenylephrine, a homogeneous response was observed with no change in SV and an increase in SW and dP/dt_{max} in all patients.

cessive afterload (exhaustion of afterload reserve) or to impairment of length-dependent activation in some patients (exhaustion of preload reserve).[1] Afterload reserve refers to the ability of the heart to deal with increases in afterload without impairment of LV function,[2,3] whereas preload reserve refers to the use of length-dependent activation of cardiac function in order to cope with additional load.[4,5] To analyze this issue, this study compared the hemodynamic effects of leg elevation to the effects of a bolus injection of phenylephrine. Leg elevation and phenylephrine had clearly distinct effects on LV

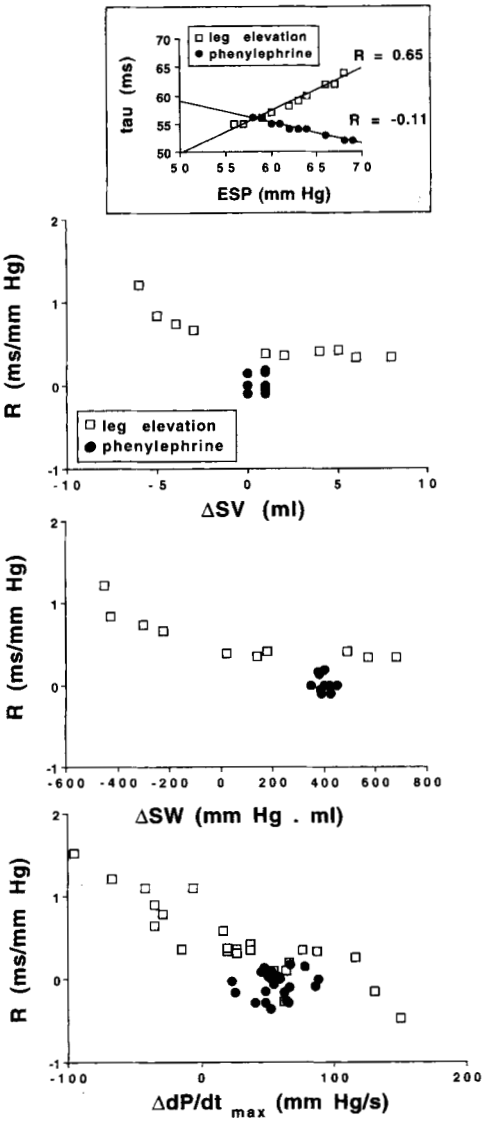

Fig. 3. Plots relating individual values of R to corresponding changes in stroke volume (SV; *A*) and dP/dt_{max} (*B*). The inset illustrates the meaning of R. Time constant τ was linearly fit to the corresponding end-systolic pressure (ESP), and the slope R (ms/mmHg) of this relation was calculated. R quantified changes in τ, induced by the change of ESP and quantified afterload dependence of the rate of LV pressure decrease. A close relationship was observed between individual R values and corresponding changes in SV, SW, and dP/dt_{max} with leg elevation but not with phenylephrine.

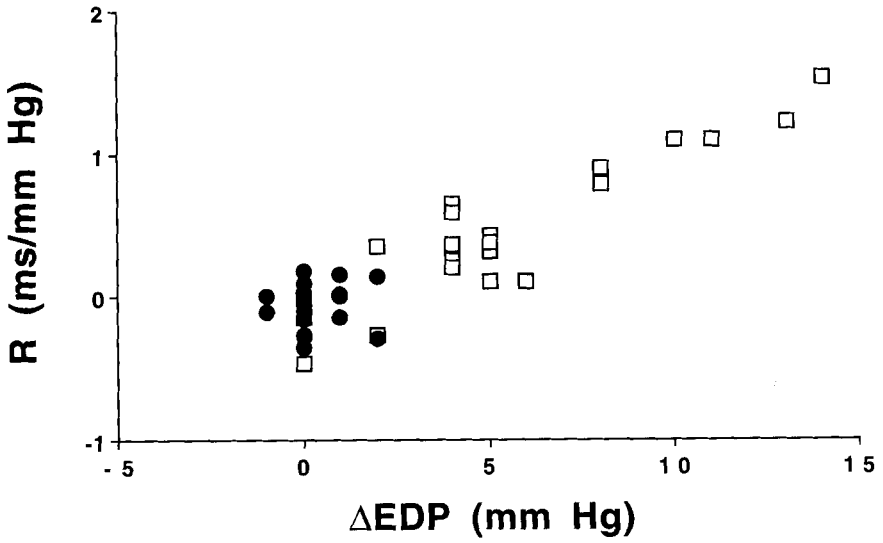

Fig. 4. Plot relating individual values of R with corresponding changes in end-diastolic pressure (EDP) with leg elevation (*open squares*) and phenylephrine (PE; *closed circles*). R is the slope of the τ–end-systolic pressure relationship and quantifies afterload dependence of the rate of LV pressure decrease. A close relationship between these variables was observed with leg elevation but not with phenylephrine.

function. The effects of leg elevation were variable, with improved LV function in some patients, and unchanged or even impaired LV function in other patients. In the same patients, a similar increase in systolic pressures obtained with phenylephrine resulted in a homogeneous response of LV function. It therefore appeared that leg elevation impaired LV function in some patients, although the response to phenylephrine indicated preserved afterload reserve (*i.e.*, ability of the heart to deal adequately with increased systolic pressures).

An intriguing observation of the present study was that not the increase in ESP but instead the change in ESV appeared to be the determinant factor. It remained to be explained why ESV increased with leg elevation in some patients and not in others. A possible hypothesis was a variability in the length-dependent regulation of myocardial function with deficient length-dependent activation of LV function in some patients. Leg elevation resulted in a homogeneous increase in EDV. Normally, an increase in EDV should result in length-dependent activation of myocardial function and recruitment of preload reserve with an increase in SV and SW. This occurred in some but not in all patients. These latter developed impairment of LV function as evidenced by the decrease in SV, SW, dP/dt_{max}, the increased load dependence of LVP fall, and the increased filling pressures. It therefore appeared that in these patients length-dependent activation of LV function was not operative. Deficient length-dependent activation of myocardial function with exhaustion of preload recruitable function might therefore have caused the impaired contractile reserve in response to an acute increase in cardiac load with leg elevation. The present study did not allow to differentiate between a physiologic interaction between LV load and function and a different pathophysiologic state due to myocardial ischemia. It could be suggested that a decrease in SW with leg elevation would occur preferentially in patients with more severe or extensive myocardial ischemia. Although no evidence of myocardial ischemia was present in these patients, further studies will have to elucidate a possible causative role for myocardial ischemia in the current observations.

Leg elevation not only revealed impaired contractile performance in some patients but also identified patients with increased load dependence of LVP decrease. Load dependence of LVP decrease reflects to what extent the rate of relaxation depends on systolic load or systolic pressures. A possible explanation for the greater load dependence of LVP decrease in patients with impaired LV function is based on the analysis of ESVs. In these patients the changes in ESV that occur with changes in ESP are greater.[14] Systolic muscle length, which is determined by ESV, is an important determinant of relaxation rate.[15] The smaller the ESV, the greater the amount of energy that is stored during systolic ejection due to compression elastic elements and changes in the configuration of the left ventricle.[16] It has been suggested that the release of this stored energy during relaxation may accelerate the rate of LVP decrease, which could in turn contribute to early diastolic filling.[15]

An alternative explanation for the absence of changes in SV with phenylephrine is related to its possible inotropic effects. Although phenylephrine is an α_1-selective agonist, which activates β-adrenergic receptors only at

higher concentrations,[17] some β-adrenergic effect of phenylephrine cannot be excluded. In addition, the role and underlying mechanisms of myocardial effects of α_1-adrenoceptor stimulation in different pathophysiologic states have not yet been conclusively determined.[18] In the present study, the dose of phenylephrine used was very low. In addition, all patients were on cardioselective β-blocking medication, which was continued until the morning of surgery. Although this makes an important phenylephrine-induced inotropic effect unlikely, a marginal positive inotropic effect remained possible. Phenylephrine slightly increased SW and dP/dt_{max} in all patients. In addition, the absence of a decrease in SV in the presence of a phenylephrine-induced vasoconstrictive effect also suggested slight improvement of LV function.

With respect to the reported results on Ees, it should be noted that the effects of leg raising should be interpreted as data projecting on the higher curvilinear part of the systolic pressure–volume relationship.[19,20] The interpretation of such data is different from the interpretation of load-independent assessment of contractility, which is performed at lower ventricular volumes and which results in truly linear systolic pressure–volume relationships.

An important point is that the present observations deal with a limited change in ESP. The conclusions with regard to presence of an afterload reserve with phenylephrine in the current observations should therefore be restricted to this pressure range. It was previously reported that a more pronounced increase in afterload with higher doses of phenylephrine result in decreased ejection fraction and slowing of relaxation.[21,22]

The variability in the observations with leg elevation could also be the consequence of diastolic ventricular interaction. Increased filling pressures may distend the ventricles to such an extent that filling of the left ventricle is impeded by the surrounding pericardium and the right ventricle.[23,24] The present observations were obtained in a situation of open chest and open pericardium and with ventilation suspended, thereby minimizing possible interfering effects of the surrounding tissues. In addition, if diastolic ventricular interaction were present, the increase in right ventricular EDV with leg elevation would have resulted in a decreased LVEDV. In the present observations leg elevation increased LVEDV homogeneously in all patients. Therefore occurrence of diastolic ventricular interaction is not likely.

Different effects of leg elevation at baseline and after phenylephrine were not caused by a time-dependent effect. From preliminary experiments it appeared that effects of leg elevation were similar when repeated twice at a 10-min interval. Ideally, the order of leg elevation or phenylephrine administration should have been randomly allocated. However, it appeared from preliminary experiments that return to baseline conditions after phenylephrine was not obvious within an acceptable time delay. In the present study, LV afterload was not really quantitatively assessed. LVESP provided a qualitative assessment of LV afterload and Ea described the arterial elastic component of LV–arterial coupling. Direct assessment of aortic input impedance was not performed. Alternatively, continuous measurement of LV wall thickness with echocardiography should allow for a quantification of LV end-systolic wall stress in the different experimental settings. Heart rates during the protocols were regulated with cardiac pacing. The use of pacing discarded variations in heart rate between patients and within the same patient as a confounding factor. However, it should be taken into account that pacing altered the normal LV conduction patterns, and that this might have somewhat enhanced load dependence of LVP decrease, as was experimentally demonstrated in the canine heart.[25] Data were obtained in anesthetized patients. This implies that neurohumoral reflexes, including those mediating cardiac function, may have been blunted or altered with anesthesia. Another point is that the data were obtained in the presence of an open chest and open pericardium. The absence of pericardium may have overdilated the heart in some patients.[26]

In conclusion, the different effects of leg elevation and phenylephrine administration suggest that the observed decrease in SV, SW, and dP/dt_{max} with leg elevation in some patients could not be attributed to an impaired contractile response to increased systolic LVP. Instead, load-dependent impairment of LV function after leg elevation appeared related to a deficient length-dependent regulation of myocardial function.

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