Background: Impairment of left ventricular function after cardiopulmonary bypass (CPB) is well recognized, but little is known about the time course of recovery of cardiac function early after separation from CPB. Therefore, recovery of left ventricular function was evaluated early after separation from CPB in patients undergoing coronary artery surgery. The authors tried to determine whether this recovery might be attributed to autoregulation of function by preload.

Methods: Left ventricular pressure was measured with fluid-filled catheters. Data were digitally recorded during increased pressure induced by elevating the legs. Transmural short-axis echocardiographic views of the left ventricle were simultaneously recorded on videotape. Systolic function was evaluated with the slope (Ees, mmHg/ml) of the systolic pressure-volume relation. Diastolic function was evaluated with the chamber stiffness constant (Kc, ml/mHg) of the diastolic pressure-volume relation. Cardiac function was assessed before CPB, after termination of CPB, and 5, 10, and 15 min later. Two different separation procedures from CPB were compared: in protocol 1, left ventricular function was determined during the standard procedure (n = 24); in protocol 2, the heart was optimally filled 10 min before separation from CPB (n = 12).

Results: In protocol 1, Ees was 2.88 ± 0.21 mmHg/ml (mean ± SEM) and Kc was 0.012 ± 0.001 ml/mHg before CPB. Within 10 min after separation from CPB, Ees increased from 1.10 ± 0.32 to 2.92 ± 0.34 (P = 0.001) and Kc decreased from 0.022 ± 0.002 to 0.011 ± 0.001 (P = 0.001). The parameters remained stable thereafter. In protocol 2, Ees was 2.92 ± 0.51 mmHg/ml and Kc was 0.011 ± 0.002 ml/mHg before CPB. Depression of systolic and diastolic function was not observed in these patients. At time 0, Ees was 2.46 ± 0.16 and Kc was 0.012 ± 0.002. These values remained stable throughout the entire observation period.

Conclusions: Significant functional recovery was observed early after separation from CPB, which was suggestive of time-dependent changes in both systolic and diastolic left ventricular function induced by preload restoration. (Key words: Heart; cardiopulmonary bypass; coronary surgery; myocardial function; preload.)

IMPAIRMENT of left ventricular (LV) function after cardiopulmonary bypass (CPB) is widely recognized, but little is known about the precise mechanisms causing the dysfunction and about the time course for recovery. Several studies have analyzed ventricular function in the hours after CPB and compared it with preoperative data, but only a few investigators focused on ventricular function immediately after separation from CPB. In patients undergoing cardiac surgery, both loading conditions and contractility may change very rapidly in the first minutes after separation from CPB. Traditional intraoperative measurements of ventricular function, such as ejection fraction and cardiac output, depend closely on such changes in loading conditions of the ventricle. Thus studies on the recovery of ventricular function immediately after CPB should rely on the use of indexes of systolic and diastolic ventricular function, which are relatively independent of load. Analysis of pressure-volume relations has been shown to be useful in assessing ventricular function in different experimental and clinical settings, including patients undergoing cardiac surgery.

The objective of the present study was to document the recovery pattern of systolic and diastolic LV function early after separation from CPB in patients having coronary artery bypass surgery. To evaluate potential underlying mechanisms of cardiac function immediately after CPB, two different regimens for preload management were compared.

Materials and Methods

Patients

This study was designed to document recovery of LV function early after separation from CPB and to establish...
possible physiologic mechanisms involved in regulating LV function during this period.

The study consisted of two protocols. In a first protocol (protocol 1), time course of recovery of LV function early after separation from CPB was documented in patients undergoing coronary artery surgery using two different surgical and myocardial protective techniques. One subset of patients was operated on using intermittent aortic cross-clamping under cardioprotection with the nucleoside transport inhibitor lidoflazine (Group A) and the other subset of patients was operated on using continuous aortic cross-clamping under cardioprotection with Bretschneider cardioplegic solution (Group B). In a second protocol (protocol 2), the time course of recovery of LV function early after separation from CPB was documented in patients with a different regimen of preload management before separation from CPB (Group C).

The study was attempted in 44 patients scheduled for elective coronary bypass surgery. The study was approved by the Institutional Ethical Committee and informed consent was obtained in all patients. Patients with an ejection fraction of more than 40% or with an LV end-diastolic pressure of less than 15 mmHg on preoperative hemodynamic evaluation were considered. Patients with unstable angina or undergoing repeated coronary surgery, concurrent valve repair, or aneurysm resection were excluded. At the time of the study patients were hemodynamically stable.

Anesthesia and Surgery
Premedication consisted of 2 μg/kg intramuscular glycopyrolate (Robinul), 30 μg/kg droperidol, and 1 μg/kg fentanyl given 90 min before surgery. In the operating room, patients received routine monitoring, including five-lead electrocardiography, radial and pulmonary artery pressure, pulse oxymetry, capnography, and blood and urine bladder temperature. After preoxygenation, anesthesia was induced with 20 μg/kg fentanyl, 0.1 mg/kg diazepam, and 0.1 mg/kg pancuronium bromide. An additional dose of 30 μg/kg fentanyl was administered before sternotomy. Patients' lungs were ventilated with FiO₂ was 0.5; when necessary, 0.2% to 0.4% isoflurane was added to the air-oxygen mixture. All patients routinely received 2 g methylprednisolone after induction of anesthesia and 2.10⁶ KIU aprotinin in the priming fluid of the extracorporeal circuit.

Echocardiographic data were acquired using a biplane 5-MHz esophageal ultrasound probe (Aloka UST-5253S, Tokyo, Japan) connected to a SSD-830 Aloka echocardiographic unit. Short-axis transgastric incidences were selected for analysis. The midpapillary muscle level was taken as an anatomic landmark and the probe was positioned to obtain the image with the most circular overall geometry with uniform wall thickness. This plane was selected because this procedure was acceptable during surgical procedures and because earlier studies have shown that this cross-sectional area allowed fair estimation of LV volume.

Standard median sternotomy and pericardiotomy were performed and the heart was prepared for coronary artery bypass grafting. The aorta was cannulated and epicardial pacemaker wires were attached to the right atrium and right ventricle. Then a fluid-filled catheter with a broad internal lumen and a rigid wall (Cavafix; 18 G, 45 cm long, Braun Melsungen AG, Melsungen, Germany) was positioned in the LV cavity through the apical dimple to record LV pressure. The catheter was connected through 120-cm high-pressure tubing (Viggo-Spectramed, Swindon, UK) to a pressure transducer (M1006A; Hewlett Packard, Denmark). All transducers were calibrated to zero at the air at the beginning of the protocol. Zeroes were checked before each set of measurements. Dynamic response (natural frequency and damping coefficient) of the catheter-transducer system was evaluated using the flush method described by Gardner before and after each experiment. For the LV pressure measurement system, mean frequency response was 32 Hz, with a mean damping coefficient of 0.41. All individual measurements were within the adequate range of dynamic response requirements for direct pressure measurements. The output signal of the pressure transducer system was digitally recorded together with the electrocardiographic signals (Codas; DataQ, Akron, OH).

Depending on the surgeon's preference, two types of surgical technique and cardiac protection were used during coronary artery bypass grafting. One surgeon (J.E.R.) performed coronary bypass surgery using intermittent cross-clamping under cardioprotection with the nucleoside transport inhibitor lidoflazine (0.5 mg/ml concentration; Janssen Pharmaceuticals, Beerse, Belgium). This technique involved intravenous administration of 1 mg/kg lidoflazine before the start of CPB. Distal anastomoses were performed under aortic cross-clamping. After each distal anastomosis, the aortic cross-clamp was released and a reperfusion period of one half the period of ischemia was allowed before the next distal anastomosis was started. The other surgeon (L.H.) performed coronary bypass surgery after coronary perfusion.
LV FUNCTION EARLY AFTER CPB

nary perfusion with cold (i°C) Bretschneider cardioplegic solution without blood (composition per 1,000 ml: 15 mM NaCl; 9 mM KCl; 1 mM K hydrogen-2-oxoglutamate; 4 mM MgCl-2-H2O; 0.015 mM CaCl2-2 H2O; 18 mM histidine HCl-H2O; 180 mM histidine; 2 mM tryptophane; and 30 mM mannitol). Patients were randomly assigned to one of the two collaborating surgeons into two equal groups.

Venous drainage during CPB was obtained with a twostage venous cannula inserted into the right atrium. A ventricular sump was inserted into the left ventricle through the right superior pulmonary vein. Perfusion flow on CPB was 2.4 ± m^2·min^-1 in nonpulsatile mode. Patient body temperatures 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.

Experimental Protocol

The heart was paced for the duration of the protocol at a fixed rate of 90 bpm in atroventricular sequential mode, with an atrioventricular interval of 150 ms. No vasoactive or inotropic drugs were allowed during the study.

Measurements were obtained with the ventilation suspended at end-expiration. Measurements consisted of high-speed recordings of digitized electrocardiographic and LV pressure tracings and echocardiographic images on videotape. These data were recorded during a progressive increase of systolic and diastolic LV pressures obtained by tilting the caudal part of the surgical table by 45 degrees, thus elevating the patients' legs. Measurements of pressure and dimension data were synchronized by sending a synchronized electronic signal at the beginning and at the end of the recording. Care was taken to have at least 15 consecutive beats for analysis. After recording, the surgical table was returned to the horizontal position.

Baseline measurements (before CPB) were obtained when the surgical preparation was completed. After this measurement, the ventricular catheter was removed, the venous cannula inserted, and CPB initiated. 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, the ventricular pressure catheter was repositioned in the LV cavity and patients were separated from CPB. The heart was paced again and filled until a pulmonary capillary wedge pressure of 13 to 15 mmHg or a central venous pressure of 8 to 10 mmHg was achieved. When, after termination of CPB, cardiac index exceeded 2 l·m^-2·min^-1 with a systolic systemic arterial pressure greater than 75 mmHg or a mean arterial pressure greater than 50 mmHg, the venous cannula was withdrawn and the experimental protocol was resumed. Measurements were obtained immediately after stabilization following venous decannulation (time 0) and after 5 (time 5), 10 (time 10), and 15 (time 15) min.

Protocol 1: Recovery of Left Ventricular Function Early after Separation from Cardiopulmonary Bypass: Effects of Surgical Technique of Coronary Bypass Grafting. Adequate data for analysis were obtained in 24 of the 30 patients. In one patient in Group A, atrioventricular sequential pacing was not possible in the pre-CPB period because of frequent supraventricular extrasystoles. In one patient in Group B, no high-quality transgastric echocardiographic images suitable for analysis were obtained. Two patients were excluded because they required nitroglycerin before and immediately after CPB to control their hemodynamic parameters (one patient in each group). Two other patients were excluded because they needed inotropic support with a continuous infusion of 5 μg·kg^-1·min^-1 dobutamine (one in each group).

Protocol 2: Recovery of Left Ventricular Function Early after Separation from Cardiopulmonary Bypass: Effects of Preload Management Regimens. To evaluate possible underlying physiologic mechanisms that regulate LV function early after separation from CPB, a second protocol was started in which a different preload management was followed. These patients were also randomly assigned into two equal groups to the two collaborating surgeons. Adequate data for analysis were obtained in 12 of 14 patients (Group C). Two patients were excluded because no high-quality transgastric echocardiographic images suitable for analysis were obtained. In the patients enrolled in protocol 2, the separation procedure was adapted by using a different preload management at the end of CPB. The heart was filled until a pulmonary capillary wedge pressure of 13 to 15 mmHg or a central venous pressure of 8 to 10 mmHg was achieved 10 min before anticipated separation from CPB. Total reperfusion time in these patients was also 50% of the aortic cross-clamp time, which means that reperfusion time was identical in both groups. The heart was paced and allowed to eject while flow on CPB was slightly reduced (maximum, 15%) to prevent emptying of the venous reservoir of the extracorporeal circuit. This situation was kept

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stable for 10 min and then separation from CPB was initiated. For both protocols, separation procedures were standardized to take 3 min in all patients.

Surgery was uncomplicated in all patients studied and no patients developed a perioperative infarction based on the appearance of elevated creatine kinase-MB > 20 or new Q waves on an electrocardiogram. Table 1 summarizes the clinical demographic and intraoperative data of the patients included in the study.

Data Analysis

End-diastolic pressure was timed at the peak of the R wave on the electrocardiogram. The first derivative of LV pressure (dp/dt) was calculated using digitized data with a seven-point smoothing algorithm.

Echocardiographic data were recorded on VHS videotape (Panasonic, AG-7330, Matsushita, Japan) and analyzed off-line blinded from the LV pressure data. 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 was not readily available, en-diastole and end-systole were measured when the electrocardiograph-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 end-diastole and end-systole were timed in the same way in the consecutive measurements of each patient. Endocardial borders were manually outlined from the video screen with a trackball. Images were evaluated according to the position and quality scores proposed by London and associates. Only patients with a position score of 1 (optimal short-axis orientation) and a quality score of 3 (good endocardial and epicardial resolution) were included 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 Hel-lige GmbH, Freiburg, Germany). The measured cross-sectional area corresponded to $\pi \cdot r^2$. Assuming a spherical model, ventricular cavity volume (V) was calculated with the formula: $V = (4/3) \pi r^3$. The measured cross-sectional cavity areas were reported in the tables and derived cavity volumes were used to compute ventricular systolic elastance and diastolic stiffness. Regional wall motion abnormalities may influence the accuracy of calculating ventricular volumes based on a spherical model using a radius calculated from cross-sectional areas measured by echocardiography. In our study, none of the patients exhibited wall motion abnormalities such as dyskinetic or akinetic segments. All patients exhibiting akinetic or dyskinetic regional segment wall behavior also had ejection fractions less than 35% and were already excluded from the protocol for this reason.

Ten to 15 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:

$$P = A \cdot e^{k \cdot d - V} + B$$

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

Systolic performance was assessed by evaluating the end-systolic pressure/volume relation. End-systolic volume was taken as minimal systolic area and end-systolic pressure was defined as pressure at dp/dt_min. The corresponding systolic pressure and volume data were fit by linear least-squares analysis to the following equation:

$$P = E\text{s}(V - V_0)$$

where $P = LV$ pressure, $E\text{s}$ = the slope of the systolic pressure – volume relation, $V$ = LV systolic volume, and $V_0$ = the volume intercept of the systolic pressure – volume relation. Sample correlation coefficients of the end-diastolic and the end-systolic pressure-volume relationship yielded values of $r > 0.92$ in all patients.
In addition, mean arterial pressure, mean pulmonary arterial pressure, right atrial pressure, and cardiac index were measured using the thermodilution technique. These variables were used to calculate systemic vascular resistance with the equation:

\[
\text{SVR} = \frac{\text{MAP} - \text{RAP}}{\text{CO}} \times 80
\]

Left ventricular stroke work index were calculated using the equation:

\[
1.36 \times (\text{MAP} - \text{LVEDP}) \times \text{SI}/100
\]

where LVEDP is left ventricular end-diastolic pressure and SI represents the stroke index.

**Statistics**

Data for protocol 1 were analyzed using a two-factor analysis of variance for repeated measurements to assess the effects of time in both types of surgical procedure. Interaction analysis showed whether the type of surgical procedure had a significant effect on the repeated measurements. Post-test hypothesis used the Scheffé F-test when appropriate. Measurements in both surgical techniques appeared to be identical for all parameters measured. Data from protocol 1 thus were pooled and compared with data from protocol 2 using a two-factor analysis of variance for repeated measurements to assess the effects of time in both types of preload management before separation from CPB. Interaction analysis showed whether the preload management regime had a significant effect on the repeated measurements. Post-test hypothesis used the Scheffé F-test when appropriate. Pre- and intraoperative data between both groups were compared using Fischer’s exact test. Data were reported as means ± 1 SEM. Statistical significance was accepted at \( P < 0.01 \).

**Results**

**Protocol 1: Recovery of Left Ventricular Function Early after Separation from Cardiopulmonary Bypass: Effects of the Technique for Coronary Surgery**

Data on LV function in groups A and B, at baseline, time 0, time 5, time 10, and time 15 are summarized in table 2. Compared with baseline data, LV data at times 0 and 5 showed higher end-diastolic pressure, lower peak LV pressure, and decreased systolic function (dP/dt\(_{\text{max}}\)). From time 0 to time 10, a rapid recovery of LV function was observed: end-diastolic pressure decreased, peak LV pressure recovered, and systolic function improved to baseline levels. dP/dt\(_{\text{max}}\) remained lower than at baseline throughout the entire observation period. Left ventricular data at the different points of measurement were similar in both groups. Interaction analysis showed no difference in the effect of time on recovery of LV function for both groups.

Hemodynamic data in groups A and B at baseline and at times 0, 5, 10, and 15 are summarized in table 3. Compared with baseline, mean arterial pressure was lower after sepsis from CPB, whereas mean pulmonary arterial pressure and right atrial pressure were increased. These data returned to baseline within 10 min after separation from CPB. Cardiac Index (CI) was also depressed at time 0 and returned progressively toward baseline values within 10 min. Systemic vascular resistance was decreased after CPB and remained lower throughout the observation period. Left ventricular stroke work index was decreased after CPB but also returned to baseline values within 10 min. All hemodynamic data at the different points of measurement were similar in both groups and there was no different effect of time on recovery of hemodynamics for both groups.

Load-independent evaluation of LV function was obtained by analyzing end-systolic and end-diastolic pressure-volume data. A representative set of systolic and diastolic pressure-volume data from patient 13 are shown in figure 1 (left). From time 0 (open squares) to time 10 (open circles), the systolic pressure-volume relation became steeper, whereas the diastolic pressure-volume relation shifted downward, confirming a rapid improvement of systolic and diastatic LV function. These two aspects of cardiac function were quantitatively assessed by the slope Ees of the systolic pressure-volume relation and by the ventricular stiffness constant Kc of the diastolic pressure-volume relation for all observations in both groups (fig. 1, right panel). Ees decreased significantly after CPB but returned to baseline values within 10 min and remained constant thereafter in both groups. Evolution of Ees was similar in both groups. Kc increased after CPB, returned to baseline values within 10 min, and remained also constant thereafter. Evolution of Kc was also similar in both groups. The volume-axis intercept (VOes) at time 0 was de-
Table 2. Left Ventricular Data of Protocol 1 at Baseline and Time 0, 5, 10, and 15

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Time 0</th>
<th>Time 5</th>
<th>Time 10</th>
<th>Time 15</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>EDP (mm Hg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>group A</td>
<td>12 ± 2</td>
<td>19 ± 2*</td>
<td>16 ± 1*</td>
<td>14 ± 2</td>
<td>14 ± 1</td>
<td>0.008</td>
</tr>
<tr>
<td>group B</td>
<td>12 ± 2</td>
<td>18 ± 1*</td>
<td>16 ± 1*</td>
<td>15 ± 2</td>
<td>14 ± 1</td>
<td>0.009</td>
</tr>
<tr>
<td>P between groups</td>
<td></td>
<td>n.s.</td>
<td>n.s.</td>
<td>n.s.</td>
<td>n.s.</td>
<td></td>
</tr>
<tr>
<td>Peak LVP (mm Hg)</td>
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</tr>
<tr>
<td>group A</td>
<td>96 ± 8</td>
<td>86 ± 4*</td>
<td>89 ± 3*</td>
<td>92 ± 2</td>
<td>93 ± 3</td>
<td>0.007</td>
</tr>
<tr>
<td>group B</td>
<td>95 ± 6</td>
<td>84 ± 2*</td>
<td>89 ± 2*</td>
<td>91 ± 3</td>
<td>93 ± 3</td>
<td>0.005</td>
</tr>
<tr>
<td>P between groups</td>
<td></td>
<td>n.s.</td>
<td>n.s.</td>
<td>n.s.</td>
<td>n.s.</td>
<td></td>
</tr>
<tr>
<td>dp/dt max (mm Hg/s)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>group A</td>
<td>976 ± 89</td>
<td>616 ± 34*</td>
<td>703 ± 51*</td>
<td>799 ± 48*</td>
<td>830 ± 38</td>
<td>0.002</td>
</tr>
<tr>
<td>group B</td>
<td>983 ± 125</td>
<td>635 ± 45*</td>
<td>721 ± 33*</td>
<td>805 ± 37*</td>
<td>817 ± 37</td>
<td>0.004</td>
</tr>
<tr>
<td>P between groups</td>
<td></td>
<td>n.s.</td>
<td>n.s.</td>
<td>n.s.</td>
<td>n.s.</td>
<td></td>
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<tr>
<td>dp/dt min (mm Hg/s)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>group A</td>
<td>692 ± 64</td>
<td>573 ± 21*</td>
<td>604 ± 24*</td>
<td>642 ± 38</td>
<td>659 ± 36</td>
<td>0.008</td>
</tr>
<tr>
<td>group B</td>
<td>705 ± 56</td>
<td>591 ± 41*</td>
<td>623 ± 44*</td>
<td>656 ± 35</td>
<td>652 ± 43</td>
<td>0.009</td>
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<tr>
<td>P between groups</td>
<td></td>
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<td>n.s.</td>
<td>n.s.</td>
<td>n.s.</td>
<td></td>
</tr>
<tr>
<td>ED area (cm²)</td>
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<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>group A</td>
<td>21 ± 1</td>
<td>21 ± 2</td>
<td>20 ± 1</td>
<td>20 ± 1</td>
<td>21 ± 1</td>
<td>n.s.</td>
</tr>
<tr>
<td>group B</td>
<td>20 ± 1</td>
<td>20 ± 1</td>
<td>19 ± 1</td>
<td>20 ± 1</td>
<td>20 ± 1</td>
<td>n.s.</td>
</tr>
<tr>
<td>P between groups</td>
<td></td>
<td>n.s.</td>
<td>n.s.</td>
<td>n.s.</td>
<td>n.s.</td>
<td></td>
</tr>
<tr>
<td>ES area (cm²)</td>
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<td></td>
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</tr>
<tr>
<td>group A</td>
<td>11 ± 2</td>
<td>13 ± 1*</td>
<td>13 ± 1*</td>
<td>12 ± 1</td>
<td>11 ± 1</td>
<td>0.007</td>
</tr>
<tr>
<td>group B</td>
<td>11 ± 3</td>
<td>13 ± 2*</td>
<td>13 ± 1*</td>
<td>12 ± 1</td>
<td>12 ± 1</td>
<td>0.009</td>
</tr>
<tr>
<td>P between groups</td>
<td></td>
<td>n.s.</td>
<td>n.s.</td>
<td>n.s.</td>
<td>n.s.</td>
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<tr>
<td>Area EF (%)</td>
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<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>group A</td>
<td>42 ± 3</td>
<td>35 ± 3*</td>
<td>37 ± 4*</td>
<td>40 ± 5</td>
<td>41 ± 3</td>
<td>0.001</td>
</tr>
<tr>
<td>group B</td>
<td>41 ± 4</td>
<td>33 ± 2*</td>
<td>36 ± 3*</td>
<td>38 ± 4</td>
<td>40 ± 2</td>
<td>0.001</td>
</tr>
<tr>
<td>P between groups</td>
<td></td>
<td>n.s.</td>
<td>n.s.</td>
<td>n.s.</td>
<td>n.s.</td>
<td></td>
</tr>
</tbody>
</table>

Data are means ± SEM; EDP = end-diastolic pressure; LVP = left ventricular pressure; ED = end-diastolic; ES = end-systolic; EF = ejection fraction; P = significance of differences between repeated measurements; P between groups = significance of differences between groups; n.s. = not significant.

* Statistically significant difference from baseline for P < 0.01.

Increased compared with baseline and progressively returned to baseline values within 15 min. This change was comparable in both groups (group A: baseline, 11 ± 11 ml; time 0, −37 ± 14 ml; time 5, −18 ± 5 ml; time 10, −7 ± 6 ml; time 15, 5 ± 7 ml [significance of differences between repeated measurements: P = 0.008]; group B: baseline, 12 ± 13 ml; time 0, −41 ± 16 ml; time 5, −13 ± 6 ml; time 10, −11 ± 5 ml; and time 15, 7 ± 4 ml [P = 0.004]). The pressure-axis intercept (B) was 7 ± 3 mmHg for group A and 8 ± 2 mmHg for group B and remained constant at all times of measurement in both groups. Given the limited range of obtained pressure and dimension measurements, no further consideration was given to these intercepts.

Recovery of systolic and diastolic LV function early after separation from CPB was confirmed by evaluating other indices of myocardial function. Figure 2 (upper) displays the effects of increasing end-diastolic volume (by elevating patients’ legs) on stroke volume for each patient in groups A and B for the different times of measurement. For a comparable increase in end-diastolic volume, increases in stroke volume were significantly higher at time 10 than at time 0 (P = 0.005). A linear relation was found between the increase in end-diastolic volume and the increase in stroke volume for time 0 (r = 0.89; P = 0.004) and for time 10 (r = 0.91; P = 0.007). This was also apparent when effects of increasing end-diastolic volumes on changes in dp/dt max were compared at the different times of measurement.

In group A at time 0, leg raising increased end-diastolic volume by 11 ± 3 ml, with a corresponding change in dp/dt max of 20 ± 7 mmHg/s. At time 10, leg raising increased end-diastolic volume by 12 ± 6 ml, with a corresponding increase in dp/dt max of 110 ± 12 mmHg/s. This increase was significantly different (P = 0.0048). The same phenomenon was noticed in patients in group

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**Table 3. LV Function**

MAP (mm Hg) group A group B P between groups
RAP (mm Hg) group A group B P between groups
CI (l/min/m²) group A group B P between groups
SVR (dyne · s · cm⁻⁵) group A group B P between groups
LVSWI group A group B P between groups

Data are means ± SEM (l/min/m²) and l/min

LVSWI = LV stroke work index

B. At time 0, leg raising by 14 cm raised dp/dt max. Overall, dp/dt max increased significantly with LVEDV.

The natriuretic peptide evaluation was also performed in groups A and B (fig. 2, lower), with end-diastolic and diastolic filling pressures.

Protocol 2: Early Post-CPB Recovery

Early Post-CPB Recovery

CPB was terminated in group A.

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Table 3. Hemodynamic Data of Protocol 1 at Baseline and Time 0, 5, 10, and 15

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Time 0</th>
<th>Time 5</th>
<th>Time 10</th>
<th>Time 15</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAP (mm Hg)</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>group A</td>
<td>84 ± 5</td>
<td>64 ± 7*</td>
<td>68 ± 5*</td>
<td>74 ± 6</td>
<td>80 ± 5</td>
<td>0.006</td>
</tr>
<tr>
<td>group B</td>
<td>82 ± 7</td>
<td>66 ± 5*</td>
<td>71 ± 4*</td>
<td>76 ± 5</td>
<td>81 ± 6</td>
<td>0.008</td>
</tr>
<tr>
<td>P between groups</td>
<td>n.s.</td>
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<td>n.s.</td>
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</tr>
<tr>
<td>MPAP (mm Hg)</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>group A</td>
<td>17 ± 3</td>
<td>24 ± 4*</td>
<td>22 ± 4*</td>
<td>19 ± 3</td>
<td>19 ± 4</td>
<td>0.009</td>
</tr>
<tr>
<td>group B</td>
<td>18 ± 2</td>
<td>25 ± 5*</td>
<td>22 ± 4*</td>
<td>20 ± 4</td>
<td>18 ± 4</td>
<td>0.009</td>
</tr>
<tr>
<td>P between groups</td>
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<td>n.s.</td>
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<tr>
<td>RAP (mm Hg)</td>
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<tr>
<td>group A</td>
<td>7 ± 2</td>
<td>12 ± 3*</td>
<td>10 ± 3</td>
<td>9 ± 4</td>
<td>8 ± 3</td>
<td>0.009</td>
</tr>
<tr>
<td>group B</td>
<td>8 ± 3</td>
<td>13 ± 2*</td>
<td>11 ± 2</td>
<td>9 ± 3</td>
<td>9 ± 3</td>
<td>0.009</td>
</tr>
<tr>
<td>P between groups</td>
<td>n.s.</td>
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<td>n.s.</td>
<td>n.s.</td>
<td>n.s.</td>
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<tr>
<td>CI (l/min)</td>
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<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>group A</td>
<td>2.5 ± 0.4</td>
<td>2.2 ± 0.3*</td>
<td>2.4 ± 0.5</td>
<td>2.7 ± 0.3</td>
<td>3.0 ± 0.5</td>
<td>0.008</td>
</tr>
<tr>
<td>group B</td>
<td>2.6 ± 0.3</td>
<td>2.1 ± 0.2*</td>
<td>2.4 ± 0.4</td>
<td>2.6 ± 0.2</td>
<td>2.8 ± 0.4</td>
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<tr>
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<td>n.s.</td>
<td>n.s.</td>
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<tr>
<td>SVR (dyne. sec. cm⁻²)</td>
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<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>group A</td>
<td>1193 ± 215</td>
<td>992 ± 125*</td>
<td>994 ± 144*</td>
<td>995 ± 115*</td>
<td>1078 ± 133</td>
<td>0.01</td>
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<tr>
<td>group B</td>
<td>1219 ± 108</td>
<td>995 ± 110*</td>
<td>1001 ± 141*</td>
<td>1004 ± 121*</td>
<td>1091 ± 112</td>
<td>0.008</td>
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<tr>
<td>P between groups</td>
<td>n.s.</td>
<td>n.s.</td>
<td>n.s.</td>
<td>n.s.</td>
<td>n.s.</td>
<td></td>
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<tr>
<td>LVESVI (g/m³)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>group A</td>
<td>29 ± 7</td>
<td>18 ± 6*</td>
<td>21 ± 4*</td>
<td>27 ± 3</td>
<td>31 ± 6</td>
<td>0.004</td>
</tr>
<tr>
<td>group B</td>
<td>28 ± 6</td>
<td>17 ± 4*</td>
<td>22 ± 4*</td>
<td>26 ± 6</td>
<td>32 ± 5</td>
<td>0.007</td>
</tr>
<tr>
<td>P between groups</td>
<td>n.s.</td>
<td>n.s.</td>
<td>n.s.</td>
<td>n.s.</td>
<td>n.s.</td>
<td></td>
</tr>
</tbody>
</table>

Data are means ± SEM.

MAP = mean arterial pressure; MPAP = mean pulmonary arterial pressure; RAP = right atrial pressure; CI = cardiac index; SVR = systemic vascular resistance; LVESVI = left ventricular stroke work index.

* Statistically significant difference from baseline for $P < 0.01$.

B: At time 0, leg raising increased end-diastolic volume by $14 ± 5$ ml, with a corresponding increase in $dP/dt_{\text{max}}$ of $25 ± 8$ mmHg/s, whereas at time 10, an increase in end-diastolic volume of $13 ± 6$ ml increased $dP/dt_{\text{max}}$ with $120 ± 14$ mmHg/s ($P = 0.0062$).

The recovery of diastolic function was confirmed by evaluating the effects of leg raising on end-diastolic volume and end-diastolic pressure for each patient in groups A and B. In the different times of measurement (fig. 2, lower), at time 10, corresponding increases in end-diastolic volume induced lower increases in end-diastolic pressures, confirming recovery of ventricular compliance and diastolic function.

Protocol 2: Recovery of Left Ventricular Function Early after Separation from Cardiopulmonary Bypass: Effects of Different Preload Management Regimens

Recovery of ventricular function after separation from CPB was evaluated in 12 patients after a different regimen of preload management. In these patients, the hearts were optimally filled 10 min before anticipated separation time and the heart was allowed to eject. Data obtained in this group of patients (Group C) were compared with the pooled data of groups A and B. Aortic cross-clamp time, CPB time, and total reperfusion time of patients in group C were similar to those in patients in groups A and B.

Table 4 summarizes left ventricular and hemodynamic data of patients in group C. Baseline data were similar to data for patients in groups A and B. Left ventricular and hemodynamic parameters of patients in Group C remained unchanged at the different times of measurement and were comparable to values obtained at baseline. Only $dP/dt_{\text{max}}$ and SVR were decreased in a similar way as in groups A and B.

Data on Ees and Kc are displayed in figure 3 (filled squares) and compared with pooled data on Ees and Kc of protocol 1 (filled circles). Ees and Kc remained unchanged at the different times of measurement ($P$ for
repeated measurements = 0.491 and 0.631, respectively). Accordingly, there was a significant difference between the data obtained in both protocols (Ees: P = 0.002; Kc: P = 0.003). Compared with baseline, systolic and diastolic LV functions in protocol 1 (normal separation procedure) were impaired after separation from CPB but recovered within 10 min. In protocol 2 (modified separation procedure), systolic and diastolic LV function were not impaired after separation from CPB and remained stable throughout the observation period.

Discussion

Maintenance or improvement of cardiac function is an important goal in the postoperative phase after open heart surgery, because adequate cardiac function ultimately determines patient survival. In patients undergoing coronary bypass grafting, various results on recovery of postoperative ventricular function have been reported. Most studies mention a decrease in ventricular function between 2 and 6 h after operation, with a return to normal within 24 h to 7 days. However, studies on recovery of ventricular function after coronary artery surgery do not always mention impaired function after surgery. Reduto and colleagues reported variable effects on LV ejection fraction after surgery. Of the 57 patients studied, 26 had a decrease in LV ejection fraction at the end of the measurements (110 min after the end of surgery), whereas 25 patients exhibited an increase in LV ejection fraction. By the time of the discharge study (7 days later), LV ejection fraction had returned to preoperative values in 24 of 26 and in 23 of 25 patients, respectively. Six of the 57 patients had no change in ejection fraction after operation. Mangano described two distinct patient populations with regard to the ventricular dysfunction-recovery sequence: (1) a moderate biventricular dysfunction immediately after CPB (first measurement made 15 min after the end of CPB) with almost complete recovery within 4 h; and (2) more severe dysfunction with no recovery even after 24 h.

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Thus, although various dysfunction–recovery sequence patterns were described, ventricular dysfunction is a common phenomenon after coronary bypass surgery. All of the previously mentioned studies focused on recovery patterns during the first hours and days after surgery, with the earliest reported evaluation of ventricular function made 15 min after the end of CPB. Little is known about the short-term effects of coronary artery surgery on myocardial function. Recently Gorcsan and associates\(^\text{67}\) found pressure-area estimates of end-systolic elastance, maximal elastance, and preload-recruitable stroke force to be significantly decreased immediately after the end of CPB. Load-dependent measures of LV function, such as stroke volume, cardiac output, and fractional area change, were unchanged after surgery in these patients. However, that study did not describe recovery patterns during the first minutes after CPB. We evaluated that in the absence of confounding interventions such as inotropic or vasodilating support. A progressive improvement of systolic and diastolic ventricular function was observed within the first 10 min after separation from CPB. For technical reasons (further course of the operation), ventricular pressure data could not be obtained beyond 15 min and therefore our observations were limited to the first 15 min after CPB. Ventricular function at time 15 was not entirely similar to baseline because \(\Delta P/\Delta t_{\text{max}}\) was still lower at time 10. Based on these observations and the results reported in the literature, it seems that recovery of ventricular function after cardiac surgery is rather complex and may occur in different phases, with one period of early progressive recovery of function within 10 to 15 minutes after separation from CPB and a second period of recovery with return of parameters of ventricular function toward preoperative values only after several hours or even days.

Time course of recovery suggested a mechanism that might be related to restoration of preload. In isolated cardiac muscle, an abrupt increase in diastolic length resulted in an immediate increase in systolic force, which was followed by a secondary slow increase in force in about 10 min.\(^{21-23}\) These changes in systolic function were also observed in the intact canine heart.\(^{24,25}\) Based on the similarity of the time dependency of preload-dependent changes in cardiac function and data of the present study, we hypothesized that changes in systolic and diastolic function might be related to time-dependent increase in LV function after acute volume loading immediately before separation from CPB.

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**Fig. 2.** (Upper) Changes in end-diastolic volume (EDV) (induced by raising the legs) are plotted against corresponding changes in stroke volume for each patient in Group A (open icons) and Group B (filled icons) at time 0 and time 10. At time 10, similar increases in EDV induced greater increases in stroke volume, suggesting enhanced contractile function. (Lower) Changes in EDV (induced by raising the legs) are plotted against corresponding changes in end-diastolic pressure (EDP) for each patient in Group A (open icons) and Group B (filled icons) at time 0 and time 10. At time 10, similar increases in EDV induced lower increases in EDP, suggesting enhanced ventricular function.
We tested this hypothesis by altering the regimen of preload management before the separation procedure. When preload was optimized 10 min before anticipated separation time and the heart was allowed to eject, it appeared that diastolic and systolic function immediately after termination of CPB reached values that were otherwise obtained only after 10 min and that were similar to baseline values. These data therefore suggested that by optimizing preload conditions, 10 min before anticipated separation time, the characteristic time-dependent improvement of systolic and diastolic function after CPB was no longer observed. Instead ventricular function was optimal from time 0 and remained constant during the observation period that followed.

A possible explanation for this phenomenon thus might be the time-dependency of autoregulation of ventricular function by preload. This was characterized by an immediate increase in performance with administration of preload before separation from CPB, followed by a more gradual improvement in ventricular function within the next 10 min. Time-dependent changes in contractility related to preload were described extensively in vitro. The acute increase in contractility was attributed to a length-dependent interaction between the contractile proteins and calcium, whereas the secondary, more gradual increase in myocardial function appeared to be related to intracellular calcium fluxes, as shown with acouerin signals.

More recently, similar findings were reported in the intact canine heart. These changes were not due to neural or humoral factors but represented length-dependent alterations in excitation-contraction coupling, which were reviewed earlier. Our study suggested that this particular inotropic mechanism might be clinically relevant and present with a similar time course in the cardiac patient. As far as we know, changes in diastolic function related to preload were not previously described in vitro, either experimentally or clinically. In isolated cardiac muscle, however, this phenomenon has been described: Cardiac muscle becomes stiffer at lower preload and more compliant at optimal preload each time within 10 min after the acute change in preload was induced.

The observed differences between both regimens of preload management could not be attributed to differences in study population or pre- and perioperative conditions because there were no differences in demographic and intraoperative parameters. Number of grafts, aortic cross-clamp time, reperfusion time, and total CPB time were similar in all groups. However, possible other mechanisms must be considered in our observations. Pulsatile perfusion to the heart and the systemic circulation developed 10 min earlier in patients in group C than in patients in groups A and B. Earlier start of pulse pressure may enhance perfusion of peripheral organs and the heart itself, and this could contribute to the functional differences.

Several investigators have studied the effects of pulsatil flow on CPB. Pulsatile perfusion of the nonbeating heart was shown to increase subendocardial perfusion and to maintain a better endocardial-to-epicardial flow ratio. Others, however, failed to confirm these observations.

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Fig. 3. Mean data (± SEM) on systolic (Es [upper]) and diastolic (Kc [lower]) function at the different times of measurement (before the start of cardiopulmonary bypass [CPB; Baseline]; immediately after separation from CPB [time 0]; and 5 min [time 5], 10 min [time 10], and 15 min [time 15] later). Data of the two protocols are shown. In protocol 1 (filled circles), preload was optimized just before the start of the separation procedure from CPB. In protocol 2 (filled squares), preload was optimized 10 min before the anticipated separation time and kept constant during the period before the separation procedure was started. Duration of the separation procedure was similar in both groups. In protocol 1, ventricular function after separation from CPB was impaired, with a decrease in Es and an increase in Kc, and a progressive improvement of ventricular function within the first 10 min after separation from CPB. These observations were not present in protocol 2, in which ventricular function remained unchanged and comparable to baseline values. Difference between both groups is statistically significant at P < 0.01.

Observations either in the beating or the fibrillating heart.29-32 In the last few years, increasing evidence was gathered on the impact of the inflammatory response to CPB on postoperative myocardial function. It was recently suggested that inflammatory mediators released during CPB may adversely affect postoperative ventricular function.83 Although in our study reperfusion time was similar in both protocols, we cannot preclude the fact that the start of pulsatile flow throughout myocardial vasculature 10 min before anticipated time of separation of CPB might have induced a better washout of such inflammatory mediators. This might result in earlier better ventricular performance. Several drugs have been reported to blunt effects of CPB and reperfusion-induced inflammatory mediators, among these glucocorticoids84 and aprotinin.85 All patients in both protocols of the present study routinely received 2 g methylprednisolone after induction of anesthesia and 2.106 KIU aprotinin in the priming fluid of the CPB circuit. Thus it is less likely that the effects of the preload management regimen depended on mechanisms that might be influenced by one of these drugs.

We carefully omitted inotropic or vasoactive medication in this study to evaluate recovery of ventricular function without these confounding elements. This means that patients necessitating inotropic or vasoactive support were not included in the present data analysis. This might imply that a selection has occurred of patients with good ventricular and hemodynamic function, including mainly patients in whom rapid recovery of ventricular function might be expected. In this selection of patients it seems reasonable to observe the recovery of cardiac function for 10 min, rather than rushing pharmacologic interventions. This conclusion, however, might not apply for patients whose hearts have poor ventricular function.

Limitations of the Study

A first limitation of our study is the use of a single two-dimensional plane to describe changes in overall LV volume. The accuracy of calculating ventricular volumes based on a spherical model using a radius calculated from cross-sectional areas measured by echocardiography may be impaired in the presence of regional wall motion abnormalities. However, none of the patients we evaluated had dysskinetic or akinetic segments on echocardiographic examination, so this phenomenon did not influence the data.

We used fluid-filled catheters to measure LV pressures. All individual measurements conformed to the dynamic responses required for fluid-filled pressure transducer systems, which indicates that pressure and dP/dt measurements were reliable. The only drawback is that measurement of time intervals might be delayed with respect to measurements by micromanometers. Thus we gave no further consideration to measuring time intervals.

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Loading conditions were altered with leg elevation to construct pressure-dimension relations. This implies that the present data cannot simply be compared quantitatively with data obtained by other means of altering loading conditions. In addition, the simple transformation of area data to volume data will provide the smallest possible ventricle (sphere based on short-axis area) and therefore elevate the slope of the end-systolic and end-diasstolic pressure-volume relations. Determining end-systolic and end-diastolic pressure-volume relations was based on pressure and dimension data that were obtained for a relatively limited range. This was due to the specificity of the clinical situation, which did not allow us to vary ventricular loading conditions over a wide range of pressures and dimensions. This implies that quantitative determination of axis intercepts may be hazardous. The repetitive observations in the same patient, however, were within the range of pressure and dimension data, and thus we could compare repetitive measurements for one patient. In addition, recovery of systolic and diastolic ventricular function early after CPB was confirmed by other determinants of ventricular function.

The present data obtained in patients with good LV function who had coronary artery surgery showed improvement of both systolic and diastolic ventricular function immediately after separation from CPB, which recovered progressively within the first 10 min after CPB. Restoring preload to normal 10 min before anticipated separation from CPB and allowing the heart to eject during this period prevented this transient impairment of ventricular function after CPB. The underlying mechanisms of this phenomenon remain to be established definitively. A possible explanation is that this recovery reflected time dependency of regulation of ventricular function by preload.

References


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