Left ventricular performance, regional blood flow, wall motion, and lactate metabolism during transluminal angioplasty

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ABSTRACT The response of left ventricular function, coronary blood flow, and myocardial lactate metabolism during percutaneous transluminal coronary angioplasty (PTCA) was studied in a series of patients undergoing the procedure. From four to six balloon inflation procedures per patient were performed with an average duration per occlusion of 51 ± 12 sec (mean ± SD) and a total occlusion time of 252 ± 140 sec. Analysis of left ventricular hemodynamics in 19 patients showed that the relaxation parameters, peak negative rate of change in pressure, and early time constants of relaxation, responded earliest to short-term coronary occlusion (peak effect at 17 ± 7 sec) while other parameters, such as peak pressure, left ventricular end-diastolic pressure, and peak positive rate of change in pressure, responded more gradually, suggesting a progressive depression of myocardial mechanics throughout the procedure. Left ventricular angiograms, available for 14 patients, indicated an early onset of asynchronous relaxation concurrent with the early response in peak negative dP/dt and the time constant of early relaxation. All hemodynamic functions fully recovered within minutes after the end of PTCA. Mean blood flow in the great cardiac vein and proximal coronary sinus and the hyperemic response were measured in 20 patients. Before PTCA mean flow in the great cardiac vein was 69 ± 17 ml/min and in the coronary sinus it was 129 ± 34 ml/min. Reactive hyperemia (great cardiac vein) was 55% after the first PTCA and 91% after the third. A more pronounced reaction was observed when the residual functional coronary stenosis was reduced in subsequent dilatations. Arteriovenous lactate difference appeared constant during the first two occlusions (control +0.11 mmol/liter, first PTCA −0.87 mmol/liter, and second PTCA −0.82 mmol/liter) and did not increase during subsequent occlusions. Within minutes after the procedure lactate balance was again positive, demonstrating the reversibility of the metabolic disturbances after repeated ischemia. The results of this study indicate that there is no permanent dysfunction of global or regional myocardial mechanics, myocardial blood flow, or lactate metabolism after PTCA with four to six coronary occlusions of 40 to 60 sec.
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UNTIL RECENTLY the measurement in man of left ventricular geometry and hemodynamics early after an abrupt occlusion of a major coronary artery has not been feasible. Percutaneous transluminal coronary angioplasty (PTCA), however, now provides a unique opportunity to study the time course of changes during the transient interruption of coronary flow by the balloon occlusion sequence in patients with single-vessel disease and without angiographically demonstrable collateral circulation.[1, 2] We report the dynamic changes in left ventricular hemodynamics in 19 patients and the concurrent left ventricular geometric changes assessed by angiography in another group of 14 patients during PTCA. In a third group of patients regional blood flow and lactate metabolism were analyzed during reactive hyperemia after repeated occlusions of the left anterior descending coronary artery. These different studies were undertaken to investigate the sequence of events during transient ischemia induced by PTCA and to determine whether or not the effects of ischemia after repeated occlusions were reversible.

Materials and methods

Study population and protocol. After a feasibility study of the effect of nonionic contrast media on left ventricular func-

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tion, permission from the Thoraxcenter Ethics Committee was granted to obtain left ventricular angiograms during transluminal occlusions. All patients in this study gave their informed consent and there were no complications directly related to the research procedure.

For the first part of the study data were collected from 19 adult patients undergoing temporary coronary occlusion of a diseased left coronary artery during PTCA. Four of these patients had had a previous myocardial infarction. Records were analyzed during the first successful PTCA procedure for each patient.

For the second part of the study 14 patients were selected from 356 consecutive patients in whom angioplasty was attempted. These patients met the inclusion criteria by having isolated obstructive lesions of one coronary vessel (left anterior descending artery in 10 patients, right coronary in four, left circumflex in one) and normal resting left ventricular function and wall motion. Four patients had mild essential hypertension and elevated left ventricular filling pressures (end-diastolic pressure $\geqslant$25 mm Hg). During the PTCA procedure the number of transluminal occlusions performed per patient was 4.9 ± 2.2 (mean ± SD). The average duration of each occlusion was 51 ± 12 sec (mean ± SD) and the total occlusion time during the whole procedure was 252 ± 140 sec (mean ± SD). With a tipmanometer on a No. 8F pigtail catheter pressures were recorded and derived indexes were calculated off-line by a computer system.[3, 4] Three to four ventriculograms (30 degrees right anterior oblique at 50 frames/sec) were obtained by injection of 0.75 ml/kg of a nonionic contrast medium (metrizamide, Amipaque). The hemodynamic and angiographic investigations were performed before the PTCA procedure was begun, after 20 sec of occlusion during the second dilatation, after 50 sec of occlusion during the fourth dilatation, and again 5 min after completion of the PTCA procedure. These sequential left ventricular angiograms were made only after the values for left ventricular end-diastolic pressure and the various isovolumetric parameters had returned to those recorded before the initial angiogram. In all cases the interval between two angiograms was at least 10 min. Care was taken to maintain the patient's position in relation to the x-ray equipment during the consecutive angiograms. Diaphragm movement was kept to a minimum by instructing patients to keep inspiration shallow and to avoid the Valsalva maneuver.

For the third part of the study, data were collected from 20 other patients who presented with proximal lesions of the left anterior descending artery. Coronary sinus and great cardiac vein blood flow were measured by the continuous thermodilution method with a Baim catheter.[5, 6] The main objective of this measurement was to detect changes in the global and regional blood flows, as well as in the regional lactate metabolism, during the reactive hyperemia after consecutive episodes of transluminal occlusion. In the beginning of the investigation the position of the distal thermistor in the great cardiac vein was determined by injection of 3 ml of contrast medium. After each balloon deflation coronary sinus and great cardiac vein flows were measured for 10 sec. The continuous infusion for thermodilution was then interrupted to allow blood withdrawal from the great cardiac vein. Lactate was assayed enzymatically according to Apstein et al.[7] with the AutoAnalyzer II (Technicon, Tarrytown, NY). Blood (4 ml) for lactate measurements was rapidly deproteinized with an equal volume of cold 8% perchloric acid ($HClO_4$) and centrifuged. The supernatant was analyzed on the AutoAnalyzer and compared with standard curves made with lithium lactate in 4% $HClO_4$.

Analysis of pressure-derived indexes during systole and diastole. Left ventricular pressure was measured with a Millar micromanometer catheter and digitized at 250 samples/sec. Combined analog and digital filtering resulted in an effective time constant of less than 10 msec. We used an updated version of the beat-to-beat program described previously[3, 4] that also incorporates the capability of acquiring a calibrated pressure signal and storing it on disk or tape for subsequent off-line analysis. The latter procedure was followed for all PTCA procedures. For off-line analysis of pressure relaxation the following definitions were used: (1) pressure at the beginning of isovolumetric relaxation (P_b) is the pressure at the point at which dP/dt is minimal (maximum negative dP/dt), and (2) pressure at end of isovolumetric relaxation (P_e) is the pressure less than or equal to the previous end-diastolic pressure, but not less than 1 mm Hg.

Although it is possible that the latter definition may result in P_e being measured just after mitral valve opening, estimation of the time constants by more stringent criteria, such as end-diastolic pressure + 10 mm Hg, did not result in a significantly better estimation, and on the contrary failed to measure the time constants during high heart rates.

Peak left ventricular pressure, left ventricular end-diastolic pressure, peak negative dP/dt, peak positive dP/dt, and the relationship between dP/dt/pressure and pressure linearly extrapolated to pressure = 0 (V_{max}), where V_{max} is maximal velocity, were computed on-line after a data acquisition of 20 sec.

Determination of relaxation parameters. Three techniques have been implemented for the off-line beat-to-beat calculation of the relaxation parameters.[8-10] All require a minimum of eight samples (over 32 msec) between P_b and P_e.

SEMILOGARITHMIC MODEL. The semilogarithmic model used was: $P(t) = P_0e^{-t/T}$, where P is pressure; t is time; P_0 is equivalent to P_b when a true exponential decay is present starting from the time of peak negative dP/dt; the fit for the first 40 msec ($n \geqslant 8$), T_1, is biexponential[10]; the fit after 40 msec ($n \geqslant 3$), T_2, is biexponential[10]; and the fit for all points ($n \geqslant 8$), T, is monoexponential. The P_0 and T parameters are estimated from a linear least squares fit of $LnP = -t/T + LnP_0$.

EXPONENTIAL MODEL. The exponential model used was: $P(t) = P_0e^{-t/T} + P_1$, with nonlinear least squares fit of P for P_0, P_1, and T. P_1 represents the offset pressure the system relaxes to for $t \geqslant T$. The isovolumetric relaxation period is modeled only monoexponentially.

DERIVATIVE MODEL. The derivative model used was: $P(t) = P_0e^{-t/T} + P_1$ or $dP/dt = -1/T\,(P(t) - P_1)$, with linear least squares fit of dP/dt vs P for T and P, starting at 16 msec after P_b until P_e.

Analysis of global and regional left ventricular function during systole and diastole. A complete cardiac cycle was analyzed frame by frame from all cineangiograms. The ventricular contour was detected automatically.[11] For each analyzed cine frame left ventricular volume was computed according to Simpson's rule. After the end-diastolic and end-systolic frames were obtained, stroke volume, global ejection fraction, and total cardiac index were computed. End-diastolic pressure was defined as that point on the pressure trace at which the derivative of the pressure first exceeded 200 mm Hg/sec and in all cases coincided with the maximal measured left ventricular volume.[3] End-systole was defined, with reference to the pressure tracing, at the occurrence of the dicrotic notch of the central aortic pressure. To analyze the regional left ventricular function, the computer generated a system of coordinates along which the left ventricular displacement was determined frame by frame in 20 segments (figure 1). The definition of the 20 segmental coordinates was derived from the mean trajectories of endocardial sites in 23 normal individuals[12] and generalized as a mathematical expression amenable to automatic data processing.[13, 14]

Segmental wall velocity was computed as the first derivative of the instantaneous displacement function. Mean ejection

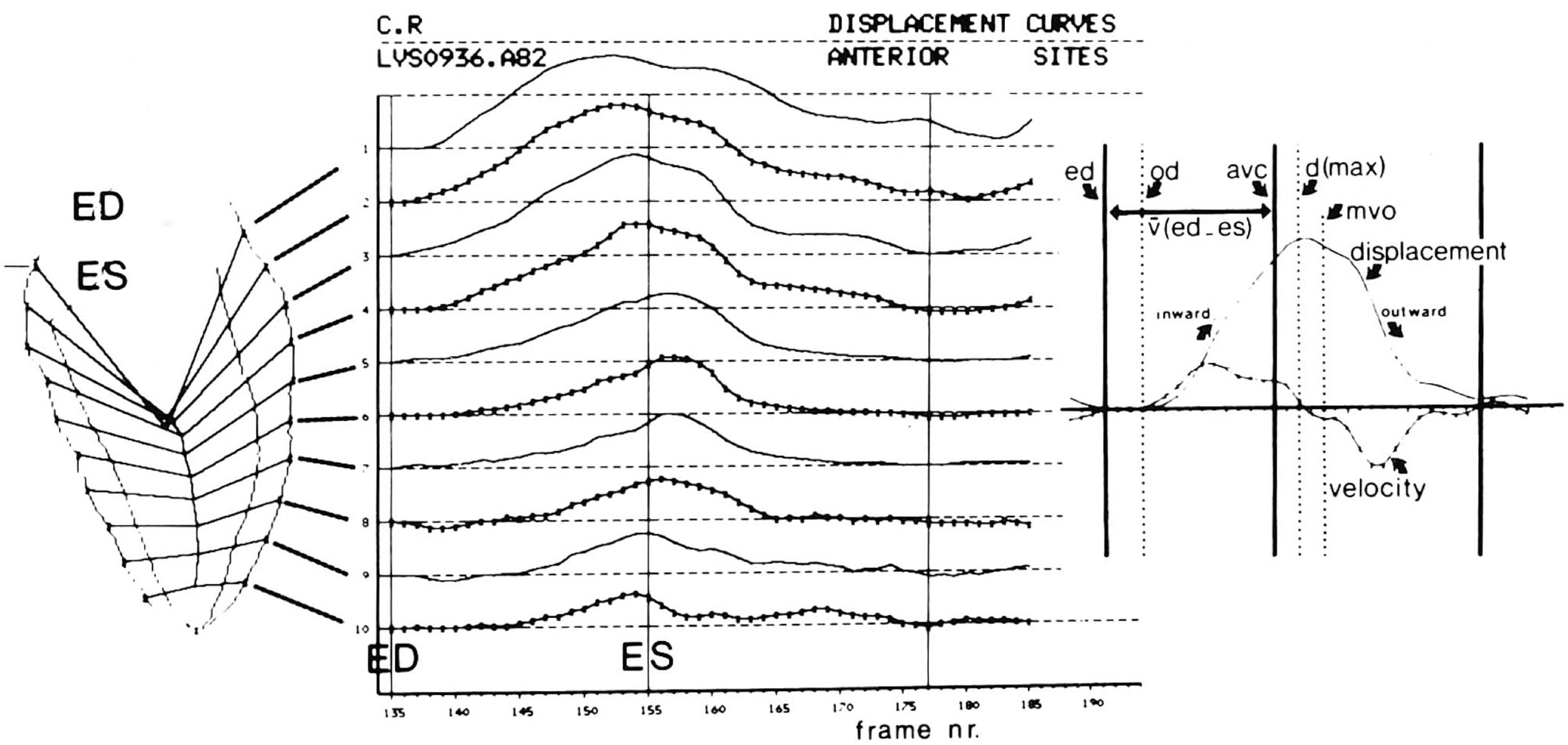

FIGURE 1. End-diastolic and end-systolic left ventricular contours, as detected by the automated analysis system. Superimposed on these silhouettes is a system of coordinates along which segmental left ventricular wall displacement is detected. Left ventricular wall velocity, the first derivative of wall displacement, is derived from these data. ed = end-diastole; es = end-systole; od = onset of displacement; v(ed-es) = mean ejection phase wall velocity; d(max) = maximal inward wall displacement; mvo = mitral valve opening.

phase wall velocity for each segment was calculated from end-diastole to end-systole (figure 1). Segmental volume was computed from the local radius (R) and the height of each segment (1/10 of left ventricular long-axis length L) according the formula $1/20\ \pi R^2L$. When normalized for end-diastolic volume, the systolic segmental volume change can be considered a parameter of regional pump function (figure 2). During systole this parameter quantitatively expresses the contribution of a particular segment to global ejection fraction, termed regional contribution to global ejection fraction.[13] The sum of the values for all 20 segments equals the global ejection fraction. Diastolic function was analyzed in terms of volume stiffness. Pressure-volume relationships were determined from the lowest diastolic pressure to the beginning of the "a" wave. The natural logarithm of pressure was used in a linear regression analysis of pressure and volume from which a slope (K) was derived. Changes in K were taken as changes in volume stiffness.[15]

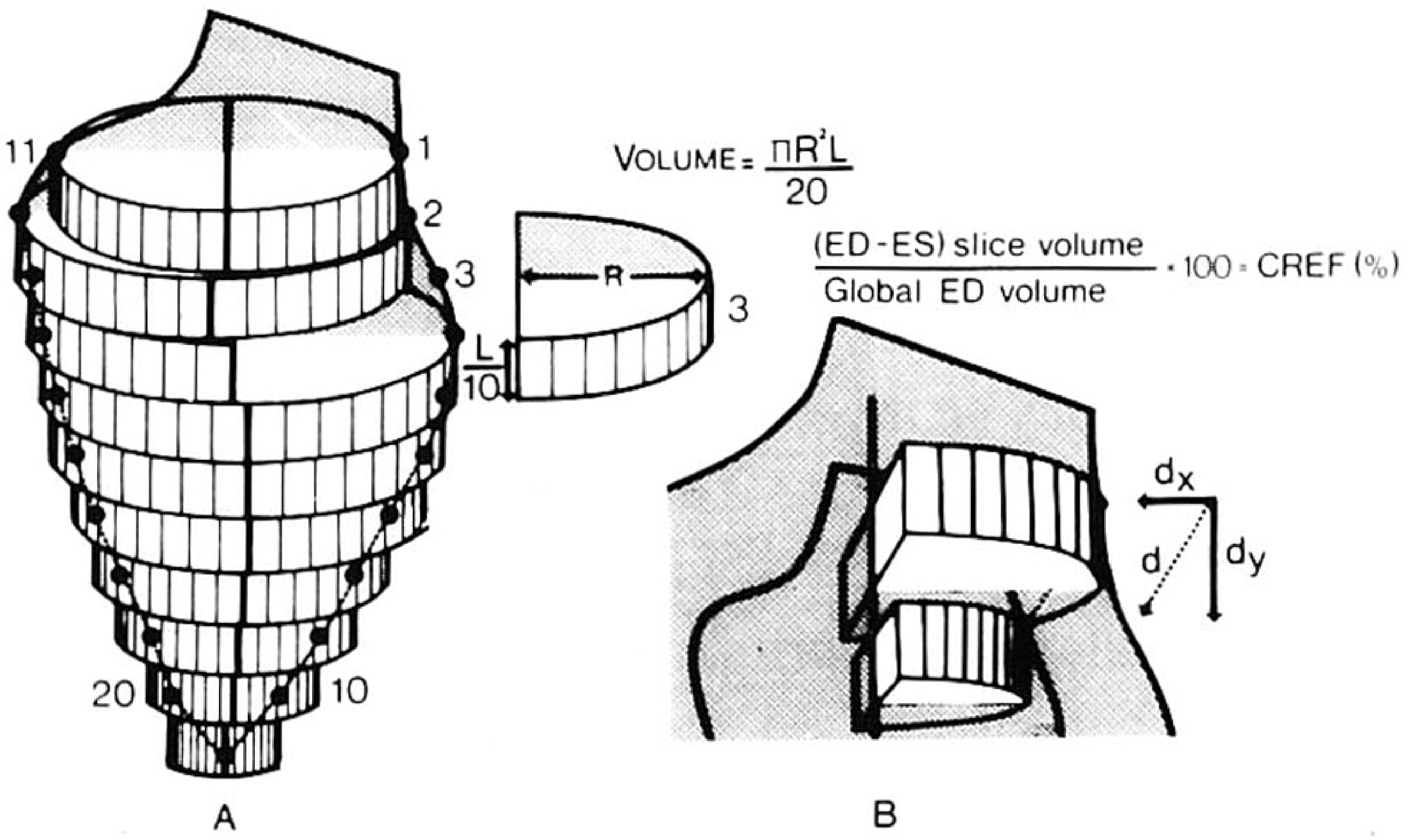

FIGURE 2. Method for computing regional contribution to ejection fraction (CREF): The volume of each segment (slice volume) is computed according to the formula shown in the figure. The change in systolic volume is derived from regional displacement and is mainly a consequence of the decrease in radius (R) of a half slice, which is expressed by the x component (dx) of the displacement vector (d). L = left ventricular long-axis length extending from base to apex.

Results

Analysis of pressure-derived indexes during systole and diastole. Hemodynamic parameter values for a control beat just before occlusion, at peak effect in terms of the change in negative dP/dt and T_1 (occurring, on average, at 17 ± 7 sec), and at the end of the occlusion (occurring, on average, at 53 ± 12 sec) are summarized in table 1. No attempt was made to average consecutive beats or to select beats with respect to the respiratory cycle. An example of a continuous recording of V_{max}, positive and negative dP/dt, T_1, T_2, T, end-diastolic pressure, and peak pressure is illustrated in figure 3.

There was no important change in heart rate during the PTCA procedure. The patterns of change in peak left ventricular pressure, left ventricular end-diastolic pressure, peak positive dP/dt, and V_{max}, however, suggest a progessive depression in myocardial mechanics without any indication of an early peak. The pressure at which the isovolumetric relaxation phase was considered to begin (P_b) was not altered appreciably during PTCA in spite of the drop in peak left ventricular pressure and peak negative dP/dt.

Within 4 or 5 beats after occlusion, a deformation appeared in the ascending limb of the negative dP/dt curve (figure 4) and in the next 10 sec this deformation gradually increased so that the irregularity in the curve

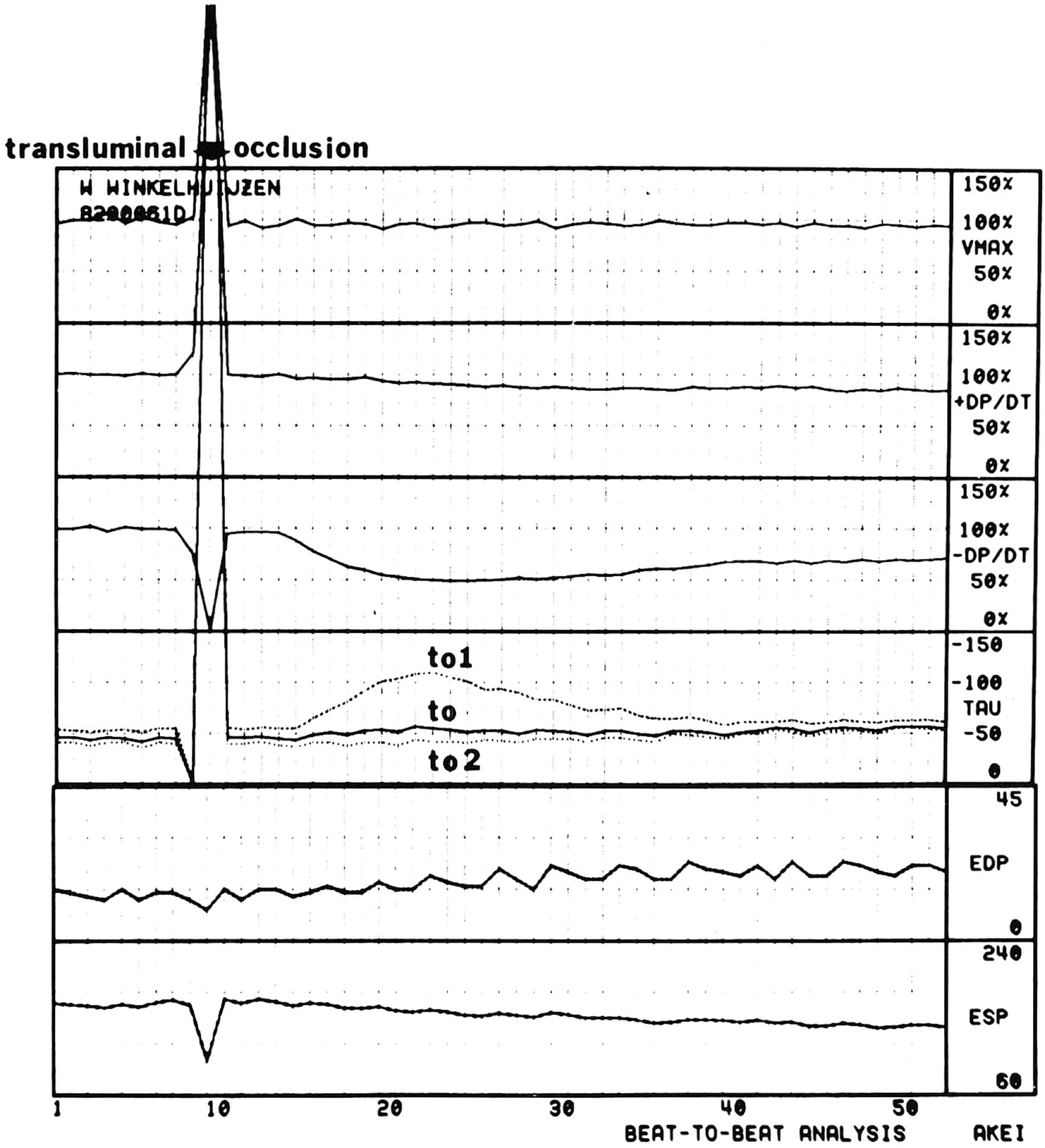

FIGURE 3. Hemodynamic measurements in a patient during PTCA. From top to bottom, maximal velocity of the contractile elements (V_{max}); peak negative and positive dP/dt expressed as percentages of control values; the time constants of relaxation to_1 (dashed line), to (solid line), and to_2 (dotted line) (scale 50 msec); end-diastolic pressure (EDP; scale 15 mm Hg); and peak systolic pressure (ESP; scale 60 mm Hg with 60 mm Hg offset). The break in the data at beat 10 corresponds to inflation of the PTCA balloon.

reached the same height as peak negative dP/dt, which had progressively decreased to its nadir. In the next 20 to 50 sec, peak negative dP/dt began to return toward control levels with a resolution of the irregularity in the ascending limb of its curve. At 50 sec this parameter recovered to 77% of the preocclusion value and the deformity was no longer present.

This deformation of the negative dP/dt signal at the early phase of the occlusion indicates that the time course of left ventricular pressure decay deviates substantially from the monoexponential model usually proposed and also that asynchronous contraction or relaxation may be involved at the very beginning of the transluminal occlusion. Therefore, biexponential fitting of the pressure curve was computed during isovolumetric relaxation, primarily because the pressure curve, when plotted on semilogarithmic paper, was observed to follow two straight lines rather than the one predicted by the monoexponential mode.

The second half of table 1 summarizes the results with the different techniques for computing the relaxation parameters. While major differences were apparent in the magnitude of the time constants, however computed, they all showed a highly significant slow-

TABLE 1

Hemodynamic parameter values at control before PTCA, at peak effect with respect to T_1 and peak negative dP/dt (17 ± 7 sec), and at the end of the occlusion (52 ± 12 sec)

Variables	Control (mean ± SD)	Peak effect Mean ± SD	Peak effect p value	End PTCA Mean ± SD	End PTCA p value
Heart rate (bpm)	67 ± 12	66 ± 11	NS	69 ± 12	NS
Peak LVP (mm Hg)	137 ± 21	133 ± 20	NS	124 ± 19	<.0003
LVEDP (mm Hg)	16.4 ± 6.4	19.3 ± 7.4	<.0003	23.7 ± 5.0	<.0001
Peak +dP/dt (mm Hg)	1490 ± 330	1300 ± 200	<.0001	1260 ± 250	<.0001
P_b (mm Hg)	86 ± 14	90 ± 15	<.04	84 ± 13	NS
Peak −dP/dt (mm Hg)	1710 ± 320	1240 ± 260	$<10^{-6}$	1320 ± 380	$<10^{-5}$
T (model A)	46.4 ± 8.1	58.4 ± 10.8	$<10^{-6}$	59.4 ± 10.2	<.0001
T_1 (model B)	53.0 ± 7.6	81.7 ± 15.3	$<10^{-6}$	66.2 ± 13.0	<.0001
T_2 (model B)	41.3 ± 8.8	48.0 ± 8.7	<.001	55.1 ± 10.8	<.0001
T_2/T_1 (model B)	0.77 ± 0.10	0.60 ± 0.11	<.0001	0.83 ± 0.09	<.002
T (model C)	72.6 ± 18.5	178 ± 96	<.0001	85.5 ± 26.4	<.04
T (model D)	63.2 ± 11.8	120 ± 57	<.0001	76.3 ± 24.3	<.01

All time constant values are in milliseconds.

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

Computation models: A = single time constant without offset; B = double time constant without offset; C = time constant from dP/dt; D = single time constant with offset P_1.

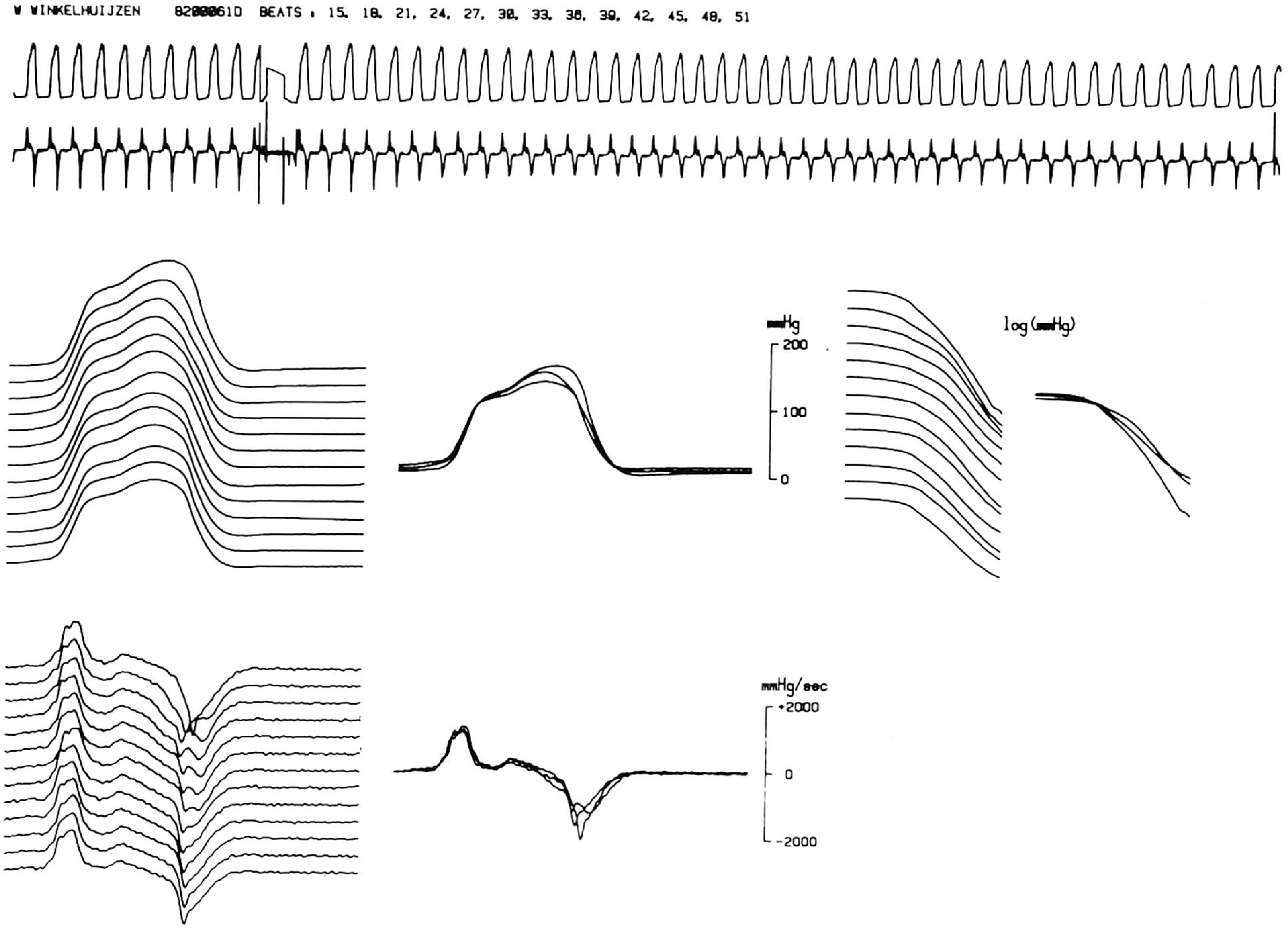

FIGURE 4. Effects of coronary artery occlusion on left ventricular pressure (mm Hg) and positive and negative dP/dt (mm Hg/sec). The break in the recording at beat 15 corresponds to inflation of the balloon. On the left are displayed the left ventricular pressures and positive and negative dP/dts of individual beats (15, 18, 21, and so forth) while the natural logarithm of the pressure is shown on the right. The decrease in negative dP/dt is associated with an irregularity in the upstroke of the negative dP/dt curve. After 30 sec (beat 42) peak negative dP/dt starts to return toward a more normal shape of the signal.

ing of relaxation early during PTCA and recovery and return to near-control levels by the end of the procedure. The behavior of the two time constants (T_1, T_2) during PTCA is illustrated in figure 3.

Generally the time constants computed from the logarithm of pressure were smaller and showed less variation than those computed from the other two models. The major discrepancies are apparent at the peak effect of PTCA. This is also reflected in the p (significance) value. The ratio T_2/T_1, an index of asynchrony,[10] showed a drop of 0.17 from 0.77 (control) to 0.60 (peak effect), but within 53 sec not only returned to the control level but exceeded it slightly. After 53 sec of occlusion, the region perfused by the occluded coronary artery could no longer be considered to be asynchronous, but was probably akinetic and not actively contributing to either contraction or relaxation.

Global left ventricular function during systole and diastole. The left ventricular pressures and volumes measured before, during, and after angioplasty are listed in table 2. During the four sequential cineangiographic investigations the heart rates were almost identical, whereas the isovolumetric indexes of contraction and relaxation recorded during the second (20 sec occlusion) or the third (50 sec occlusion) left ventricular angiograms showed changes very similar to those described in the first group of results (table 1). Occlusion of a major coronary artery for only 20 sec resulted in a significant ($p < .005$) increase in end-systolic volume (from 31 ± 9 to 38 ± 9 ml/m^2), while the end-diastolic volume remained unchanged after 20 sec and even after 50 sec of transluminal occlusion. At 50 sec the ejection fraction decreased from 62% to 48% ($p < .005$) and this decrease was essentially due to an increase in end-systolic volume from 29 ± 7 to 41 ± 9 ml/m^2 ($p < .005$).

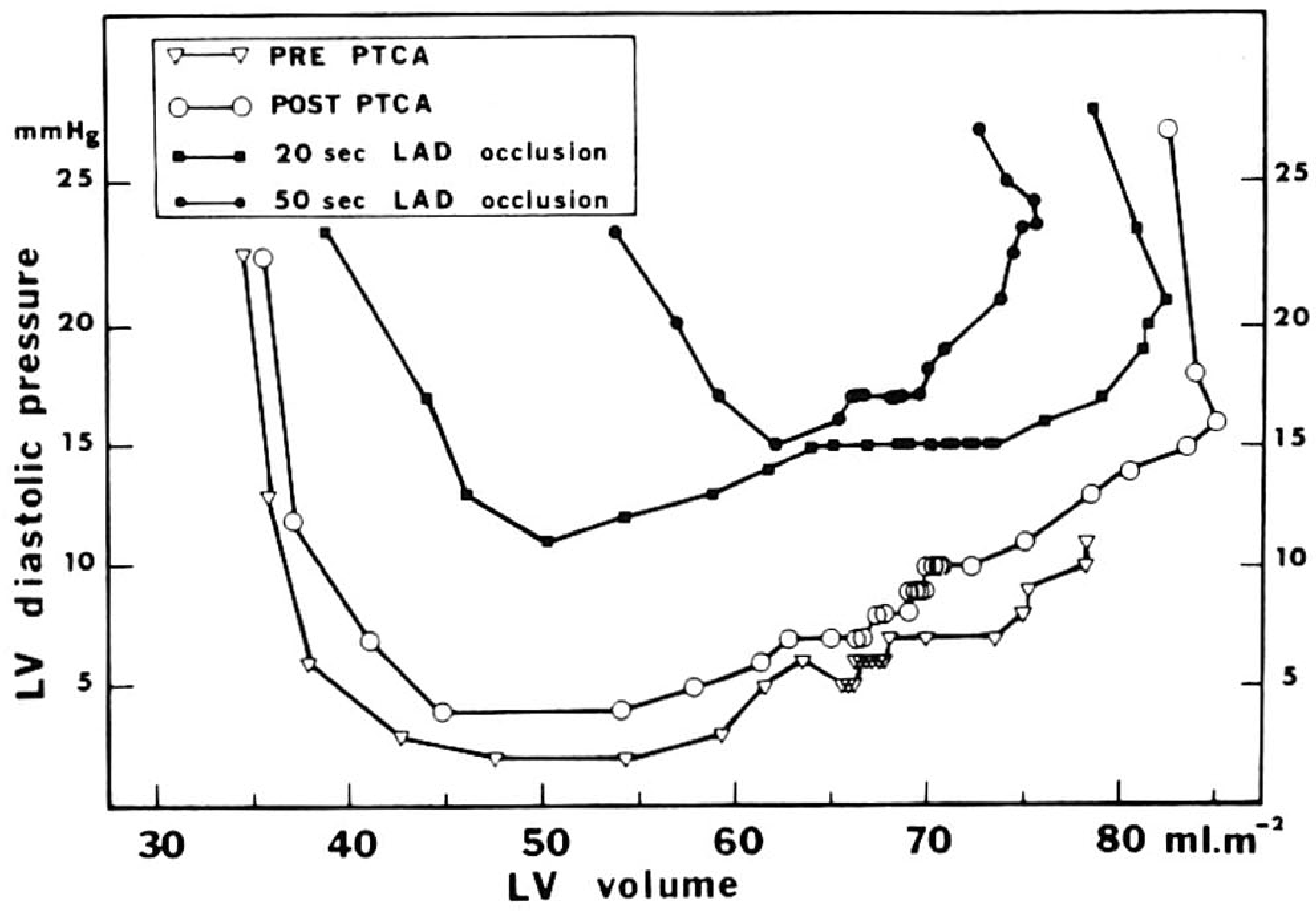

FIGURE 5. Diastolic pressure-volume relationships during PTCA. During occlusion there is a gradual shift upward and to the right in the diastolic pressure-volume relationship. LAD = left anterior descending artery.

An example of the relationship between left ventricular diastolic pressure and volume during transluminal occlusion is illustrated in figure 5. It is evident that the

TABLE 2
Hemodynamic parameter values before PTCA, at 20 and 50 sec after occlusion, and after the PTCA procedure

	Before PTCA		20 sec occlusion	50 sec occlusion	After PTCA	
Variables	Total group (n = 14)	Subgroup (n = 9)	(total group; n = 14)	(subgroup; n = 9)	Subgroup (n = 9)	Total group (n = 14)
HR (bpm)	62 ± 16	59 ± 18	61 ± 13	62 ± 14	63 ± 11	64 ± 11
EDV (ml/m^2)	81 ± 15	79 ± 14	81 ± 15	81 ± 16	78 ± 11	77 ± 11
ESV (ml/m^2)	31 ± 9	29 ± 7	37 ± 9^B	41 ± 9^B	26 ± 15	27 ± 7^A
SV (ml/m^2)	50 ± 11	49 ± 11	44 ± 12^A	39 ± 14^A	52 ± 10	50 ± 9
EF (%)	61 ± 8	62 ± 6	54 ± 8^B	48 ± 12^B	66 ± 6	64 ± 7
Peak LVP (mm Hg)	154 ± 30	151 ± 35	142 ± 29	145 ± 37	148 ± 25	147 ± 21
Peak +dP/dt (mm Hg·sec^{-1})	1403 ± 304	1356 ± 257	1312 ± 320	1278 ± 317	1442 ± 384	1412 ± 333
V_{max} (sec^{-1})	39 ± 9	40 ± 8	39 ± 9	34 ± 10^A	43 ± 12	42 ± 11
ESP (mm Hg)	95 ± 18	92 ± 22	90 ± 19	98 ± 24	91 ± 15	90 ± 14
Peak −dP/dt (mm Hg·sec^{-1})	1727 ± 322	1614 ± 267	1268 ± 355^B	1404 ± 370^A	1665 ± 296	1664 ± 243
T_1 (msec)	55 ± 8	55 ± 6	79 ± 17^B	68 ± 16^B	56 ± 7.5	54 ± 7
T_2 (msec)	44 ± 7	43 ± 7	51 ± 8^A	59 ± 8^B	45 ± 8	45 ± 9
Pmin (mm Hg)	10 ± 5	8 ± 3	11 ± 4	16 ± 6^B	8 ± 5	8 ± 4
EDP (mm Hg)	22 ± 8	18 ± 6	22 ± 7	29 ± 5^A	21 ± 5	20 ± 6
K ln P/V (ml^{-1})	0.0244 ± 0.009	0.0239 ± 0.008	0.0314 ± 0.016	0.0431 ± 0.018	0.0349 ± 0.016	0.0339 ± 0.013

HR = heart rate; EDVI = end-diastolic volume index; ESVI = end-systolic volume index; SVI = stroke volume index; EF = ejection fraction; LVP = left ventricular pressure; ESP = end-systolic pressure; Pmin = left ventricular minimal diastolic pressure; EDP = left ventricular end-diastolic pressure; K ln P/V = natural logarithmic slope of diastolic pressure-volume relationship.

^{A}$p < .05$ compared with before PTCA, paired Student t test; ^{B}$p < .005$, compared with before PTCA, paired Student t test.

entire diastolic pressure-volume relationship during transluminal occlusion was gradually shifted upward and to the right so that at any given volume, the diastolic pressures were higher. This effect was consistently observed after 50 sec of occlusion. Furthermore, the K constant, considered to be an index of volume stiffness, was significantly increased after 50 sec of transluminal occlusion (table 2). Nevertheless, the hemodynamic and cineangiographic investigations performed after completion of the PTCA procedure demonstrated the perfect reversibility of these changes in volume as well as the normalization of the different pressure-derived indexes.

Regional left ventricular function. The profound effect of a 20 sec occlusion of the left anterior descending artery on left ventricular wall motion and its time sequence is shown in figure 6. The delay in onset of displacement with respect to end-diastole as well as the timing relationship between the aortic valve closure and the occurrence of the maximal wall displacement is illustrated in figure 7. The onset of displacement of the anterior and inferior walls was not significantly affected after a 20 sec occlusion of the left anterior descending artery. On the contrary, the moment of maximal wall displacement for the anterior wall shifted from end-systole to early diastole. The anterolateral segment (Nos. 6 and 7 on figure 7), the apical segment (Nos. 9 and 10) of the anterior wall, and the apical segment (Nos. 20 and 19) of the inferior wall appeared to be most affected.

The measurement of mean ejection phase velocity after 20 and 50 sec occlusions of the left anterior descending artery showed a decrease that was again more pronounced in the anterior wall segments (figure 8). The regional wall motion and wall velocity (figure 8) showed a similar response to occlusion of this coronary artery. These data clearly demonstrate a progressive myocardial depression that affected specifically the anterolateral and apical segments (table 3).

It must be emphasized that all these ischemic changes were transient and perfectly reversible, as demonstrated by the regional analysis of the last cineangiogram obtained after completion of the procedure.

Coronary blood flow and lactate metabolism. During the initial dilatation the mean duration of balloon inflation was 41 ± 13 sec and during the subsequent dilatations the duration of inflation was gradually increased up to 54 ± 12 sec in a subset of four patients who underwent six consecutive dilatations (table 4).

The mean blood flow in the great cardiac vein in 20

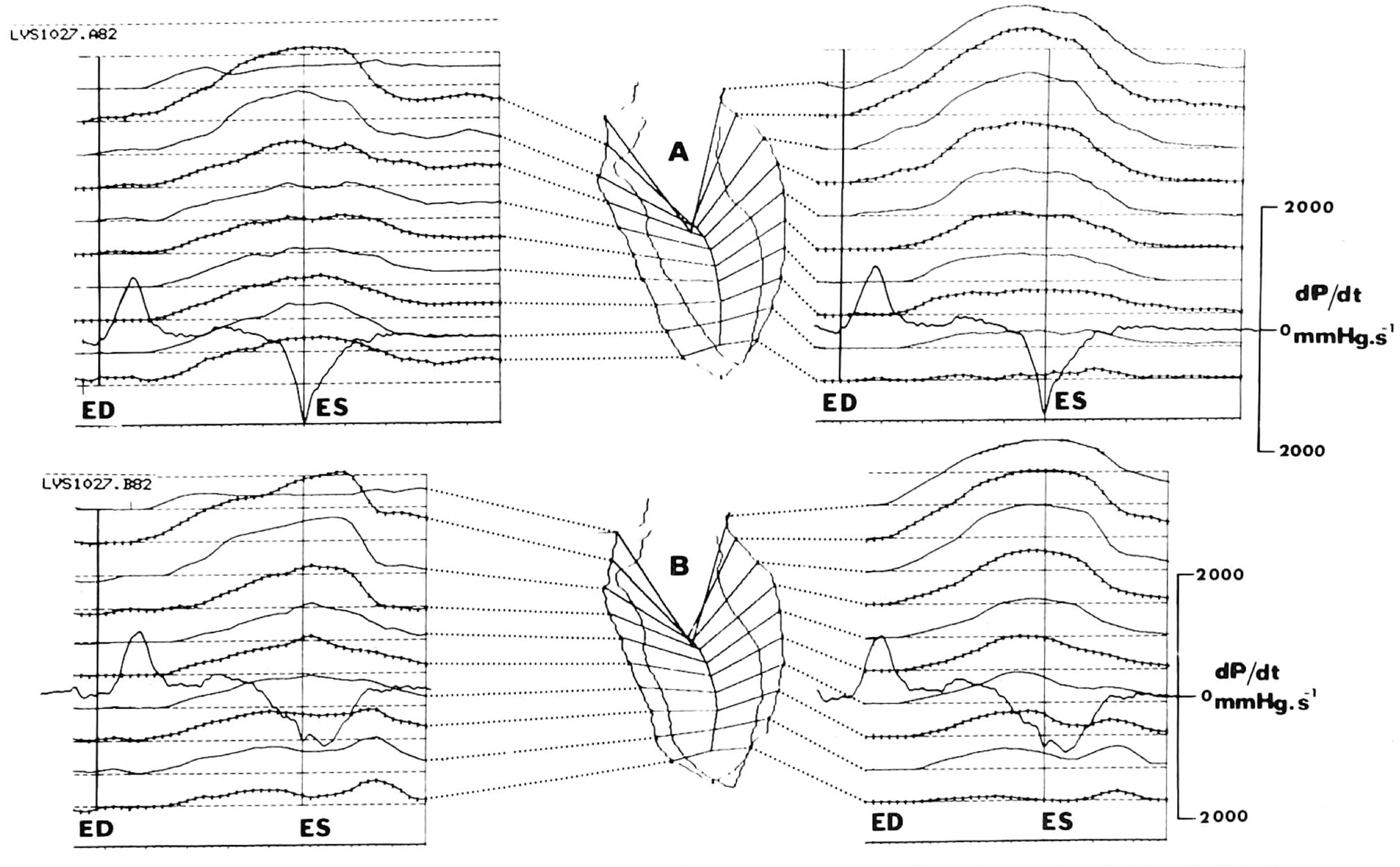

FIGURE 6. Left ventricular wall displacement studied in 20 separate segments, 10 in the anterior (right) and 10 in the inferoposterior (left) wall. A typical example of the relationship between segmental wall displacement and dP/dt curve is observed before PTCA (*A*) and after 20 sec (*B*) of occlusion of the left anterior descending artery. After 20 sec of occlusion, the notch in the dP/dt curve corresponds to a second wave of inward wall displacement in the anteroapical and inferoapical segments.

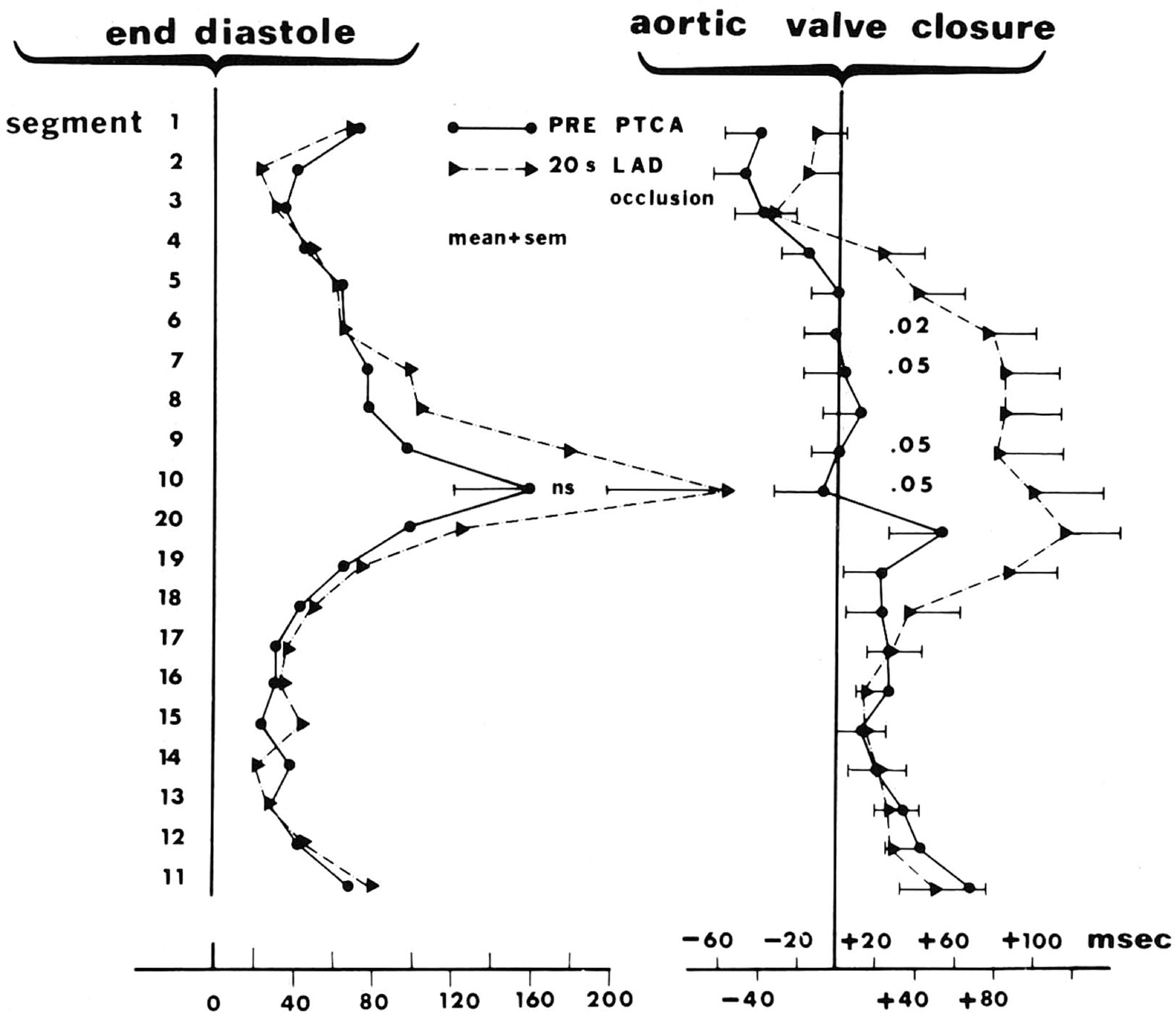

FIGURE 7. Delay (msec) in onset of displacement for the 20 individual wall segments with respect to end-diastole (time zero) before and after 20 sec of occlusion of the left anterior descending artery. Time relationship between aortic valve closure (time zero) and the occurrence of maximal wall displacement before and after 20 sec of occlusion of the left anterior descending artery.

patients before the first inflation was 69 ± 17 ml/min, falling to 49 ± 23 ml/min ($p < 10^{-5}$) during the first inflation and rising to 107 ± 31 ml/min ($p < 10^{-5}$) after the first balloon deflation.

The mean hyperemic increase in great cardiac vein flow was 38 ml/min above the control flow value after the first inflation compared with 63 ml after the third inflation ($p < .01$; figure 9).

Proximal coronary sinus blood flow before the first dilation was 129 ± 34 ml/min, falling to 92 ± 27 ml/

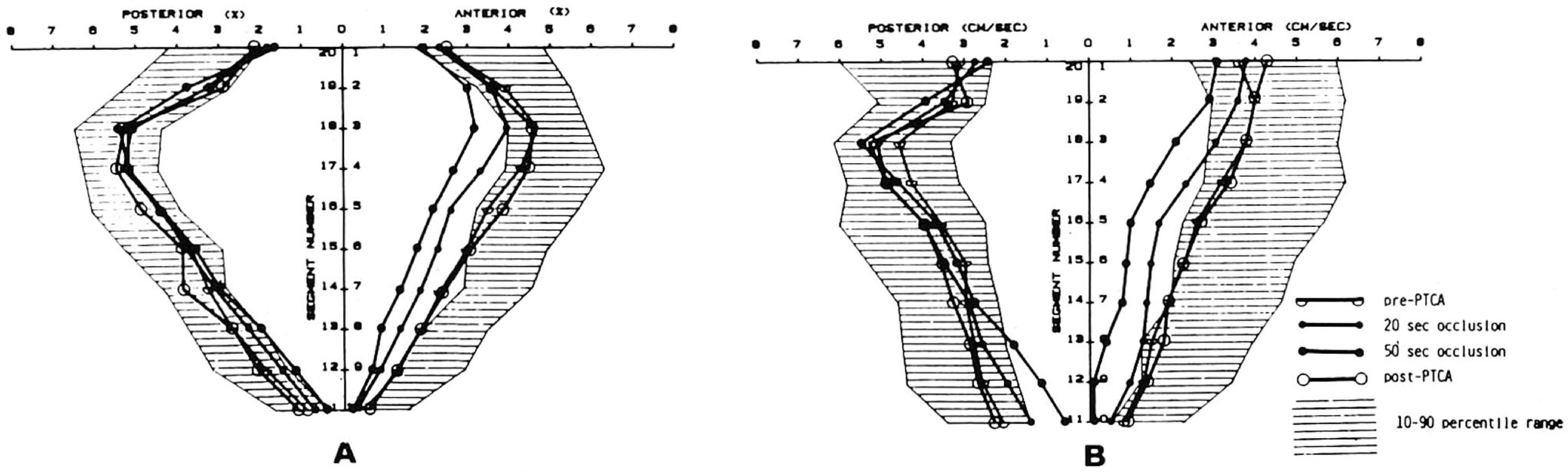

FIGURE 8. *A*, Display of the computed CREFs (regional contributions to ejection fraction) after a 20 or 50 sec occlusion of the left anterior descending artery. On the x axis the CREFs of the anterior and inferoposterior wall areas are displayed (%), while on the y axis the segment numbers of the anterior wall (1 to 10) and of the inferoposterior wall (11 to 20) are depicted. The shaded zones represent the 10th to 90th percentile area of CREFs in normal individuals. *B*, Mean ejection phase velocity before PTCA and after 20 and 50 sec occlusions of the left anterior descending artery. On the x axis the velocity values of the anterior and inferoposterior wall areas are displayed (cm/sec) while on the y axis the segment numbers of the anterior wall (1–10) and of the inferoposterior wall (11–20) are depicted. The shaded zones represent the 10th to 90th percentile area in normal individuals.

TABLE 3
Ejection phase velocity and regional contribution to ejection fraction (CREF)

	Mean ejection phase velocity (cm/sec)				CREF (%)			
Segment No.	Before PTCA (n = 10)	15 sec occl. (n = 10)	45 sec occl. (n = 7)	After PTCA (n = 10)	Before PTCA (n = 10)	15 sec occl. (n = 10)	45 sec occl. (n = 7)	After PTCA (n = 10)
1	3.6±1.0	3.8±1.5	3.1±1.5	4.3±1.5[A]	2.3±0.4	2.3±0.5	1.9±0.7	2.5±0.5[B]
2	4.0±1.3	3.6±1.2[A]	2.9±1.5[B]	4.0±1.8	3.9±0.9	3.6±0.8	3.0±1.0[A]	3.6±0.8
3	3.8±1.2	3.1±1.3[A]	2.1±1.4[C]	3.8±1.6	4.7±0.9	4.0±0.8[C]	3.2±1.0[C]	4.6±0.8
4	3.2±1.0	2.4±1.3[A]	1.5±1.5[C]	3.4±1.4	4.3±1.0	3.4±1.0[B]	2.7±1.4[C]	4.5±0.7
5	2.6±0.9	1.7±1.1[A]	1.0±1.4[C]	2.7±1.1	3.5±1.0	2.6±1.0[A]	2.2±1.6[C]	3.9±0.6
6	2.3±0.8	1.5±0.9[B]	0.9±1.3[C]	2.3±0.8	3.0±0.8	2.3±0.9[B]	1.8±1.5[B]	3.1±0.4
7	1.9±0.8	1.4±1.0	0.8±1.3[A]	1.9±0.7	2.4±0.7	1.9±0.1[A]	1.4±1.2[B]	2.5±0.5
8	1.5±0.6	1.3±0.9	0.4±1.2[A]	1.8±1.0	1.9±0.5	1.4±0.7[A]	0.9±0.8[C]	1.9±0.7
9	1.3±0.5	1.0±1.0	0.1±1.0	1.4±0.9	1.3±0.4	0.9±0.6[A]	0.7±0.8[A]	1.3±0.6
10	0.8±0.7	0.5±1.3	0.1±0.9	0.9±0.9	0.6±0.3	0.3±0.5	0.2±0.6	0.6±0.5
11	3.1±1.0	2.7±0.7	2.4±0.7[A]	3.3±0.9	2.1±0.4	1.8±0.3	1.6±0.3[C]	2.1±0.4
12	3.3±2.0	3.5±2.1	4.0±2.3	2.9±1.5	3.3±1.2	3.3±1.4	3.8±1.5	2.9±1.3
13	4.6±1.3	5.1±1.0	5.5±1.2[A]	5.3±1.7	5.2±0.7	5.1±0.7	5.4±1	5.3±1.1
14	4.3±1.0	4.9±0.8[A]	4.6±1.0	4.9±1.4	5.2±0.5	5.3±0.3	5.2±0.4	5.5±0.8
15	3.6±0.6	4.0±0.7[A]	3.7±1.0	4.0±1.1	4.5±0.4	4.4±0.5	4.4±0.4	4.9±0.6[A]
16	3.0±0.5	3.5±0.9	3.2±1.1	3.6±1.3	3.7±0.4	3.8±0.4	3.6±0.3	3.9±0.5
17	3.0±0.6	2.9±1.0	2.8±1.2	3.3±1.3	3.3±0.5	3.1±0.5	3.0±0.7	3.9±0.5
18	2.8±0.7	2.6±0.9	1.9±1.1[A]	2.9±1.2	2.7±0.5	2.3±0.3[A]	2.0±0.5[C]	2.7±0.5
19	2.6±0.5	2.0±0.7[A]	1.2±1.0[C]	2.7±1.1	1.9±0.5	1.5±0.3[A]	1.2±0.4[C]	2.1±0.5
20	2.1±0.9	1.4±1.1	0.6±1.0[C]	2.3±1.2	0.9±0.4	0.7±0.3	0.4±0.5[C]	1.1±0.4

Values are mean ± SD.
[A]p < .05; [B]p < .01; [C]p < .005 vs before PTCA.

TABLE 4
Reactive hyperemia and arteriovenous lactate difference after sequential transluminal occlusions

	Before PTCA (range)	First occl. (range)	Second occl. (range)	Third occl. (range)	Fourth occl. (range)	Fifth occl. (range)	Sixth occl. (range)	After PTCA (range)
No. of patients	20	20	20	19	9	7	4	20
Average duration of transluminal occlusion per patient (sec)	— —	41±13[A] (10,60)	44±14 (20,70)	51±15 (25,90)	52±11 (30,70)	54±11 (30,65)	54±12 (40,75)	— —
p value (vs first occlusion)			<.005	<.005	<.02	<.02	NS	
Coronary sinus blood flow (ml/min)	129±34 (101,152)	152±44 (97,203)	155±37 (101,203)	161±31 (110,210)	167±40 (116,200)	161±44 (95,187)	— —	144±35 (110,189)
p value (vs before PTCA)		<.001	<.001	<.0005	<.01	<.01		NS
GCV flow (ml/min)	69±17 (40,99)	107±31 (66,152)	127±39 (81,210)	132±22 (109,167)	112±33 (66,160)	109±33 (67,167)	110±33 (99,152)	82±9 (63,87)
p value (vs before PTCA)		<.001	<.0005	<.0005	<.002	<.02	NS	NS
Aorto-GCV difference in lactate (mmol/l)	+0.11±0.2 (−0.45,0.4)	−0.87±0.70 (−2.10,0.17)	−0.82±0.57 (−2.10,0.02)	−0.44±0.34 (−0.89,0.0)	−0.62±0.42 (−1.50,0.18)	−0.64±0.37 (−1.30,0.13)	— —	+0.18±0.09 (0.06,0.31)
p value (vs before PTCA)		$<10^{-4}$	$<10^{-6}$	$<10^{-4}$	$<10^{-5}$	<.01		NS

GCV = great cardiac vein.
[A]Mean ± SD.

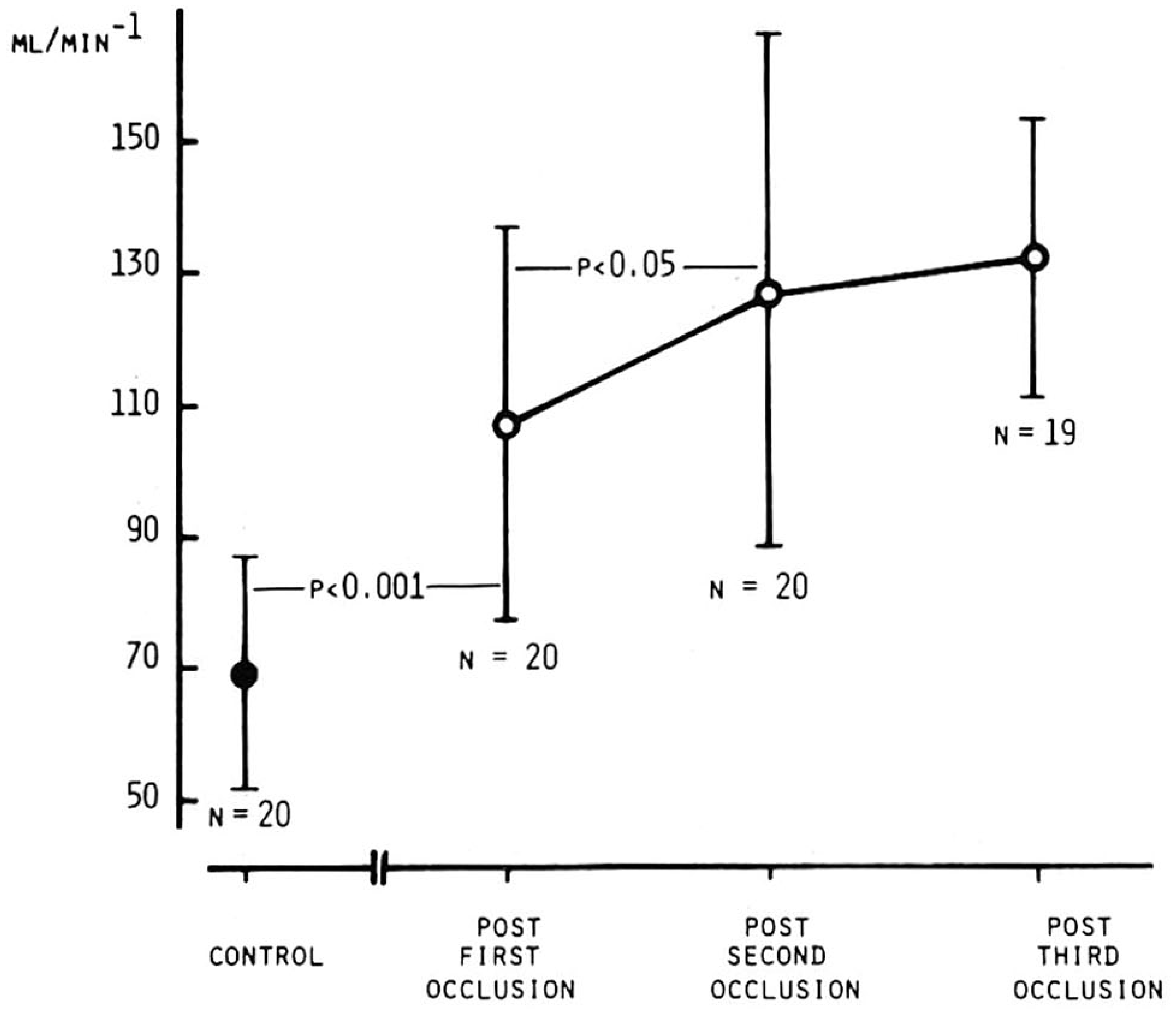

FIGURE 9. Great cardiac vein flow during control measurements and after three sequential episodes of reactive hyperemia.

min ($p < 10^{-5}$) during transluminal occlusion and rising to 152 ± 44 ml/min ($p < 10^{-4}$) after the first balloon deflation.

During the peak reactive hyperemia that followed the third dilatation, the coronary sinus blood flow was 161 ± 31 ml/min. There was no difference in resting pre-PTCA and post-PTCA levels of great cardiac vein or coronary sinus blood flow.

The arteriovenous lactate measurements are also listed in table 4. The control measurements showed a difference of +0.11 ± 0.2 mmol/liter, which decreased to −0.87 ± 0.70 and −0.82 ± 0.57 mmol/liter, after the first and the second dilatations, respectively. After the third dilatation the lactate difference was −0.44 ± 0.34 mmol/liter, which was not significantly different from the values recorded after the first and the second dilatation; after the fourth, the fifth, and the sixth dilatations the number of measurements was too small to demonstrate a significant increase or decrease in lactate production.

Discussion

Global and regional left ventricular performance. The earliest (1 to 15 sec after occlusion) and most sensitive hemodynamic indicator of regional perfusion deficit proved to be an impairment in early relaxation, with extreme prolongation of T_1, the time constant of the early relaxation phase. If the premise of the two time constant model previously described[10] is correct, then the early change in T_1 with constant T_2 represents an exacerbation in the asynchrony of relaxation. This is illustrated by the change in negative dP/dt and wall displacement induced by a 20 sec coronary occlusion (figure 6, *B*). Within 4 or 5 beats after occlusion, a distinct deformation appears in the ascending limb of the negative dP/dt curve and in the next 10 sec this deformation reaches the same height as peak negative dP/dt, which in the meantime has progressively decreased to its nadir. Accompanying this change in negative dP/dt, the ischemic segments exhibit a biphasic inward-outward wall displacement that occurs after valve closure and peak negative dP/dt. During the remainder of relaxation and rapid filling the ischemic segments display a second wave of inward wall displacement. The beginning of this second wave of wall displacement in early diastole corresponds closely in time to the irregularity in dP/dt. In the same way, the peak inward displacement of the control segment is consistently observed near the notching in the dP/dt. Shortly after this point, the pressure ceases to have a relaxation time constant T_1 and abruptly switches to T_2. On the other hand, after 50 sec of occlusion the majority of the ischemic segments are akinetic and exhibit an increased regional stiffness, whereas T_1 tends to return toward less abnormal values. In our study, at 50 sec the deformity in negative dP/dt was no longer present.

The connection between transient asynergy, myocardial ischemia, and alteration in the time course of relaxation was pointed out as early as 1969 by Tyberg et al.,[16] who designed an experimental preparation consisting of two papillary muscles in series. They demonstrated that when one muscle of the pair is hypoxic but still contracting it disturbs the time course of the total fall in tension generated by the two muscles much more than when one of the muscles in series is not contracting at all and is infinitely stiff.[16] More recent studies in conscious animals after experimental coronary occlusion have indicated that ventricular dyssynchrony due to late systolic contraction and relaxation in different regions can produce marked effects on the linearity and maximal rate of fall in pressure in the left ventricle.[17–19]

Our results suggest that a similar phenomenon may occur in the intact human heart during acute ischemia. At 20 sec the late systolic outward displacement of the ischemic segment is probably passive and due to a simultaneously increased and active inward displacement of the nonischemic segments. Conversely the early diastolic inward displacement of the ischemic segments must correspond to an accelerated outward displacement of the normal segment. Ultimately after 20 sec of ischemia the ischemic zone acts as an additional elastic element in series with the actively contracting and relaxing nonischemic segment. This mechanism is consistent with the model of left ventricular pressure relaxation recently proposed by our group[10] in which it is assumed that the observed time constant T_1 results from the combined action of that fraction of the myocardium in the process of relaxing and the remaining fraction in which relaxation has not yet been initiated.

Coronary hemodynamics. The mean great cardiac vein flow of 69 ml/min reported here is well within the range previously reported.[5, 6, 20] This is in agreement with Rothman et al.,[21] who reported a flow of 76 ml/min before angioplasty. In their study the mean hyperemic increase in great cardiac vein flow was 29.9% above control flow after the first inflation, compared with 59.3% above control after the final inflation.

In our patients the mean hyperemic increase in great cardiac vein flow was 55% after the first dilatation and 91% after the third dilatation (figure 9). In a subset of nine patients who needed more than three dilatations to satisfactorily reduce the transstenotic gradient, the values of reactive hyperemia were less elevated, ranging between 58% and 63%. As observed by Rothman et al.,[21] more pronounced reactive hyperemia developed when the residual functional coronary stenosis associated with the deflated PTCA balloon was reduced by subsequent dilatations.

In general, our values for reactive hyperemia are higher than those found by Rothman et al.[21] This difference might be explained by the difference in the mean duration of balloon inflation, which was 9.8 ± 3.7 sec in their patients compared with 41 ± 13 sec in our patients. These prolonged occlusion times (41 to 54 sec) are due to the fact that we kept the balloon inflated as long as the patient did not manifest any clinical signs of ischemia. In fact, we have noticed that the duration of balloon inflation could be gradually prolonged during subsequent dilatations, as if the anginal threshold had increased after these repeated occlusions.

Metabolic disturbances. Recently, coronary sinus K^+ concentration was measured continuously in two patients undergoing angioplasty of significant stenoses of their left anterior descending coronary arteries.[22] The recordings obtained from these patients showed that, although coronary sinus K^+ levels did not change significantly during coronary occlusion, a transient rise occurred when the occlusion was removed. After reducing pressure in the balloon, the coronary sinus K^+ levels began to rise within 8 sec. This fits exactly with the timing of peak reactive hyperemia observed in our study and by Rothman et al.[21] In our patients, blood samples were obtained 10 to 15 sec after the start of deflation. Since we could not record the great cardiac vein flow during the sampling period, we did not express our results in terms of lactate efflux. The less elevated concentration (−0.44 mmol/liter) in the great cardiac vein after the third sequential occlusion does not necessarily reflect a reduction in lactate production since the reactive hyperemia measured before the sampling was significantly ($p < .05$) greater (132 ml/min) than that measured after the first and second occlusions.

As a first approximation, the amount of lactate lost from the ischemic tissue during the first two occlusions seems to be constant and at least does not increase with subsequent occlusions. The crucial conclusion to be drawn from the observation that a few minutes after termination of this procedure the lactate balance again becomes positive is that metabolic disturbances induced by repeated ischemia are reversible.

Clinical implications. Experimental data on atherosclerotic vessel segments have shown that volume reduction of atherosclerotic tissue is related to the duration of pressure application. These findings have led many clinicians to use longer inflation durations (30 to 60 sec) during PTCA.[23, 24] On the other hand, Braunwald and Kloner[25] have recently addressed the question of whether the myocardium can become chronically, even permanently, "stunned" as a consequence of repeated episodes of myocardial ischemia. Although most episodes of transient ischemia produced in our patients during PTCA were not as severe as those produced in animal studies,[17, 18, 26] the total duration of episodes of occlusion used during PTCA has increased considerably since our initial experience; the median is now 4 min and in a few cases it has exceeded 10 min in our laboratory.[2] The total occlusion time of 4 min might be excessive since it has been demonstrated in conscious dogs that the return of myocardial function is delayed after periods of coronary occlusion as brief as 100 sec. In this case, however, hyperemia that occurs normally during reperfusion is prevented by a residual subtotal occlusion[27] and there is no such occlusion after successful PTCA. In this respect, the results of the present study seem to be reassuring since there is no evidence of global or regional myocardial dysfunction even after four to six coronary occlusions of 40 to 60 sec each.

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