Exercise-induced Ischemia: The Influence of Altered Relaxation on Early Diastolic Pressures

JOHN D. CARROLL, M.D., OTTO M. HESS, M.D., HEINZ O. HIRZEL, M.D., AND HANS P. KRAYENBUEHL, M.D.

SUMMARY Left ventricular pressure (LVP) decay and early diastolic pressures were studied at rest and during exercise in three groups of patients. Patients in the ischemia group (n = 15) had coronary artery disease and developed new regional wall motion abnormalities documented by biplane LV cineangiography during exercise. Patients in the control group (n = 4) had a normal exercise response. Patients in the scar group (n = 5) had prior infarction, akinetic scars and no ischemia with exercise. Isovolumic pressure data were used to compute the time constant (T) of LVP decay (from the linear relation of LVP and negative dP/dt) and an extrapolated baseline pressure (P0) at dP/dt = 0. During exercise in the ischemia group, minimal LV diastolic pressure (P0) increased from 9 ± 3 to 21 ± 5 mm Hg (p < 0.001), end-systolic volume increased from 38 ± 7 to 55 ± 8 ml/m² (p < 0.001) and P0 rose from −10 ± 7 to 11 ± 8 mm Hg (p < 0.001); T decreased (from 55 ± 9 to 37 ± 8 msec, p < 0.001), although inadequately, compared with the decrease in the control group (from 49 ± 15 to 22 ± 2 msec, p < 0.01). Relaxation at P0 during exercise was incomplete in the ischemia group (2.2 ± 0.4 T) and complete in the control group (3.8 ± 0.7 T, p < 0.05). The time course of LVP fall was extrapolated from the isovolumic period into the passive LV filling phase. The extrapolated pressure at the time P0 occurred (P0) rose from 0 ± 4 to 20 ± 7 mm Hg with ischemia (p < 0.001). Thus, the characteristics of LVP decay can account for the elevated early diastolic pressures during ischemia.

In contrast, the scar group maintained a low P0 during exercise (11 ± 3 to 8 ± 3 mm Hg), even though T decreased inadequately (from 66 ± 10 to 36 ± 5 msec, p < 0.01), because P0 did not shift upward. Ischemia-related pressure elevations involve both delayed relaxation and a pressure baseline shift.

During exercise, LVP decay is normally adjusted to maintain low diastolic pressures; with exercise-induced ischemia, LVP decay is abnormal and early diastolic pressures are severely elevated.

DIASTOLIC PRESSURES frequently increase dramatically during ischemia. The mechanism for the pressure increase has attracted much attention in both clinical and experimental studies.1,3 Impaired relaxation, ventricular interaction, viscous effects, and intrinsic myocardial compliance changes are only some of the proposed mechanisms. Because late as well as early diastolic pressures rise with ischemia, different mechanisms may be operative at different times. Late diastolic pressures are believed to reflect the ventricle’s passive properties. Ventricular interaction would be increasingly important later in diastole. Early diastolic pressures would be expected to reflect the decay of pressure from the preceding systole. This study describes the influence of pressure decay on early diastolic pressures and provides information regarding the abnormalities in relaxation produced by ischemia and by prior infarction.

Previous clinical studies have most often used pacing tachycardia to induce ischemia.2,4 Most episodes of ischemia in patients with coronary artery disease are provoked by exercise. We used dynamic exercise to induce ischemia during cardiac catheterization. Alterations in relaxation and diastolic pressures in patients with ischemia were compared with the normaladjustments in left ventricular pressure decay in control patients.

Brutsaert and co-workers5 reviewed the factors that may determine relaxation in isolated muscle and the intact ventricle. The changes in loading conditions, adrenergic tone, and synchrony that accompany both exercise and ischemia appear to alter left ventricular pressure decay. The relative contribution of each of these and other factors is difficult to measure in clinical studies. Therefore, we also compared the patients with exercise-induced ischemia with patients who have akinetic scars from previous infarction and no ischemia during exercise. During exercise, the scar group, like the ischemia group, has an inhomogenous contraction pattern that may affect left ventricular pressure decay.

Methods

Patients

Twenty-four patients (23 men and one woman) were evaluated by right- and left-heart catheterization and biplane cineangiography at rest and during supine bicycle exercise. The control group consisted of four patients who had no or minimal cardiovascular disease (two no abnormalities, one minimal coronary artery disease and one minimal mitral valve prolapse). The ischemia group consisted of 15 patients who had significant coronary artery disease (> 50% diameter narrowing (13 with three-vessel, one with two-vessel, and one with one-vessel disease). All had no or minimal regional hypokinesis on the resting angiogram and an exercise-induced regional wall motion abnormality; 10 also had angina. The scar group consisted of five patients who had had an infarction and also had a large

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akinetic area on the resting angiogram and no new regional wall motion abnormalities during exercise. None had angina, two had normal coronary arteries and three had one-vessel disease of the coronary artery corresponding to the site of infarction.

Catheterization and Cineangiography

All patients gave informed consent. Premedication consisted of 10 mg of chlordiazepoxide given orally 1 hour before catheterization. Cardiovascular medications were withheld for 12–24 hours before catheterization. Left ventricular pressure was measured with a Millar pigtail angiographic micromanometer introduced from the femoral artery. The pressures were recorded at a paper speed of 250 mm/second (Electronics for Medicine, VR-16) with the first derivative of pressure (dP/dt), (dP/dt)/P, and an intracardiac electrogram from the right-sided catheter (fig. 1). Before both resting and exercise recordings, the pressure was calibrated against a fluid-filled system.

Biplane left ventricular cineangiography was performed in the right anterior oblique (30°) and left anterior oblique (60°) projections at a filming rate of 50 frames/sec. End-diastolic and end-systolic volumes were calculated using the area-length method.

Exercise Protocol

All patients underwent precatheterization bicycle exercise testing to determine achieved work load and exercise limitations. At catheterization, pressures were recorded before and after the patient’s feet were attached to the pedals of the bicycle. All resting data presented here were recorded during the first angiogram while the legs were in this semielevated position, which accounts, in part, for the elevation in end-diastolic pressure. After the resting angiogram and a subsequent 12–15-minute pause, exercise was begun at a low level. Patients exercised at progressively higher work loads until either angina or other limiting symptoms occurred or until they achieved a predicted submaximal heart rate according to sex, height, and age. At peak exercise, pressures were again recorded and simultaneous cineangiography was completed. Coronary arteriography was performed after exercise using the Judkins technique.

Data Analysis

Resting and exercise data were derived from beats selected during simultaneous pressure measurement and left ventricular cineangiography. The beat analyzed was well opacified and within 5 seconds of the beginning of contrast injection. All beats were nonpotentiated sinus beats. Resting beats were from midinspiration and exercise beats were average beats if any respiratory-related changes were noted. The Valsalva maneuver was avoided by patient instruction, observation of the diaphragm, and right atrial pressure monitoring. No patient included had significant mitral regurgitation at rest or with exercise.

Pressure tracings were digitized for an entire cardiac cycle by an electronic digitizer (Numonics Corp.) interfaced with a Digital computer (PDP 11/10). A previously described program produced a printout of pressure and dP/dt values with a time interval of 3–10 msec, depending on heart rate (each cycle was divided into 130 time intervals).6 The time constant of relaxation (T) was calculated as the negative reciprocal of the slope of the linear regression of pressure and dP/dt coordinates.7 These coordinates were taken from the isovolumic period defined as from immediately after maximal negative dP/dt to the time pressure had fallen to 5 mm Hg above left ventricular end-diastolic pressure. The linear regression of pressure and dP/dt coordinates was also characterized by its pressure axis intercept. This extrapolated baseline pressure (P_B), calculated at dP/dt = 0, represents a baseline to which pressure would fall if decay continued indefinitely. We compared this extrapolated pressure decay to the observed pressures after mitral valve opening. At the time of the lowest observed diastolic pressure (P_D), an extrapolated pressure (P_E) was calculated from the following equation adapted from Raff and Glantz2:

\[ P_E = (P_0 - P_B)e^{-t/T} + P_B, \]

where \( P_0 \) = the pressure at maximum negative dP/dt, \( t = \) the time of the lowest diastolic pressure after maximal negative dP/dt, and \( T = \) the time constant of isovolumic pressure decay (fig. 2).

To study the completeness of relaxation we used the technique of Weisfeldt and co-workers,8 which assumes relaxation to be 97% complete at 3.5 time con-
Figure 2. The observed fall in left ventricular pressure (LVP) is compared with the extrapolated pressure decay. The early relaxation period (ERP) is between maximal negative dP/dt and mitral valve opening (MVO). During this isovolumic period, pressure decay can be characterized by a time constant (T) and a baseline pressure (P_b). Using these values, pressure decay was extrapolated (P_e) to where the observed diastolic pressure reached its nadir (P_e).

stants (T's) after maximal negative dP/dt. The number of T's elapsed was computed at the time of lowest diastolic pressure in the rest and exercise states.

The normal relation between T and heart rate was described by a linear regression of values during graded exercise in the control patients.

Differences between resting and exercise values were tested for statistical significance by paired t test. Differences between the three groups were tested with an analysis of variance.

The application of a monoexponential model of pressure decay was tested by comparing the correlation coefficients from pressure vs dP/dt plots in the three groups. At rest, the mean correlation coefficient was -0.991 (range 0.975–0.999) in the control group, -0.989 (range 0.967–0.998) in the ischemia group and -0.994 (range 0.991–0.997) in the scar group. During exercise there were no significant changes. The control group had a correlation coefficient of -0.980 (range 0.962–0.993), the ischemia group -0.985 (range 0.974–0.997), and the scar group -0.985 (range 0.971–0.993). A one-way analysis of variance failed to find any significant differences between groups.

Results

Left ventricular pressures and derived data are presented in table 1. Table 2 contains angiographically derived data. Data are presented in tables and text as the mean ± SD.

An example of the left ventricular pressure curve at rest and during exercise-induced ischemia (ischemia group) is presented in figure 1.

Patients in the ischemia group achieved a mean maximal work load of 123 W after 4.4 minutes of exercise. Control patients exercised for a mean of 3.9 minutes to a mean maximal work load of 113 W. Scar group patients exercised for a mean of 5.4 minutes to a mean maximal work load of 131 W. No patient in the scar or control groups had exercise-induced angina.

During exercise in the ischemia group, left ventricular end-diastolic pressure increased from 22 to 38 mm Hg (p < 0.001) and end-diastolic volume increased from 105 to 114 ml/m² (p < 0.001). End-systolic volume increased from 38 to 55 ml/m² (p < 0.001) and ejection fraction decreased from 64% to 52% (p < 0.001).

With leg elevation in preparation for exercise, the left ventricular end-diastolic pressure of the control group increased from 11 to 24 mm Hg, reflecting the preload increase and also the bradycardia present in two of the patients. During exercise, the control group had no rise in end-diastolic pressure or volume. End-systolic volume decreased from 37 to 26 ml/m² (p < 0.001) and ejection fraction increased from 63% to 75% (p < 0.001). The scar group had an insignificant increase in end-diastolic pressure with exercise (from 22 to 26 mm Hg) and volume (from 101 to 108 ml/m²). There was no significant change in end-systolic volume (from 52 to 54 ml/m²) or ejection fraction (from 49% to 50%).

During exercise, the ischemia group increased its heart rate from 64 to 118 beats/min (p < 0.001), and T decreased from 55 to 37 msec (p < 0.001). In the control group, the heart rate increased from 68 to 128 beats/min (p < 0.01) and T decreased from 49 to 22 msec (p < 0.05). This change in T was significantly greater than that in the ischemia group (p < 0.05). The scar group also had a decreased T with exercise (from 66 to 36 msec, p < 0.05), but the change was less than that in the control group (p < 0.05). The relationship between heart rate and T is further illustrated in figure 3. In the control group, heart rate and T correlated strongly (r = -0.90, n = 15). For a given heart rate during exercise, T was prolonged in patients in the ischemia and scar groups compared with the control group values.

Representative plots of pressure and negative dP/dt isovolumic coordinates from the three groups are shown in figure 4. All three had a steeper slope (reduced T) with exercise; yet the relative position of the exercise coordinates in the plots in the ischemia group differs from those in the other two groups. The pressure intercept at dP/dt = 0 (P_e) increased from -10 to 11 mm Hg in the ischemia group (p < 0.001). P_e changed only slightly (from 0 to 3 mm Hg) in the control group and declined insignificantly in the scar group (from -7 to -22 mm Hg). Therefore, pressure decay during exercise-induced ischemia is altered by both a failure to increase relaxation rate adequately and a rise in baseline pressure.
TABLE 1. Left Ventricular Pressure Data

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*p < 0.05, rest vs exercise.
†p < 0.01, rest vs exercise.
‡p < 0.001, rest vs exercise.

Abbreviations: LVP = left ventricular pressure; LVEDP = left ventricular end-diastolic pressure; T = time constant of relaxation; P_E = pressure baseline; P_E = extrapolated pressure; P_L = lowest pressure.

P_L rose dramatically in the ischemia group, from 9 to 21 mm Hg (p < 0.001). In the control group, P_L decreased insignificantly, from 11 to 4 mm Hg, as it did in the scar group, from 11 to 8 mm Hg. The elevated P_L during exercise in the ischemia group was significantly greater than that in the other two groups (p < 0.05). P_E also rose in the ischemia group, from 0 to 20 mm Hg (p < 0.001), but declined insignificantly in the control group, from 7 to 3 mm Hg, and in the scar group, from 3 to -6 mm Hg. The elevated P_E during exercise in the ischemia group was significantly greater than that in the other two groups (p < 0.05). Thus, the observed changes in early diastolic pressures are paralleled by shifts in pressures extrapolated from isovolumic data. The elevated P_L during ischemia is primarily composed of incompletely decayed pressure from the previous contraction accompanied by a pressure baseline shift.

The completeness of pressure decay at P_L was measured as the number of T's elapsed (fig. 5). The ischemia group had incomplete relaxation both at rest and with exercise (2.4 to 2.2 T, NS). During exercise, relaxation became complete in the control group (2.5 to 3.8 T). The scar group had incomplete relaxation at P_L both at rest and with exercise (2.1 to 1.8 T). During exercise the number of T's elapsed was significantly greater in the control group than the other two groups (p < 0.05). The time between P_L and maximal negative dP/dt did not differ at rest or with exercise among the three groups. For all patients, the time of P_L was 127 msec at rest and 77 msec during exercise. Therefore, relaxation is normally completed at P_L during
exercise, but is incomplete in the presence of ischemia or scar from prior infarction.

Discussion

Complex alterations in cardiovascular function during exercise allow a large increase in cardiac output while maintaining normal diastolic pressures. Our data show that during exercise-induced ischemia there is a dramatic rise in early diastolic pressures that is chiefly explained by an abnormal pressure decay. The rate of pressure fall is inadequate, resulting in incomplete relaxation into early diastole. In addition, $P_E$ shifts upward, which may prevent pressure from falling to normal levels.

The alterations in left ventricular relaxation we have shown are probably related to changes in multiple determinants of relaxation. Loading conditions, adrenergic tone, synchrony of contraction and relaxation, and contractility have been shown by multiple investigators to influence the rate of left ventricular pressure decay. Brutsaert and co-workers have recently summarized the evidence for the controlling mechanisms of relaxation. Ischemia, as well as exercise, may alter the determinants of relaxation in a complex fashion. In all groups we observed an increased rate of pressure decay after exercise, which probably reflects the significant influence of enhanced adrenergic tone. Craig and Muro$^8$ have shown similar reductions in $T$ during exercise in normal man. In our ischemia and scar groups, $T$ decreased inadequately compared with controls. The presence of a large akinetic area or ischemic region may impair the rate of pressure decay because of the inhomogenous contraction pattern. Blaustein and Gaasch$^9$ have shown prolonged rates of pressure decay when a temporal disruption of ventricular contraction is produced by ventricular pacing in the canine left ventricle. An additional influence on relaxation during exercise-induced ischemia is the acute increase in end-systolic volume. Animal studies have shown that acute end-systolic volume changes prolong $T$. Thus, loading conditions and ventricular synchrony may, by themselves, be responsible for delayed relaxation in ischemia.

The net effect of ischemia on the determinants of relaxation is to prolong group relaxation relative to controls. This prevents pressure decay from being completed early in diastole. In the normal left ventricle during exercise, the rapid relaxation rate achieves a low pressure very early in diastole, which balances the effect of a tachycardia-induced shortening of diastole. After infarction, the residual scar limits the rate of pressure decay, yet early diastolic pressures are not elevated during exercise. This illustrates the importance of combined alterations of $T$ and $P_E$ in determining early diastolic pressures. The combined influence of $T$ and $P_E$ can be quantitated in $P_E$ at $P_L$. The scar group and the ischemia group both had abnormal $T$'s with exercise, but only the ischemia group had a significant upward shift in $P_E$, which caused $P_E$ to rise during exercise in the ischemia group, but not in the scar group. This paralleled the changes in the observed pressure $P_L$. This key distinction in the relax-
TABLE 2. Left Ventricular Volume Data

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*p < 0.01, rest vs exercise.
†p < 0.001, rest vs exercise.

Abbreviations: EDVI and ESVI = end-diastolic and end-systolic volume indexes; EF = ejection fraction; R = rest; E = exercise.

FIGURE 4. Negative dP/dt and left ventricular pressure (LVP) data from representative patients. The time constant (T, in milliseconds) of relaxation is the negative reciprocal of the slope of the linear regression of dP/dt and pressure coordinates during isovolumic relaxation. The regression line is extended by the dashed line to the pressure-axis intercept (P_b). In each patient, T decreased with exercise, although the control patient achieved a lower T. In addition, the exercise data from the control and scar patients were clearly shifted to a lower position on the dP/dt axis. The ischemia patient did not have this shift and P_b became greater.
During dissociation relaxation, pressure falls 97% from its initial value when 3.5 T's have elapsed. In all groups at rest (R), relaxation was incomplete at $P_L$. During exercise (E), three of four control patients had complete relaxation at $P_L$. All patients developing ischemia or who had scars from prior infarction had incomplete relaxation during exercise.

FIGURE 5. To quantitate the extent of pressure decay at the early diastolic pressure nadir ($P_D$), the number of time constants (T) elapsed was computed. According to this technique, pressure has fallen 97% from its initial value when 3.5 T's have elapsed. In all groups at rest (R), relaxation was incomplete at $P_L$. During exercise (E), three of four control patients had complete relaxation at $P_L$. All patients developing ischemia or who had scars from prior infarction had incomplete relaxation during exercise.

The calculation of relaxation variables is based on a simplified mathematical model of pressure decay. Raff and Glantz discussed the deviations of observations from this model. The extrapolation of pressure past the isovolumic period assumes that pressure decay continues in the same manner. Deviations from a monoexponential pressure fall clearly would influence these extrapolated pressures. Yellin and co-workers showed in the transiently nonfilling canine heart that for alterations in $P_B$. In addition, some investigators have suggested that elastic recoil may be an important mechanism in early diastolic mechanics. In animal studies where ventricular filling is prevented by acute mitral orifice occlusion, pressure decay continues to negative intraventricular values. The degree of negativity appears to be modulated by end-systolic volume, which may represent the stored, potential energy for elastic recoil. The $P_B$ we observed did not always follow directional changes in end-systolic volume. The baseline pressure measured by Yellin and co-workers and our $P_B$ are not, therefore, equivalent. It is not known whether elastic recoil is present in the normal heart under resting conditions. The disruption by ischemia of an elastic recoil mechanism may be complex; some areas of the myocardium have an acute increase in end-systolic length (possible loss of recoil), while others have hypercontractile function and decreased end-systolic lengths during exercise (enhanced recoil). Our data on global pressure decay cannot separate the possible effects of these various mechanisms during exercise and ischemia.

Our extrapolation of pressure decay utilizes the characteristics of the actual pressure decay during isovolumic relaxation. Pressure in early diastole would be expected to reflect not only pressure decay from the preceding contraction, but also ventricular volume, filling, and viscosity. During ischemia the extrapolated pressure is very similar to the elevated diastolic pressure, which suggests a major influence of pressure decay.

FIGURE 6. Theoretical pressure decays are shown when the rate of relaxation ($T$) is alone altered (right) or when the pressure baseline ($P_B$) is alone altered (left). Pressure decay is characterized by not only its rate of fall, but also by a pressure baseline. Ischemia during exercise involves an alteration in both factors.
relaxation rate increases slightly after the point when mitral valve opening would normally occur. In the filling ventricle, relaxation may be augmented by the load from the rapid early filling. Despite these potential limitations, the consistency and magnitude of our observations during ischemia support a major role of altered relaxation in the production of elevated diastolic pressures.

Grossman, Mann, and co-workers found elevated diastolic pressures during pacing-induced ischemia in man associated with abnormal relaxation variables. Despite differences in ischemia induction and characterization of relaxation, our studies agree that relaxation abnormalities are important in the pathophysiology of ischemia. Recently, Brown and co-workers reported evidence of delayed relaxation during exercise-induced angina in man.

Our resting data demonstrate that in most patients, including controls, relaxation is not completed at the lowest diastolic pressure. This has important implications for the calculation of passive left ventricular properties from pressure-volume data. The assessment of passive properties should begin with data taken after relaxation is complete.

Our data are evidence of the key role of relaxation in normal exercise physiology and its disruption with ischemia in man. Changes in loading conditions, heart rate, and contractile state allow augmentation of cardiac output, but a concomitant adjustment in relaxation is necessary to maintain low diastolic pressures. During exercise-induced ischemia in man, the adjustment is inadequate and clinically important elevations of intraventricular pressures are produced.

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