Immediate enhancement of left ventricular relaxation by coronary artery bypass grafting: intraoperative assessment


ABSTRACT  We investigated the effect of coronary artery bypass grafting on the rate of left ventricular relaxation as defined by the time constant for isovolumetric relaxation, T, measured in milliseconds. Completeness of relaxation at rapid heart rates was determined by comparison of the relationship between left ventricular pressure and echocardiographic left ventricular cross-sectional cavity area during rapid ventricular pacing with that obtained after a prolonged diastole when the ventricle was maximally relaxed. Twelve patients with coronary artery disease had significantly higher T values (94.5 ± 6.2) than six patients without coronary artery disease who were undergoing other open heart procedures (39.5 ± 5.0, p < .001). T was significantly reduced after coronary artery bypass grafting (68.2 ± 5.1, p = .007), but was unchanged in the six control patients after cardiopulmonary bypass (37.8 ± 4.5, p = .54). Similar changes were found during rapid pacing to 100, 120, and 140/min. Incomplete relaxation was detected in three of 10 (heart rate 120 beats/min) and nine of 11 (heart rate 140 beats/min) patients with coronary artery disease and this decreased to 0 of 10 (heart rate 120 beats/min) and six of 11 (heart rate 140 beats/min) patients after coronary artery bypass. Incomplete relaxation before bypass at a heart rate of 120 beats/min averaged 0.9 ± 0.3 mm Hg. At a heart rate of 140 beats/min, incomplete relaxation averaged 5.6 ± 1.6 mm Hg before and 1.4 ± 0.5 mm Hg after bypass. Intake of β-blockers or calcium-channel blockers, body temperature, and systolic blood pressure were not found to be related to these changes. We conclude that immediately after coronary artery bypass relaxation of left ventricular muscle is enhanced and incomplete relaxation at rapid heart rates is less likely. The most probable cause of this improvement in ventricular relaxation after coronary artery bypass grafting is relief of ischemia.


RELAXATION of left ventricular muscle during diastole is an active, energy-requiring process that is prolonged during or after ischemia. The rate of relaxation can be quantified by a time constant, T, derived from the exponential fall in left ventricular pressure after peak negative dP/dt and before mitral valve opening. The magnitude of T reflects in part the extent to which relaxation is impaired by ischemia. In addition, as T becomes greater, a longer diastolic time is required for the ventricle to relax completely and incomplete relaxation becomes a possibility, particularly at higher heart rates.

Coronary artery bypass grafting (CABG) restores blood flow to ischemic myocardium, which results in immediate improvement in systolic function. The immediate effects of CABG on left ventricular relaxation in man are not known. Reversal of ischemia could result in return of T to the normal range, either immediately after surgery or gradually thereafter. Alternatively, the obligate period of ischemia during cross-clamping of the aorta could result in further impairment of relaxation during the immediate postbypass period. This impairment might then predispose to delayed or incomplete relaxation, which would affect postbypass ventricular compliance and filling. This study was devised to investigate the immediate effect of CABG on left ventricular relaxation as assessed by simulta-
neous transesophageal echocardiography and high-fidelity left ventricular pressure measurements.

**Methods**

**Patient population.** Twelve randomly selected patients scheduled for CABG gave informed consent for the protocol, which was approved by The Johns Hopkins Joint Committee on Clinical Investigation. For comparison, a group of six patients without known coronary artery disease scheduled for other open heart surgery consented to be studied. Four of these patients had atrial septal defects repaired, one underwent closure of a ventricular septal defect, and one had a mitral valve replacement for subacute bacterial endocarditis. Clinical data are summarized in table 1.

**Anesthetic and operative techniques.** All patients received their regularly scheduled medications on the morning of surgery along with anesthetic premedication consisting of 0.1 mg/kg im morphine sulfate, 0.2 to 0.4 mg im scopolamine, and either 10 mg diazepam or 2 mg lorazepam orally. Pulmonary and radial artery catheters were inserted before induction of anesthesia. The anesthetic technique before cardiopulmonary bypass (CPB) consisted of 25 to 50 µg/kg fentanyl supplemented by small doses of diazepam (5 to 20 mg) and/or enflurane (0.5% to 1.5%). Pancuronium, 0.1 mg/kg, provided neuromuscular blockade. During CPB patients received 25 mg sodium thiopental every 15 min that was supplemented by additional fentanyl in some cases.

Aortocoronary grafts were constructed entirely during CPB. Internal mammary arteries were used for grafts to the left anterior descending (LAD) system; all other grafts were constructed with saphenous veins. Distal anastomoses were performed during one period of aortic cross-clamping. Myocardial protection was achieved by 30 to 50 mCi thio-2-[14C]tritiated methylglucamine (Cardioplexia, Miles Laboratory, Elkhart, IN) delivered through aortic root catheters at 25 to 35 mpm saline infusion (in place of sodium lactate) or 25 to 40 mpm potassium chloride infusion (in place of potassium lactate) (mean = 30 mpm) for 10 to 15 min before reperfusion.

**TABLE 1**

<table>
<thead>
<tr>
<th>Patient characteristics</th>
<th>Medications</th>
<th>Cardiac disease</th>
<th>ECG No. of bypasses</th>
<th>Global LV function</th>
<th>Regional function</th>
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<tbody>
<tr>
<td>No. Age Sex BB CB Other disease ECG</td>
<td>LM</td>
<td>IMI ALT</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>1 51 M Yes Yes N 3 VD</td>
<td>5</td>
<td>EF 51% Hypokinesis — IB, AL</td>
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<tr>
<td>2 50 F No Yes P 3 VD</td>
<td>3</td>
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<tr>
<td>3 74 F No Yes Q, N, L 2 VD</td>
<td>3</td>
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<tr>
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<tr>
<td>5 44 F Yes Yes N I 2 VD</td>
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<tr>
<td>6 60 F Yes Yes N 3 VD</td>
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<tr>
<td>7 70 F Yes Yes N 3 VD</td>
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<tr>
<td>8 58 F No Yes N 3 VD</td>
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<tr>
<td>9 50 M No Yes N D, L 3 VD</td>
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<tr>
<td>10 71 M Yes Yes N 3 VD</td>
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<td>Not done Akinesis — I</td>
<td></td>
<td></td>
<td></td>
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<tr>
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<td>EF 37% Akinesis — I; Dyskinesia — AP</td>
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<tr>
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<td>Not done Normal</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>13 34 M No No D MR</td>
<td>N/A</td>
<td>EF 61%* Normal*</td>
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<tr>
<td>14 32 F No No ASD</td>
<td>N/A</td>
<td>EF 66% Normal</td>
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<tr>
<td>15 19 F No No ASD</td>
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<td>Not done Not done</td>
<td></td>
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<tr>
<td>16 23 F No No ASD</td>
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<td>EF &quot;good&quot; Normal</td>
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<td>18 23 F No No ASD</td>
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<td>Not done Not done</td>
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</table>

BB = β-blockers; CB = calcium-channel blockers; N = nitrates; P = premarin; Q = quinidine; L = lasix; I = insulin; D = digoxin; 2 VD = two-vessel coronary artery disease; 3 VD = three-vessel coronary artery disease; MR = mitral regurgitation; ASD = atrial septal defect; VSD = ventricular septal defect; NL = normal; SB = sinus bradycardia; AMI = old anterior myocardial infarction; NSSSTT = nonspecific ST-T wave changes; IVCD = intraventricular conduction delay; ALT = anterolateral T wave inversions; 1° AVB = first-degree atrioventricular block; LAD = left-axis deviation; IMI = old inferior myocardial infarction; ALMI = old anterolateral myocardial infarction; LVH = left ventricular hypertrophy; IT = inferior T wave inversions; RAD = right-axis deviation; IRBBB = incomplete right bundle branch block; PQT = prolonged QT interval; LV = left ventricular.

Global LV function (ventriculography, except * = echocardiography); EF = ejection fraction.

Regional LV function (ventriculography, except * = echocardiography): I = inferior; IB = inferobasilar; A = anterior; AL = anterolateral; AA = anteropapical; AP = apical; L = lateral.
provided by coronary perfusion with 500 ml of cold potassium (30 meq/liter) cardioplegic solution and continuous topical hypothermia with cold saline (4°C). Left ventricular decompression was achieved with pulmonary artery venting. Modest systemic hypothermia (28°C to 30°C) was used. After removal of the aortic cross-clamp, the heart spontaneously debubbled (eight instances) or countershock was applied to restore sinus rhythm (four instances). Proximal anastomoses were then constructed to an isolated portion of the ascending aorta while the patient was rewarmed. Ischemic and CPB times averaged 71 ± 21 and 112 ± 27 min, respectively. Ischemic and CPB times for the non-CABG group averaged 33 ± 17 and 64 ± 42 min. Calcium chloride, 300 to 1000 mg, was administered to eight of 12 patients in the CABG group and two of six of those in the non-CABG group during weaning from CPB and at least 5 min before the postbypass study measurements. No other vasoactive substances were given.

Data acquisition. After induction of general anesthesia and tracheal intubation, a gastroscope tipped with a miniature 3.5 MHz phased-array two-dimensional echocardiographic transducer (Diasonics) was positioned in the esophagus to provide a short-axis left ventricular view through the base of the papillary muscles. Echocardiograms were recorded by a Diasonics CV 3400-R Ultrasonograph. A No. 6F micromanometer-tipped catheter (Millar Instruments, Houston) was advanced into the left ventricle from either the superior pulmonary vein or the aorta. Pressure data from both the micromanometer and its fluid-filled aorta were recorded on a Hewlett-Packard eight-channel recorder, allowing correction for drift in the electronic signal during CPB. Drift was 1 mm Hg or less in all cases. The electronic pressure signal was input to a Hewlett-Packard analog-to-digital converter along with a synchronized square-wave pulse from the echocardiogram for each echocardiographic frame (field rate = 60/sec, frame rate = 30/sec). This permitted subsequent synchronization of left ventricular pressure and cross-sectional cavity area on a frame-by-frame basis.

Control data were obtained after cannulation but before initiation of CPB. Post-CPB data were derived 5 min after discontinuation of CPB (cannulas remained in place). No patient experienced ischemia or significant hemodynamic compromise during data acquisition.

After positioning of monitors, the heart was ventricularly paced to a rate of 100 beats/min at three different filling pressures, achieved by either infusion of volume from the bypass pump or administration of a small bolus of sodium nitroprusside (25 to 50 μg). Simultaneous left ventricular echocardiographic cross-sectional cavity area and electronic pressure recordings were made for 5 sec-intervals, beginning while the heart was being paced and continuing as pacing was terminated and sinus rhythm resumed. Similar recordings were made while pacing to 120 and 140 beats/min (figures 1 and 2). Ventricular pacing was chosen to avoid the tendency for atrioventricular block at the higher heart rates.

Data analysis. The time constant for relaxation, T, was determined by the method of Thompson et al. from dp/dt vs P after peak negative dp/dt yields T as the positive inverse of the slope (figure 3). P0/T, the y intercept, need not be determined. T values were calculated in milliseconds for both paced and un-paced beats that were selected on the basis of absence of artifacts in the pressure waveform. If more than one beat was available for analysis, all beats in which the dp/dt vs P relationship resulted in a correlation coefficient of .80 or greater were averaged.

The influence of long-term intake of β-blockers on T was determined by separating the patients with coronary artery disease into two groups: those who were and those who were not being treated with a β-blocker. The baseline T before CABG and the magnitude of any change in T as a result of CABG, ΔT, were compared for these two groups. Additionally, since calcium channel-blocking agents have been associated with prolongation of T and since all 12 patients with CABG were treated with these agents, an additional four patients not so treated were subsequently studied.

Frame-by-frame echocardiographic left ventricular cross-sectional cavity area was determined with use of a Micronsonics Easy View light-pen digitizer (Indianapolis), both at end-diastole and for single paced beats. "Fully relaxed" pressure-area lines were

![FIGURE 1](image_url)

**FIGURE 1.** Schema of study protocol. The filling pressures were varied between runs with either volume (VOL) or sodium nitroprusside (SNP). The third filling pressure was then used for both fast paced runs. The arrows indicate the time points at which the pacer was turned on and off. The brackets indicate the 5 sec time period during which data were captured by the computer.
FIGURE 2. Left ventricular pressure waveforms recorded during pacing and interruption of pacing. The pressure-area relationship at the end of the ensuing prolonged diastole (arrow) was used to generate "fully relaxed" pressure-area lines.

constructed from simultaneous left ventricular pressures and areas at the end of the prolonged diastole after interrupted pacing at multiple filling pressures. Pressure-area loops for individual paced beats were generated similarly by plotting the natural log of pressure vs left ventricular cross-sectional cavity area for each beat. These single-beat pressure-area loops were compared to the fully relaxed pressure-area line. Incomplete relaxation, when present, was quantified as the pressure difference between the lowest pressure-area point of the paced beat and the fully relaxed pressure-area line (figure 4). Relaxation to within 1 mm Hg of this line was considered complete. Data were analyzed by analysis of variance (ANOVA, Human Systems Dynamics, Northridge, CA). Values were expressed as means ± SEM.

FIGURE 3. Determination of T in a patient with coronary artery disease before revascularization (left) and a patient without coronary artery disease before repair of atrial septal defect (right). T is determined from the relationship between dP/dt and left ventricular pressure between maximum negative dP/dt (max -dP/dt, large arrows) and mitral valve opening (left ventricular end-diastolic pressure of preceding beat, small arrows).

Results

Mean systolic arterial blood pressure and nasopharyngeal temperature are shown in table 2 for each group of patients before and after bypass. These values were comparable between groups and within groups at each time point.

Time constants. Relaxation time constants are displayed in figures 5 to 8. Figure 5 compares the patients in the CABG and non-CABG groups before bypass. T was significantly elevated in patients with coronary disease at each heart rate compared with that in patients with normal coronary arteries. Figures 6 and 7 display T before and immediately after CPB in patients with (figure 6) and without (figure 7) coronary artery disease. T was significantly lower after CPB in the CABG group but was not significantly different in the non-CABG group.

Because of the possible influence of β-blockade on T, values of T for patients who were and were not maintained on these agents were compared (figures 8 and 9). There was no significant difference in either the prebypass T (figure 8), or the amount by which T decreased after bypass, ΔT (figure 9), between patients who were and were not receiving long-term β-blocker therapy. One patient (No. 10) used timolol eye drops and was included in the β-blocker group; however, the
FIGURE 4. Pressure-area loop for a single paced beat in a patient with coronary artery disease (heart rate = 140 beats/min), compared with the fully relaxed pressure-area line, with each line point derived from simultaneous pressure and area at the end of a prolonged diastole (see figure 2). Incomplete relaxation ($\Delta P_{IR}$) of 5.2 mm Hg is demonstrated as the distance between the lowest pressure-area point of the loop and the fully relaxed pressure-area line.

results did not differ when analysis was repeated with this patient included in the no B-blocker group.

Similarly, $\Delta T$ was compared in CABG patients who did and did not receive calcium during weaning from CPB. There was no significant difference in the amount by which $T$ decreased after CABG in these two subgroups (25.5 ± 8.6 vs. 28.0 ± 18.5 at baseline heart rate).

Four additional patients not being treated with calcium-channel blockers but otherwise comparable to the original study population had $T$ values as listed in table 3. $T$ was significantly decreased by revascularization in this group of patients by a magnitude similar to that in the original group.

Incomplete relaxation. Echocardiograms were of satisfactory quality to permit frame-by-frame analysis of single paced beats in 11 of 12 patients in the CABG group (one at a heart rate of 140 beats/min only) and five of six of those in the non-CABG group. Three of 10 patients in the CABG group had incomplete relaxation at a heart rate of 120 beats/min, ranging from 1.1 to 4.5 mm Hg (figure 10). The mean for the entire group was 0.9 ± 0.3 mm Hg. No patient had incomplete relaxation after bypass at this heart rate. This difference was not significant.

At a heart rate of 140 beats/min, nine of 11 patients in the CABG group demonstrated incomplete relaxation ranging from 1.4 to 13.4 mm Hg (mean 5.6 ± 1.6). After bypass six of 11 patients had incomplete relaxation ranging from 1.4 to 4.7 mm Hg (mean 1.4 ± 0.5) (figure 10). The difference in means was significant ($p = .027$). Incomplete relaxation was not observed in the non-CABG group before bypass. One patient had a small degree (2.2 mm Hg) of incomplete relaxation at a heart rate of 140 beats/min after bypass.

**Discussion**

Left ventricular filling commences when muscle tension has declined sufficiently to permit left ventricular cavitory pressure to fall below left atrial pressure. Both the rapidity of early diastolic relaxation and its ultimate extent can significantly affect ventricular filling and therefore cardiac output. When relaxation is extremely

**TABLE 2**

<table>
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<tr>
<th>Blood pressure and temperature</th>
<th>SBP (mm Hg)</th>
<th>p (unpaired t test)</th>
<th>NPT ($^\circ$C)</th>
<th>p (unpaired t test)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CAD</td>
<td>No CAD</td>
<td></td>
<td>CAD</td>
</tr>
<tr>
<td>Before CPB</td>
<td>95.8±2.9</td>
<td>88.8±2.5</td>
<td>NS</td>
<td>34.6±0.2</td>
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<tr>
<td>After CPB</td>
<td>93.9±4.6</td>
<td>89.7±5.0</td>
<td>NS</td>
<td>35.8±0.2</td>
</tr>
<tr>
<td>p (paired t test)</td>
<td>NS</td>
<td>NS</td>
<td>.003</td>
<td>NS</td>
</tr>
</tbody>
</table>

SBP = systolic blood pressure; NPT = nasopharyngeal temperature.
prolonged, the end-diastolic pressure-volume relationship may be altered.15

Relaxation is influenced by several factors, including catecholamines, thyroid function, temperature, ventricular hypertrophy, heart failure, and perhaps most importantly, ischemia.1, 16-18 Impaired relaxation has been demonstrated during both spontaneous19 and pacing-induced2, 3, 9, 20-23 angina in humans and after hypoxia or ischemia in isovolumic1, 24 and working4, 7 dog preparations. Abnormal relaxation and altered filling patterns have also been seen in patients with severe coronary artery disease between overt ischemic episodes.25, 26 The fact that abnormal relaxation can persist even when systolic function has returned to normal suggests that diastolic function is the more sensitive indicator of ischemia.2, 18, 20, 26

Indexes used to assess relaxation include peak negative dP/dt, total relaxation time, time to 50% relaxation, and the time constant for relaxation, T. Peak negative dP/dt suffers from its direct dependence on peak systolic pressure,16, 27 while the various time-related indexes are subject to observer bias and heart rate dependence.24 T, on the other hand, is relatively independent of loading conditions and minimally affected by heart rate,1, 15, 39 providing a valuable means of assessment of changes in relaxation when other variables simultaneously may be altered. For example, Ludbrook et al.28 showed significant improvement in T after nitroglycerin in patients with uniform diastolic wall motion, but not in those with asynchronous segmental relaxation, despite the fact that peak negative dP/dt fell in both groups as the systolic pressure declined. Finally, since beginning and ending points for deriving T are defined (peak negative dP/dt and left ventricular end-diastolic pressure (LVEDP) of the preceding beat), interobserver variability is minimized.
Numerous prior estimates of T in patients with coronary artery disease include 53 ± 16, 5 50 ± 1.9, 6 55 ± 9,10 and 43 ± 2 msec before and 58 ± 4 msec after rapid atrial pacing,3 49 ± 5 msec before and 58 ± 7 msec after ventricular pacing,9 and 80 ± 6 msec with a range of 63 to 131 msec.8 Our patients with T values ranging from 58 to 137 msec (mean 95 ± 6) are comparable to those reported by Thompson et al.8 The variation in T seen previously and within our patient group could have several possible explanations. First, a wide range in T values could represent the varying degrees of ischemia among patients. This is supported by the fact that our patients all had unstable angina and coronary artery disease severe enough to warrant surgery (table 1), while Hirota’s patients were studied after “successful medical treatment,”5 and those of Mann et al.3 and Bourdillon et al.9 only if stable angina was present. Second, the patients of Rousseau,6 Mann,3 and Bourdillon9 and their colleagues had T calculated from the log of pressure vs time, a system that has been shown consistently to underestimate T.8,14 Finally, relaxation is initiated by reuptake of calcium into sarcoplasmic reticulum, mediated by calcium ATPase. Brutsaert et al.18 have suggested that under conditions of ischemia, this process is the rate-limiting step in relaxation as persistent cytosolic calcium binds to troponin C, preventing dissociation of actin-myosin complexes. This is certainly not an all-or-none phenomenon and it is not surprising to see a graded patient response. The increase in T with increasing heart rate seen in our patients before CABG may represent added ischemic insult; although the increase was not statistically significant, one would expect, if anything, a slight decrease in T with increasing heart rate.1,2,8,29

Patients studied before and an average of 9 months after CABG by Carroll et al.30 had a significant decrease in T during exercise from 38 ± 11 msec preoperatively to 29 ± 11 msec postoperatively, but resting T values were not significantly different. This seems to be at variance with our results, which show significant improvement in T at rest, although the conditions of their study differed significantly from those in ours. Intraoperative stress has been likened to exercise stress testing; thus, perhaps our patients are more appropriately compared with their exercise group.

Coronary artery bypass surgery as performed at most institutions requires a period of ischemia during which the distal anastomoses are performed. Current techniques of myocardial preservation, including topical hypothermia and potassium cardioplegia, provide excellent protection, resulting in little or no decrement in postoperative systolic function in most instances.12,13 Nonetheless, the fact that relaxation is so readily impaired by ischemia led us to suspect that T might be further prolonged immediately after CPB. An immediate postbypass decrement in diastolic compliance has been previously demonstrated,31-34 but might possibly be attributable to the use of ischemic arrest rather than potassium cardioplegia to stop the heart35-37 or to the anesthetic agent used.34 Decreased compliance might alternatively result from cellular changes such as edema, or could occur from incomplete relaxation if T were sufficiently prolonged.

Our data show that relaxation is enhanced, not prolonged, in the immediate postbypass period. In no patient was T longer after CABG than before. There are several possible explanations for the improved relaxation rate. Certainly, relief of ischemia is likely to be a contributing factor. Intraoperative improvement in systolic function previously demonstrated suggests that beneficial effects of CABG are obtained immediately.12,13 Long-term persistence of the improvement in relaxation increases the likelihood that improved myocardial perfusion is the most important mechanism, since long-term improvement could not be related to transient perioperative events.30 Addition-

**FIGURE 10.** Extent of incomplete relaxation at heart rates of 120 and 140 beats/min, before (PRE-CABG) and after (POST-CABG) revascularization in patients with coronary artery disease. HR = heart rate. p (ANOVA) shows difference in means, before vs after, at each HR.

| TABLE 3 |
|-----------------|-----------------|-----------------|-----------------|
| Time constants in patients not treated with calcium-channel blockers (n=4) | | | |
| | Unpaced | HR 100 bpm | HR 120 bpm | HR 140 bpm |
| Before CABG | 86.0±9.0 | 96.8±8.4 | 93.0±12.5 | 82.8±10.5 |
| After CABG | 64.8±6.5 | 59.8±2.5 | 62.5±9.3 | 65.0±7.0 |
| p (ANOVA) | .004 | .021 | .002 | .056 |

HR = heart rate.

*HR = 62 ± 11 before CABG, 76 ± 4 after CPB.*
ally, immediate improvement in both relaxation and such systolic indexes as wall motion\textsuperscript{12} and thickening\textsuperscript{13} imply that patients with severe coronary artery disease may suffer varying degrees of functional impairment on the basis of chronic subclinical ischemia.

Catecholamines are known to shorten T,\textsuperscript{18, 38, 39} and postbypass catecholamine levels could be elevated.\textsuperscript{40} While catecholamine levels were not measured in this study, it is presumed that this effect is related to CPB, and therefore the effect of such elevation in individuals without coronary artery disease undergoing CPB would be expected as well. In fact, T was only minimally affected by CPB in a group of such patients undergoing procedures other than CABG.

Similarly, the use of β-blockers by our patients might have prolonged prebypass T.\textsuperscript{18, 39} Subsequent dilution of serum β-blocker concentration by the bypass pump prime could then result in shortening of T after bypass. When the patients were subdivided based on the intake of β-blockers, no significant difference was seen either in prebypass T or in the amount by which T was reduced by revascularization, ΔT.

The effects of calcium and calcium-channel blockade on isovolumetric relaxation are complex and may vary with the underlying pathology.\textsuperscript{42} In isolated muscle, a significant although slight effect of increasing calcium concentration on maximum negative dF/dt (developed force held constant) has been demonstrated by Wiegner and Bing.\textsuperscript{41} In an isolated supported dog heart, Weiss et al.\textsuperscript{1} found T was slightly lower after calcium administration, but this difference was not significant. Rousseau et al.\textsuperscript{42} found a small but significant decrease in T after calcium administration during atrial pacing, but an increase in T after pacing. T was significantly increased in postextrasystolic beats,\textsuperscript{43} a maneuver that increases myoplasmatic calcium.\textsuperscript{6} It is thus difficult to assess the effect on our results of calcium administration during weaning from CPB. In each of the above instances in which calcium administration produced a significant change in T, the magnitude of the change was 5 msec or less. At most, calcium administration could only partially explain the change in T we noted. When our CABG groups receiving and not receiving calcium were compared for change in T, there was no significant difference. Finally, with ischemia presumably corrected by CABG, the ability to sequester calcium should be improved, minimizing the effect of exogenous administration by the time of the study protocol at least 5 min later.

Calcium-channel blockers may also affect T. Rousseau et al.\textsuperscript{6} demonstrated a transient increase in T after intracoronary nifedipine in 21 patients with coronary artery disease. While it is conceivable that calcium-channel blockers could have influenced our baseline T values, a subsequent group of four patients not receiving them had similar T values before CABG and were improved to the same degree after CABG (table 3). This difference between our results and the data of Rousseau et al. is likely due to major differences in methods. Specifically, Rousseau et al. used nifedipine exclusively while only three of our patients received it, the remainder being treated with diltiazem (eight patients) or verapamil (one patient). The drug was administered orally to our patients while theirs received direct intracoronary injections. Finally, the increase in T seen in their patients was evanescent, with return to baseline T in 2 min. Our patients were studied a minimum of several hours after their last dose of medication.

Temperature is another variable affecting relaxation, prolonging it as temperature decreases.\textsuperscript{41} While we did not specifically measure intramyocardial temperatures and while significant myocardial cooling is used during CPB, we believe the hearts were adequately rewarmed at the time of the study. Warmed pump blood (37° C) was returned to the proximal aorta where it immediately entered the coronary arteries; consequently the myocardium was very likely warm by the end of CPB. Both nasopharyngeal (core) and rectal (peripheral) temperatures were also monitored and had returned to slightly above prebypass levels before CPB was discontinued in both groups (table 2). Although the temperature change was significantly different in the CABG group owing to the small intracoronary injections, the overall difference was small and quite comparable to that in the non-CABG group.

While core body temperature only varied by approximately 1° C, we cannot rule out the possibility of regional myocardial effects. Specifically, if subepicardial temperature distal to a stenotic lesion were lower than nasopharyngeal temperature, a temperature effect on prebypass results might be overlooked. This would most likely involve the LAD distribution, since this is the segment of left ventricle exposed to air and potential radiant cooling. The presence of collateral flow and the fact that only three of 12 patients had total LAD obstruction both suggest, however, that this myocardial segment was perfused with blood of body temperature, limiting segmental cooling.

Since completion of this study, our surgical technique has changed to include measurement of subepicardial temperature during administration of cardioplegia in some patients. In four patients with 90% or greater LAD stenoses in which temperature probes
were placed into the interventricular septum before instituting CPB, myocardial temperature was 0.1° to 1.6°C (mean 0.6°) higher than nasopharyngeal temperature before bypass, while the temperatures were approximately equal after bypass. It therefore seems improbable that regional temperature effects influenced our results in the study population.

The effect of loading conditions must also be considered. While it is clear that the rate of relaxation is directly dependent on load, the effect of loading conditions on T is debatable. Studies in isovolumetric and working dog hearts suggest that T is unaffected by load over a wide range of conditions. In humans, an isolated increase in preload has been shown not to affect T, while if afterload is allowed to rise, T is changed significantly, although only by 2 msec. In our patients, afterload was not different before and after bypass (table 2), while preload varied over a narrow range. Filling pressures and left ventricular cavity areas tended to be slightly higher after bypass, suggesting that patients were adequately volume loaded.

Finally, our data must be considered in light of the study of Giles et al. They found reduced global ejection fraction, measured by a computerized nuclear probe system, as a result of laryngoscopy and intubation in patients undergoing CABG, suggesting that perhaps the ischemia seen in our patients before bypass might not have been chronic but rather a result of induction of anesthesia and intubation. There are several significant differences between their study and ours. First, their anesthetic consisted of diazepam and enflurane; hemodynamic response to laryngoscopy and intubation was significant (systolic blood pressure increased by 36 mm Hg, heart rate increased by 24 beats/min). Our patients were anesthetized with high-dose fentanyl; response to intubation was minimal. Second, they examined global function only, which, as they note, could have decreased as a direct response to increased afterload. Regional function was not studied. Third, values in two-thirds of their patients returned to baseline within 10 min, while those in the remainder were within 20% of baseline. Finally, previous data from our laboratory under identical anesthetic and surgical conditions show that regional wall motion as assessed by echocardiography correlates highly with that seen during preoperative ventriculography.

Incomplete relaxation. Single-beat incomplete relaxation may be demonstrated by failure of the plotted pressure vs area points for that single beat to intersect a line constructed from pressure-area points taken when the ventricle is believed to be relaxed to the greatest possible extent. Maximal relaxation as defined by Weisfeldt et al., is obtained by producing an extended diastolic period. In dogs, this is easily achieved by ablation of the sinus node, while in humans, it is produced by pacing above the sinus rate and then interrupting pacing. Pressure-area points are determined at end-diastole, synchronous with the R wave of the subsequent beat, taken at varied filling pressures. After this fully relaxed line is constructed, it may be compared with single-beat pressure-area loops at various heart rates to detect incomplete relaxation during those beats. The magnitude of incomplete relaxation is determined from the pressure difference by which the loop fails to intersect the line. By a similar method, incomplete relaxation has been demonstrated in dogs during rapid pacing and in humans during exercise-induced ischemia and ventricular tachycardia. The magnitude of incomplete relaxation was increased after a period of hypoxia or ischemia in the dog.

Incomplete relaxation occurred infrequently in our patients at a heart rate of 120 beats/min and when present was minimal. At a heart rate of 140 beats/min, the other hand, incomplete relaxation was common among patients with coronary artery disease. In general, patients with the highest T values before CABG demonstrated the greatest amount of incomplete relaxation.

Incomplete relaxation has been suggested as the mechanism by which the end-diastolic pressure-volume relationship is altered during angina. In our patients with severe coronary artery disease, incomplete relaxation was common only under circumstances in which the diastolic time was considerably shortened in addition to relaxation being impaired. We cannot rule out the possibility, however, that our fully relaxed line was chronically elevated above normal. Carroll et al. suggested that different mechanisms may be operative in early and late diastolic pressure increases relative to volume. By comparing patients who developed ischemia during exercise with those who did not but had had a large previous myocardial infarction, they were able to distinguish between abnormal relaxation, present in both groups, which altered early diastolic compliance, and an upward shift in baseline pressure, present only in the ischemic group, which altered compliance late in diastole. The mechanism for elevated baseline pressure was unclear, although it might represent a dissociation between rate and extent of relaxation. This concept is further supported by Bourdillon et al., who showed that persistent regional stiffness is independent of slowed relaxation.

Incomplete relaxation in our patients occurred less
frequently after CABG than before and, when all patients were considered, the magnitude was significantly lower. We attribute this to increased coronary flow and improvement in ischemia, suggested by shorter time constants. Shorter time constants permit the ventricle to relax rapidly, so that faster heart rates with shorter diastolic times may be tolerated without preventing relaxation to proceed to completion. Incomplete relaxation, observed in only one patient without coronary disease, was of a small magnitude (2.2 mm Hg) and occurred after CPB.

Limitations. Several potential limitations to this study require further elaboration. As with any clinical study, control of every variable is both practically and ethically impossible. The issue of concomitant medication has been addressed by examination of subgroups to rule out major differences that might be ascribed to intake of β- or calcium-channel blockers or to intraoperative administration of calcium. Although it remains a possibility that drug effects or washout played a role in our results, this possibility is unlikely in view of these analyses.

There are significant differences in age and duration of CPB in patients in CABG and non-CABG groups. A correlation between age and T has been suggested, although the correlation coefficient is low (.65). It is possible that this relationship could have contributed to the baseline differences in T in CABG and non-CABG groups (figure 5). On the other hand, since all patients were essentially the same age before and after bypass, age certainly does not explain the significant improvement in both T and incomplete relaxation after CABG.

Duration of bypass might affect our results in two ways: (1) more profound cooling is employed in longer pump runs, which could result in less adequate myocardial rewarming, and (2) ischemic times are longer with longer CPB. Each of these factors would tend to prolong T after CPB, not shorten it. However, our data showed the opposite effect on T since the CABG group had longer CPB times than the control group.

If prebypass T were prolonged on the basis of ischemic segments becoming infarcted during CPB, the remaining normal segments might relax more quickly and completely, shortening T overall. We believe this is unlikely; previous work from our laboratory and others demonstrates that wall motion and thickening in previously dysfunctional noninfarcted segments are improved after CABG. No new wall motion abnormalities developed in our patients after CABG.

Finally, certain potential limitations of the technique for demonstrating incomplete relaxation should be noted. Echocardiographic left ventricular cavity areas taken during surgery rely on intracavitary landmarks for orientation. In a situation such as this in which the heart is moved between measurements, it is possible that short-axis views before and after CPB are not identical. This should not be a serious limitation because the control measurement in each case, the pressure-area relationship when the heart has relaxed to the fullest extent possible, is taken at the same time as the paced measurements. Neither the heart nor the gastroscope is moved between control and paced measurements. Thus, incomplete relaxation is calculated from comparable areas, and absolute areas before and after CPB are not being compared directly.

In summary, we have found prolonged time constants of relaxation in a group of patients with severe coronary artery disease who did not manifest overt ischemia as reflected by ST segment changes or acutely reduced systolic function. This supports the concept that diastolic impairment can result from ischemia insufficient to impair systolic function or produce symptoms. Incomplete relaxation in these patients was readily demonstrated during rapid pacing. Time constants were significantly improved after revascularization and incomplete relaxation was less likely. A group of patients undergoing open heart procedures other than CABG showed little or no change in T as a result of CPB, suggesting relief of ischemia as the likely mechanism for the improvement noted in the patients with coronary artery disease.

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