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Contraction–Relaxation Coupling and Impaired Left Ventricular Performance in Coronary Surgery Patients

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Background: **Dependence of left ventricular (LV) relaxation on cardiac systolic load is a function of myocardial contractility. The authors hypothesized that, if a tight coupling would exist between LV contraction and relaxation, the changes in relaxation rate with an increase in cardiac systolic load would be related to the changes in LV contraction.**

Methods: **Coronary surgery patients (n = 120) with preoperative ejection fraction > 40% were included. High-fidelity LV pressure tracings (n = 120) and transgastric transesophageal echocardiographic data (n = 40) were obtained. Hearts were paced at a fixed rate of 90 beats/min. Effects on contraction were evaluated by analysis of changes in dP/dt_{max} and stroke area. Effects on relaxation were assessed by analysis of R (slope of the relation between τ and end-systolic pressure). Correlations were calculated with linear regression analysis using Pearson's coefficient r.**

Results: **Baseline LV end-diastolic pressure was 10 ± 3 mmHg (mean ± SD). During leg raising, systolic LV pressure increased from 93 ± 9 to 107 ± 11 mmHg. The change in dP/dt_{max} was variable and ranged from −181 to +254 mmHg/s. A similar variability was observed with the changes in stroke area, which ranged from −2.0 to +5.5 cm^2. Changes in dP/dt_{max} and in stroke area were closely related to individual R values ($r = 0.87$, $P < 0.001$; and $r = 0.81$, $P < 0.001$, respectively) and to corresponding changes in LV end-diastolic pressure ($r = 0.81$, $P < 0.001$; and $r = 0.74$, $P < 0.001$, respectively).**

Conclusions: **A tight coupling was observed between contraction and relaxation. Leg raising identified patients who developed a load-dependent impairment of LV performance and increased load dependence of LV relaxation. (Key words: Cardiopulmonary bypass; coronary artery surgery; ventricular function.)**

THE magnitude of the systolic load determines the rate of myocardial relaxation.[1,2] Myocardial relaxation rate was more sensitive to systolic load when cardiac contractility was depressed with β-blocking medication[3,4] or when cardiac dysfunction was induced experimentally.[5,6] Increased load dependence of left ventricular (LV) relaxation rate with impaired LV performance also was observed in the clinical setting.[7,8] These findings indicated that the response of LV contraction and relaxation to changes in cardiac systolic load was coupled. As a consequence, analysis of the effects of an increase in cardiac load on the rate of LV relaxation could provide information on LV performance. No change or even slight acceleration of LV relaxation in response to an increase in systolic pressures would be indicative of preserved myocardial function, whereas slowing of LV relaxation would be indicative of impaired function.[9]

The current study was designed to determine, in patients undergoing coronary surgery, the relation between changes in contraction and simultaneous changes in relaxation. We hypothesized that if a tight coupling would exist between LV contraction and relaxation, changes in relaxation rate with an increase in cardiac load would be related to the changes in parameters of LV contraction. More specifically, in the presence of preserved myocardial function, an increase in systolic cardiac load would result in no changes or a slight acceleration of LV relaxation, whereas in the presence of impaired cardiac function, a similar increase in systolic load would result in slowing of LV relaxation.

To address these issues in the specific clinical perioperative setting, a safe, easily applicable, and rapidly reversible increase in cardiac loading conditions had to be performed. Leg raising met these requirements. Leg rais-

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ing represents a complex hemodynamic intervention during which systolic and diastolic LV pressures and volumes increase and which affects venous return and aortic impedance.

Methods

Patient Population

The study was performed on patients scheduled for elective coronary artery bypass surgery. The study was approved by the Institutional Ethical Committee, and written informed consent was obtained. Because of the invasive and extensive methodology, only patients with an ejection fraction of $>$ 40% and with an LV end-diastolic pressure (EDP) of $<$ 15 mmHg on preoperative hemodynamic evaluation were included. Patients undergoing repeat coronary surgery, concurrent value repair, or aneurysm resection were excluded. Patients with unstable angina pectoris, concomitant valvular disease, and severe regional wall motion abnormalities were also excluded. The included patients, therefore, represented a sample of patients undergoing routine coronary surgery in whom the complication rate was expected to be minimal.

Anesthesia and Surgery

Preoperative cardiac medication, including β-blocking agents, calcium channel–blocking agents, angiotensin converting enzyme inhibitors, and nitrates were continued until the morning of surgery. Premedication consisted of intramuscularly administered glycopyrolate 2 μg/kg, droperidol 30 μg/kg, and fentanyl 1 μg/kg. In the operating room, patients received routine monitoring including five-lead electrocardiogram, radial and pulmonary artery catheters, pulse oxymetry, 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. Patients' lungs were ventilated with a fractional inspired oxygen tension of 0.5; when necessary, isoflurane 0.2 to 0.4% was added to the air–oxygen mixture. All patients received 2 g methylprednisolone after induction of anesthesia and 2.10^6 inhibiting units aprotinin in the priming fluid of the extracorporeal circuit.

Standard median sternotomy and pericardiotomy were performed. The aorta was cannulated, and epicardial pacemaker wires were attached to the right atrium and right ventricle. A sterilized, prezeroed electronic tipmanometer (MTC P3Fc 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). Zero and gain setting of the tipmanometer were also checked against a high-fidelity pressure gauge (Druck Limited, Leicester, UK) after removal.

Venous drainage during cardiopulmonary bypass (CPB) was performed with a two-stage venous cannula inserted in the right atrium. A ventricular sump was inserted in the left ventricle through the right superior pulmonary vein. Perfusion flow on CPB was $2.4\ l \cdot m^{-2} \cdot min^{-1}$ in nonpulsatile mode. Patients were cooled to a bladder temperature of 28°C. In all patients, the left internal thoracic artery was used in addition to one or more saphenous vein grafts.

Depending on the surgeon's preference, two types of surgical technique and cardiac protection were used during coronary artery bypass grafting. One surgeon (IER) performed coronary bypass surgery using intermittent cross-clamping under cardioprotection with the nucleoside transport inhibitor Lidoflazine (Janssen Pharmaceutics, Beerse, Belgium). The other surgeon (ACM) performed coronary artery bypass surgery after coronary perfusion with cold (4°C) Bretschneider cardioplegic solution without blood (composition per 1,000 ml: NaCl 15 mmol, KCl 9 mmol, K hydrogen-2-oxoglutarate 1 mmol, $MgCl \cdot H_2O$ 4 mmol, $CaCl \cdot 2H_2O$ 0.015 mmol, histidine $\cdot$ HCl $\cdot$ H_2O 18 mmol, histidine 180 mmol, tryptophane 2 mmol, and mannitol 30 mmol). Patients were assigned randomly to one of the two collaborating surgeons. Both techniques have been shown previously to have the same effects on LV function after CPB.[10] In all patients included in this study, complete revascularization could be performed.

After the surgical procedure, reperfusion of the heart (reperfusion time was set at 50% of the aortic cross-clamp time in all patients) and rewarming to a bladder temperature of 35°C, patients were prepared for separation from CPB. The heart was paced in atrioventricular sequential mode at a rate of 90 beats/min and filled until a pulmonary capillary wedge pressure of 13–15 mmHg or a central venous pressure of 8–10 mmHg was obtained. When after termination of CPB, cardiac index exceeded $2.5\ l \cdot m^{-2} \cdot min^{-1}$ with a systolic systemic arterial pressure >85 mmHg or a mean arterial pressure >50 mmHg, the venous cannula was withdrawn. When necessary, an infusion of nitroglycerine was started to

keep mean arterial pressure between 60 and 70 mmHg. When cardiac index remained <2.5 l $\cdot$ m^{-2} $\cdot$ min^{-1} despite adequate pre- and afterload conditions, inotropic support with dobutamine was initiated at a dose of 5 μg $\cdot$ kg^{-1} $\cdot$ min^{-1}. In the patients needing this inotropic support at separation from CPB, the maneuver of increasing cardiac load with leg raising was not performed because this might have induced deterioration of LV function. Therefore, no post-CPB data on these patients were available. After separation from CPB, a stabilization period of 10 min was allowed to prevent the time-dependent changes in ventricular function with alteration of preload[10] before measurements after CPB were made.

Experimental Protocol

Data from 120 patients were included in the current study. In a subset of 40 patients, additional echocardiographic data were obtained. Echocardiographic data were acquired using a biplane 5-MHz esophageal ultrasonographic probe (Aloka UST-5233-S) connected to a SSD-830 Aloka echocardiographic unit (Aloka, Tokyo, Japan). Short-axis transgastric incidences were selected for analysis. The midpapillary muscle level was taken as anatomic landmark and the probe was positioned to obtain the image with the most circular overall geometry with uniform wall thickness. Earlier studies have shown that this cross-sectional area allowed fair estimation of LV volume.[11–13]

During the measurements, no vasoactive or inotropic medication was allowed. Measurements were obtained with the ventilation suspended at end expiration. During the protocol, heart rate was maintained constant by means of atrioventricular sequential pacing at a fixed heart rate of 90 beats/min with an atrioventricular interval of 150 ms. Paced heart rate was identical before and after CPB. In none of the patients in this study did intrinsic heart rate exceed paced heart rate. Measurements were obtained before venous cannulation (pre-CPB) and after a 10-min stabilization period after successful separation from CPB (post-CPB). Measurements consisted of recordings of consecutive electrocardiographic and LV pressure tracings during an increase in systolic and diastolic LV pressures obtained by raising the caudal part of the surgical table by 45° resulting in raising of the legs. Leg raising resulted in a rapid beat-to-beat increase in LV pressures and dimensions. Care was taken to have $\geq$10 consecutive beats for analysis. After recording the data, ventilation was resumed, and the surgical table was returned to horizontal. The output signals of the pressure transducer system were recorded digitally together with the electrocardiographic signals at 1-ms intervals (Codas; DataQ, Akron, OH). Echocardiographic images were recorded simultaneously on VHS videotape at a rate of 25 images/s. Recordings of pressure and dimension data were synchronized with an electronic pulse signal at the beginning and at the end of the recording.

Data Analysis

Research clinicians were blinded from the clinical decision-making and the management during the operative procedure and at separation from CPB. Recorded data were analyzed only after completion of surgery so that they were not available at the time of the clinical decision-making. End-diastolic pressure was timed at the peak of the R-wave on electrocardiogram. End-systolic pressure (ESP) corresponded to pressure at dP/dt_{min}. τ was calculated using LV pressure values from dP/dt_{min} to a cutoff value of 10 mmHg higher than EDP.[14,15] The following equation was used: $\ln P_t = \ln P_0 - \text{time}/\tau$.[16,17]

Time constant τ 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 end-systolic LV pressure and quantified afterload dependence of the rate of LV pressure decrease.[7] At least 10 consecutive beats were taken for the calculation of R. Sample correlation coefficients of the ESP $-$ τ relations yielded values of $r > 0.93$ in all patients.

Echocardiographic data were analyzed off-line, separately by two different observers who were blinded from the results of the other observations. Reported data represent the means of these measurements. Intraobserver variability was $<5\%$, and interobserver variability was $<8\%$ in all patients. End-diastole was measured at the point of maximal LV cavity area, whereas end-systole was measured at the point of minimal LV cavity area. If this could not be determined visually, end-diastole and end-systole were measured when the electrocardiogram-gated freeze-frame analysis of echocardiographic images corresponded to the peak of the R-wave and to the end of the T-wave, respectively. Care was taken that timing of end-diastole and end-systole was obtained in the same way in the consecutive measurements in a given patient. Endocardial borders were outlined manually from the video screen with a trackball. Images were evaluated according to the position and quality scores proposed by London *et al.*[18] Only patients with a position score of 1 (optimal short axis orientation) and a quality score of 3 (good endocardial and epicardial resolution) were in-

cluded for echocardiographic analysis. The papillary muscles were excluded when the endocardial border was traced. Left ventricular dimensions were measured and calculated using a computer program (Echo-com; PPG Hellige GmbH, Germany). The measured cross-sectional area corresponded to $\pi \cdot r^2$. Assuming a spheric model, ventricular cavity volume (V) was calculated with the formula $V = (4\ \pi/3) \cdot r^3$. The measured cross-sectional cavity areas were reported in the tables, and derived cavity volumes were used for the computation of ventricular systolic elastance, diastolic stiffness, and arterial elastance. Regional wall motion abnormalities may influence the accuracy of calculating ventricular dimensions. In the current study population, none of the patients exhibited severe wall motion abnormalities.

At least 10 consecutive beats were taken for LV pressure and dimension analysis. End-diastolic pressure–dimension relations were constructed for each set of measurements. Passive properties of the ventricle were described by fitting an exponential equation through these points using the three-constant equation that allows LV pressure to decay to a natural asymptote:

$$P = A \cdot e^{kc \cdot V} + B$$

where P and V represent the corresponding end-diastolic pressure and volume, kc corresponds to the chamber stiffness constant, and A and B are empirical constants.

Systolic performance was assessed by evaluation of the EDP/volume relationship. The corresponding systolic pressure and volume data were fit by linear least-squares analysis to the following equation:

$$P = Ees(V - V0)$$

where P = LV systolic pressure, Ees = the slope of the systolic pressure − volume relation, V = LV systolic volume, and V0 = the volume intercept of the systolic pressure − volume relationship. Sample correlation coefficient of the EDP/volume and the ESP/volume relations yielded values of $r > 0.92$ in all patients.

Arterial elastance (Ea) was calculated using the formula ESP/SV, where ESP is the pressure at dP/dt_{min} and SV is stroke volume.

Statistical Analysis

Data before and after leg raising were compared using two-way analysis of variance for repeated measurements. Interaction analysis revealed whether effects of leg raising were different before and after CPB. Posttest analysis was performed using the Bonferroni-Dunn test. Changes in hemodynamic parameters were related using linear regression analysis computing Pearson's correlation coefficient. Slopes and intercepts of the relations were compared using Student's *t* test analysis.[19] The need for inotropic support was incorporated in a *post hoc* manner. Pre-CPB hemodynamic data of the patients who needed inotropic support were compared with those of the patients who did not require inotropic support using the Mann–Whitney U test. Pre- and intraoperative characteristics in patients with and without inotropic support were compared using chi-square analysis. Data were reported as mean ± SD. Statistical significance was set at $P < 0.01$.

Table 1. Preoperative and Intraoperative Data

Preoperative data	
Male/female	80/40
Age (yr)	65 ± 8
Length (cm)	172 ± 10
Weight (kg)	77 ± 11
BSA (m^2)	1.9 ± 0.3
Diabetes	11
Hypertension	52
Previous MI	44
Medication	
Nitrates	88
β-Blocking drugs	74
Ca channel blocking drugs	38
ACE inhibitors	32
Intraoperative data	
Number of grafts	4 ± 1
Aortic cross-clamp time (min)	47 ± 10
CPB time (min)	88 ± 15

Data are mean ± SD.

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

Results

Clinical, demographic, and intraoperative data are summarized in table 1. Surgery was uneventful in all patients studied, with no patients developing a perioperative infarction based on appearance of increased creatine kinase (MB isomer) > 20 or appearance of new Q-waves on electrocardiogram. Of the 120 patients, 15 needed inotropic support during separation from CPB. No post-CPB data were obtained in these patients.

Hemodynamic data are summarized in table 2. Leg raising increased LV systolic pressure by 13 ± 3 mmHg. End-diastolic area increased by 6 ± 1 cm^2 and EDP by 6 ± 4 mmHg. Although the increase in end-diastolic area was uniform, an important variability was observed in

Table 2. Hemodynamic Data with Leg Elevation before and after Cardiopulmonary Bypass (CPB)

		Pre-CPB	Post-CPB	Interaction (*P*)
EDP (mm Hg)	Baseline	10 ± 3	12 ± 4	
	Legs up	16 ± 6*	16 ± 4*	0.390
Peak LVP	Baseline	93 ± 9	91 ± 10	
	Legs up	107 ± 11*	99 ± 11*#	<0.01
dP/dt max (mmHg/s)	Baseline	998 ± 190	865 ± 181#	
	Legs up	1053 ± 216	882 ± 175#	<0.01
τ (ms)	Baseline	64 ± 8	66 ± 11	
	Legs up	68 ± 9	68 ± 11	0.03
R (ms/mm Hg)		0.480 ± 0.515	0.558 ± 0.291	
ED area (cm^2)	Baseline	23 ± 5	22 ± 4	
	Legs up	28 ± 4*	27 ± 5*	0.553
Stroke area (cm^2)	Baseline	11 ± 4	11 ± 3	
	Legs up	12 ± 4	12 ± 4	0.652
Ea (mmHg/ml)	Baseline	1.28 ± 0.22	1.19 ± 0.23	
	Legs up	1.29 ± 0.25	1.21 ± 0.24	0.12
Ees (mmHg/ml)		2.47 ± 1.16	2.31 ± 0.84	
kc		0.009 ± 0.003	0.010 ± 0.004	

EDP = end-diastolic pressure; LV = left ventricular pressure; Ea = arterial elastance; Ees = slope of the end-systolic pressure–volume relationship; kc = chamber stiffness constant.

Data are mean ± SD; interaction analyzed whether effects of leg elevation were different before and after CPB.

the magnitude of the increase in EDP (fig. 1). The effects of leg raising on myocardial contraction were evaluated by analysis of changes in dP/dt_{max}, stroke area (SA), and by individual Ees values. The mean dP/dt_{max} and SA values remained unchanged, but a wide variability was observed in the individual values. dP/dt_{max} and SA increased in some patients but remained unchanged or even decreased in other patients.

The effects of leg raising on myocardial relaxation were evaluated by analysis of R. The inset in figure 2 illustrates the meaning of R. R is the slope of the relation between τ and ESP. A positive value means that τ increased with increased ESP (filled circles) whereas a negative value means that τ decreased with increased ESP (open squares). The mean value of R was 0.480 ± 0.515 ms/mmHg. Relaxation accelerated in some patients but remained unchanged or even slowed in other patients. Individual values of R were closely related to changes in dP/dt_{max} (fig. 2A) and to changes in SA (fig. 2B). A close relation was also observed between individual values of R and of Ees (fig. 2C). These data indicated that changes in parameters of contraction and relaxation with an increase in cardiac load were coupled.

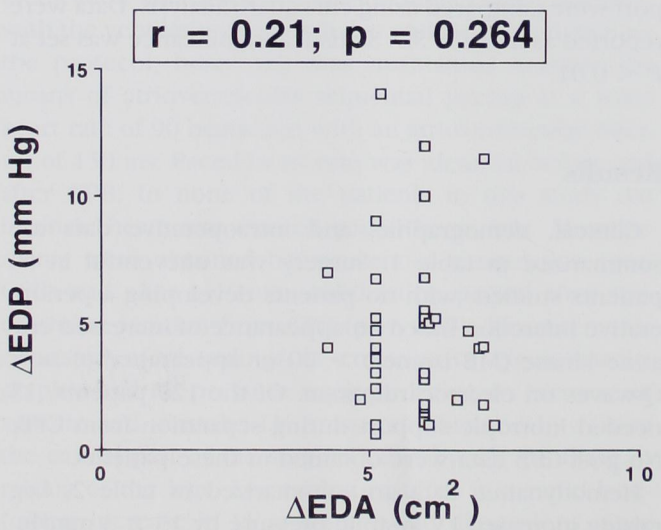

Fig. 1. Plot relating the individual changes in end-diastolic area (EDA) and end-diastolic pressure (EDP) with leg raising. The increase in EDA with leg raising is homogeneous, whereas changes in EDP show an important variability.

A close relation also was observed between individual R values and the corresponding changes in EDP with leg raising (fig. 3). Consequently, changes in EDP with leg raising were closely related to corresponding changes in dP/dt_{max} ($r = 0.81$; $P < 0.001$), corresponding changes in SA ($r = 0.74$; $P < 0.001$), and individual values of Ees ($r = 0.76$; $P < 0.001$).

No relation was found between changes in EDP with leg raising and preoperative ejection fraction ($r = 0.2$; $P = 0.12$), baseline end-diastolic area ($r = 0.14$; $P = 0.238$), baseline EDP ($r = 0.19$; $P = 0.108$), baseline dP/dt_{max} ($r = 0.2$; $P = 0.085$) and baseline SA ($r = 0.16$; $P = 0.166$). Changes in EDP, however, were related to individual kc values ($r = 0.59$; $P < 0.001$).

Intraoperative events (n° of bypasses, aortic cross-

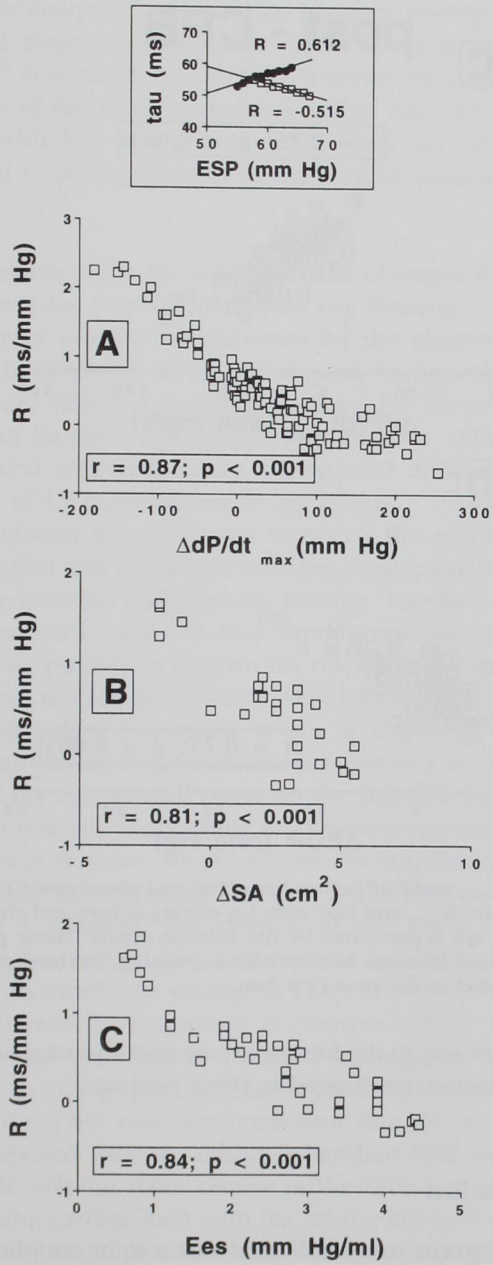

Fig. 2. Plots relating individual values of R to corresponding changes in dP/dt_{max} (*A*), stroke area (SA) (*B*), and the slope of the end-systolic pressure/volume relation (Ees) (*C*). The inset illustrates the meaning of R. Time constant τ was linearly fit to the corresponding end-systolic pressure (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 relaxation. A close relation was observed between individual R values and corresponding changes in dP/dt_{max} with leg raising, with corresponding changes in SA and with corresponding individual Ees values. This relation indicated coupling between parameters of contraction and parameters of relaxation.

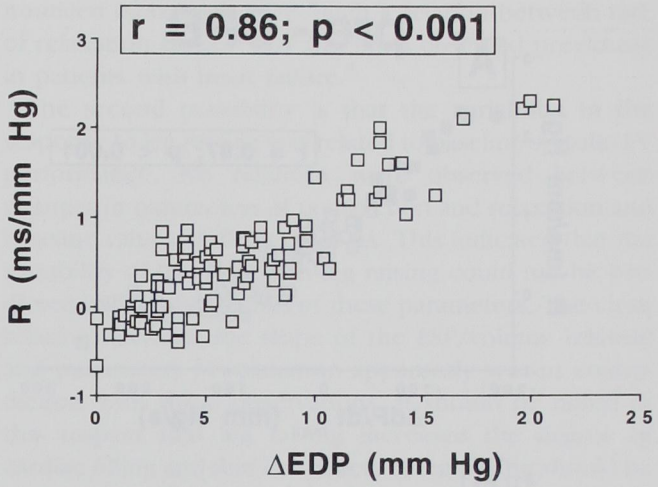

Fig. 3. Plot relating individual values of R with corresponding changes in EDP with leg raising. A close relation was observed. It appeared that the magnitude of the increase in EDP reflected the degree of load dependence of LV relaxation rate.

clamp time, total CPB time, surgical technique) and preoperative data (sex, age, length, weight, diabetes, medication) were not different in the patients with and without inotropic support. Table 3 compared baseline hemodynamic data and effects of leg raising in these patients. Baseline hemodynamic data were similar, but the effects of leg raising differed. In the patients who needed inotropic support at separation from CPB, the increase in EDP was more important and R was higher. The value of dP/dt_{max} decreased in these patients, whereas it increased in the patients who did not require inotropic support.

Table 3. Hemodynamic Data of Patients with and without Inotropic Support at Separation from Cardiopulmonary Bypass

	No Inotropic Support (n = 105)	Inotropic Support (n = 15)	*P*
Baseline data			
EDP (mmHg)	10 ± 4	13 ± 6	0.058
Peak LVP (mmHg)	93 ± 8	88 ± 10	0.063
dP/dt max (mmHg/s)	981 ± 150	913 ± 96	0.259
Effects of leg elevation			
Δ EDP (mmHg)	6 ± 3	11 ± 4	<0.001
Δ peak LVP (mmHg)	14 ± 6	9 ± 8	0.024
Δ dP/dt max (mmHg/s)	72 ± 81	(−)116 ± 44	<0.001
R (ms/mmHg)	0.370 ± 0.394	1.595 ± 0.462	<0.001

EDP = end-diastolic pressure; LVP = left ventricular pressure.

Data are mean ± SD.

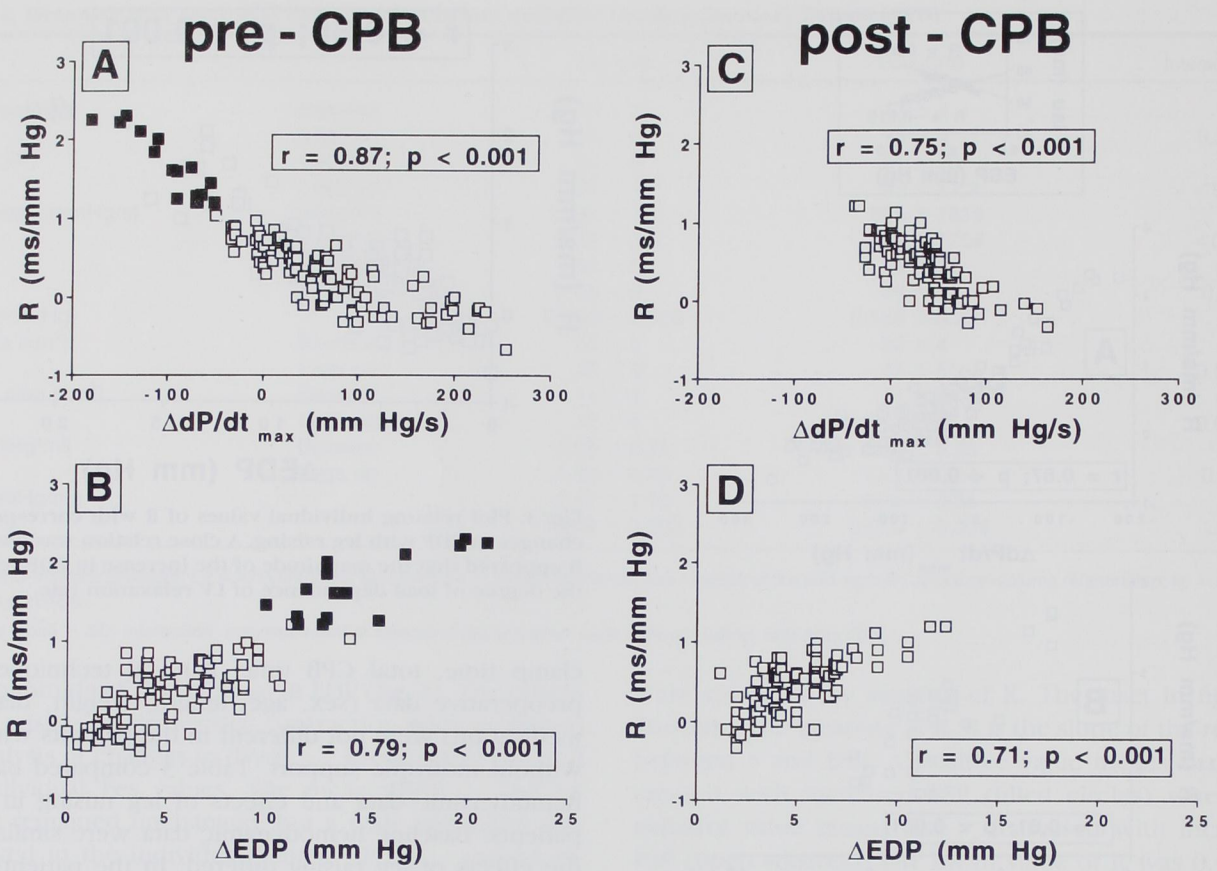

Fig. 4. Plots relating individual values of R to corresponding changes in dP/dt_{max} and EDP before (pre-CPB) and after (post-CPB) CPB. A close relation was observed between R and the corresponding changes in dP/dt_{max} and EDP with leg raising before and after CPB. Of the 120 patients, 15 needed inotropic support after CPB. These patients are represented by the filled symbols. These patients developed a decrease in dP/dt_{max}, had high R values, and showed an important increase in EDP with leg raising. In these patients, leg raising was not performed after CPB, and therefore they were not included in the post-CPB data.

Figure 4 displays the relations before and after CPB between individual R values and changes in dP/dt_{max} (top) and changes in EDP (bottom) with leg raising. The patients needing inotropic support during separation from CPB are represented by filled icons and projected at the left upper part of figures 4A and 4B. Individual values of R were closely related to changes in dP/dt_{max} (fig. 4A) and to changes in EDP (fig. 4B) with leg raising. After CPB, an identical relation as before CPB was observed with leg raising between R and changes in dP/dt_{max} (fig. 4C) and between R and changes in EDP (fig. 4D). No significant differences were observed in the slopes and the x-axis intercepts of the relationships pre- and post-CPB.

In all patients needing inotropic support during separation from CPB, dobutamine could be stopped within the first 6 h after admission to the intensive care unit. Length of stay in the intensive care unit and total hospital stay were not prolonged in these patients.

Discussion

The current study indicated that a tight coupling was present between contraction and relaxation in patients undergoing elective coronary surgery. In patients with preserved LV performance, the increase in systolic load resulted in either no change or even a slight acceleration of LV relaxation. In patients with impaired LV performance, the increase in systolic load slowed LV relaxation. Leg raising, therefore, allowed the identification of patients who developed a load-dependent impairment of LV performance. These patients developed a decrease in SA and dP/dt_{max}, an enhanced load-dependence of LV pressure decrease, and a marked increase in LV EDP.

Post hoc analysis suggested that patients developing this type of response were more likely to need inotropic support at separation from CPB. It seems, therefore, that analysis of the load dependence of the rate of LV relaxation with leg raising might constitute an alternative method to perioperatively assess cardiac contractile reserve.

Mechanisms for the Variability in Changes in Left Ventricular Performance with Leg Raising

Different possible mechanisms for the observed variability in response to leg raising can be hypothesized. These are different baseline diastolic LV performance, different baseline systolic LV performance, differential peripheral response to leg raising, and differential response of LV performance to leg raising.

No relation was observed between the response of contraction and relaxation with leg raising and baseline EDP or baseline end-diastolic volume. Baseline LV diastolic pressures and volumes, therefore, could not contribute to, predict, or explain the response to leg raising. This does not imply, however, that baseline diastolic LV function was not involved. It can be expected that an important interpatient variation was present in the position of the operational point on the diastolic pressure/volume relation. If operating on the steep portion of this curvilinear relation, small increases in end-diastolic volume cause large increases in EDP. Conversely, if operating on a relatively flat portion of the curve, then a comparable increase in end-diastolic volume is associated with much less change in EDP. The observed relation between the magnitude in changes of EDP with leg raising and the stiffness constant kc suggests that the change in EDP might have depended on the operational point of the left ventricle at the time that the leg raising was imposed. Hence, although baseline EDP and end-diastolic volume were similar in the different patients, increasing cardiac load with leg raising allowed identification of those patients who were operating on the steeper part of the curve. This manifested as a significant relation between the increase in EDP and the constant of chamber stiffness kc. This relation, however, did not help to explain the mechanism of impaired diastolic LV performance, which was observed in some patients. The rather uniform distensibility (fig. 1) suggested that passive LV properties were not involved as a major causative factor. Conversely, the close relation between R and the magnitude of the increase in LV EDP (fig. 3) suggested the occurrence of slowed and possibly incomplete myocardial relaxation in the patients with the most pronounced increase in EDP. Such a relation between rate of relaxation and LV EDP has been observed previously in patients with heart failure.[8]

The second possibility is that the variability in the response to leg raising was related to baseline systolic LV performance. No relations were observed between changes in parameters of contraction and relaxation and baseline values of dP/dt_{max} or SA. This indicated that the variability of changes with leg raising could not be predicted by baseline values of these parameters. The close relation between the slope of the ESP/volume relation and parameters of relaxation apparently was in contradiction with these observations. It should be noted in this respect that leg raising increased the degree of cardiac filling and that the effects of leg raising should be interpreted as data projecting on the higher curvilinear part of the systolic pressure/volume relation.[20,21] 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 relations.

A third possible explanation for the observed variability is a differential peripheral response of the vascular tree to leg raising. Changes in systolic LV pressure and in arterial elastance, however, did not appear to be related to parameters of contraction and relaxation. Differences in peripheral vascular response with leg raising, therefore, are probably not a major factor.

An alternative explanation is a differential response of LV performance to the increase in cardiac load. This can occur by two different causative mechanisms. Leg raising may have induced afterload mismatch[22] or exhaustion of preload reserve.[23] The variability in the observations therefore might be related either to excessive afterload or to impaired length-dependent activation of LV performance in some patients. Identification of the underlying mechanisms is the focus of ongoing research. Further elucidation of the underlying mechanisms of the current observations may be especially important in view of possible different therapeutic managements.

Limitations

The current data were obtained in a selected population of patients without obvious major risk factors in whom the complication rate was expected to be minimal. Our observations did not include detailed assessment of postoperative clinical outcome. Therefore no conclusions can be drawn regarding a possible prognostic value of the hemodynamic response with leg raising.

Patients with severely impaired preoperative LV function were not included because we were concerned that leg raising in these patients might have resulted in forward and backward LV failure.

The current study did not include an analysis of the LV filling sequence by transmitral and pulmonary venous blood flow signals. Subsequent studies with observations of changes in Doppler flow patterns with leg raising should demonstrate whether the information obtained with the current invasive methodology can also be obtained in a noninvasive way, which is more easily applicable in the clinical situation.

Several methodologic issues deserve attention. To analyze contraction–relaxation coupling, a standardized, easily applicable and rapidly reversible increase in cardiac loading conditions had to be performed. Leg raising met all these requirements. Alternative methods such as partial aortic occlusion, rapid volume infusion through the aortic cannula, or infusion of α_1-adrenergic agonists provided either technical problems or were not rapidly reversible, resulting in an increased risk for the patient. Although the method of leg raising resulted in a rapid beat-to-beat raising of LV pressures and dimensions and recording of data was shortlasting, it can not be excluded that a baroreceptor reflex occurred, which might have altered parasympathetic and sympathetic tone.

Heart rates during the protocols were regulated with cardiac pacing, which was identical before and after CPB. The use of pacing discarded variations in heart rate between patients and within the same patient as a confounding factor. It should be taken into account, however, that pacing altered the normal LV conduction patterns and that this might have somewhat enhanced load dependence of LV pressure decrease, as was demonstrated experimentally in the canine heart.[24]

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 because a rightward shift of the EDP/dimension relation has been shown after pericardiectomy.[25] In addition, all patients were taking long-term preoperative oral β-blocking medication. It is obvious that this treatment should have influenced the current observations because of the effects of β-blocking medication on rate of LV pressure decrease.[3,4]

Conclusions

In patients undergoing elective coronary surgery, a tight coupling was observed between contraction and relaxation. Leg raising allowed identification of patients who developed a load-dependent impairment of LV performance. These patients demonstrated enhanced load dependence of LV pressure decrease and a marked increase in LV EDP.

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