Initial Myocardial Adjustments to Brief Periods of Ischemia and Reperfusion in the Conscious Dog

MASSIMO PAGANI, STEPHEN F. VATNER, HANK BAIG, AND EUGENE BRAUNWALD

SUMMARY The changes in left ventricular (LV) dynamics induced by brief periods of ischemia (100 seconds) and subsequent reperfusion were analyzed in conscious dogs. Global LV ischemia, induced by partially occluding the left main coronary artery, reduced LV flow homogeneously and impaired LV function as reflected by decreases in LV stroke "work" (89 ± 4% M ± SE), systolic shortening (72 ± 4%), velocity of shortening (56 ± 6%), LV systolic pressure (34 ± 5%), and dP/dt (59 ± 6%). Regional LV ischemia, induced by occluding either the left circumflex or anterior descending coronary artery completely, reduced flow to the ischemic segment (82 ± 3%) while decreasing segment work (96 ± 5%), shortening (82 ± 3%), and velocity of shortening (70 ± 5%), with minimal depression of overall LV function. In both groups the extent of shortening was reduced more rapidly and greater (P < 0.01) than shortening velocity. Moreover, with localized ischemia, segment work was reduced more (P < 0.01) than shortening. With reperfusion, a transient overshoot in function above preischemic control levels was observed in both groups (global work increased by 60 ± 12% and regional work by 28 ± 4% above control). This overshoot was not dependent on adrenergic mechanisms, but was prevented by inhibiting reactive hyperemia. Thus myocardial ischemia induces a dissociation between extent and rate of myocardial shortening. A further dissociation between shortening and work is apparent with regional ischemia. After reperfusion there is a transient overshoot in function which appears to be dependent upon the associated reactive hyperemia.

INTEREST in the effects of coronary artery occlusion on the action of the heart was evident as early as 1698,1 and by the beginning of this century it was recognized that coronary occlusion was associated with a fall in arterial pressure2 and severe arrhythmias.3 However, it was not until 1935 that Tennant and Wiggers4 described in a quantitative manner the sequential changes in myocardial contraction which occur when brief periods of acute myocardial ischemia are induced in the experimental animal. Since these initial studies, it has become well recognized, largely as a result of investigations on open-chest anesthetized animals, that acute myocardial ischemia exerts a negative inotropic influence, characterized by reductions in the extent and velocity of myocardial fiber shortening and in the external work performed by the ischemic myocardium. However, general anesthe-sia, per se, not only interferes with the response of the circulation to a variety of perturbations,5 but it depresses myocardial contractility directly6,7 and might complicate the interpretation of the effects of acute ischemia. In the last few years, a number of studies on myocardial function in the presence of regional8-10 as well as global11 ischemia have been performed in the conscious dog. It has been observed that prompt reductions in myocardial performance occur and that function recovers completely upon reperfusion following brief episodes of ischemia.8,10 Interruptions of coronary blood flow for 5-15 minutes are followed by a reversal of the changes in the epicardial electrogram after a few minutes of reperfusion, but mechanical function returns to normal only after several hours.10 In another study, it was shown that 2-minute periods of regional ischemia are followed by a much more rapid recovery, i.e., function in the ischemic zone is not significantly different from control after 3 minutes of reperfusion.8 The responses to such brief episodes of ischemia are of particular interest since they occur frequently during ordinary episodes of angina pectoris in patients with coronary artery disease, when the heart’s demands for oxygen temporarily exceed its availability.

The goal of the present investigation was to characterize, in the conscious dog, the manner in which the mechanical performance of the left ventricle responds to the induction and relief of transient (100-second) episodes of ischemia. Since reduction in the blood flow in one coronary artery induces changes in myocardial function which differ in various portions of the left ventricle, alterations in performance observed with regional ischemia may reflect not only the behavior of the ischemic myocardium, but also the action of the adjacent, normally perfused myocardium on the ischemic segment.8-10 If the left ventricle were homogeneously ischemic, on the other hand, such interaction would be eliminated, and only the direct...
effects of ischemia would be exhibited. Therefore, two groups of experiments were carried out: one in which global left ventricular ischemia and the other in which regional ischemia was induced and relieved.

**Methods**

Nine mongrel dogs, weighing between 25 and 35 kg, were anesthetized with pentobarbital Na, 30 mg/kg, iv, and the chest opened in the 5th left intercostal space. In all nine dogs a miniature pressure (P) gauge was implanted within the left ventricle (LV) through a stab wound in the apex, and a hydraulic occluder was placed around the left main coronary artery. An electromagnetic flow probe was implanted around the left circumflex coronary artery in three of these dogs. Heparin-filled catheters were implanted in the thoracic aorta and the left atrium. A pair of piezoelectric crystals was implanted on the endocardial surfaces of the anterior and posterior walls to measure LV internal diameter (ID). In 14 additional dogs, a hydraulic occluder and a Doppler ultrasonic flow transducer were placed around either the left circumflex (six dogs) or the left anterior descending (eight dogs) coronary artery, 2-3 cm from the bifurcation of these vessels. Pairs of miniature ultrasonic segment length (SL) transducers were implanted 1-2 cm apart in the myocardium parallel to the fibers in the free wall of the LV in the area destined to become ischemic. This zone was delineated at the time of thoracotomy by brief interruption of flow distal to the occluder and inspection of the area of cyanosis. In 5 of the 14 dogs, an additional pair of crystals was implanted adjacent to the aforementioned crystals, but in this case on opposing epi- and endocardial surfaces of that segment to measure wall thickness. At autopsy, the positions of the pressure gauge and dimension crystals were confirmed.

The miniature pressure gauges were calibrated statically in vitro and dynamically in vivo, using the catheters in the left atrium and the aorta connected to Statham P23Db strain gauge manometers. An improved ultrasonic transit time dimension gauge was used to measure LV internal diameter, SL, and wall thickness. An improved ultrasonic transit time dimension gauge was used to measure LV internal diameter, SL, and wall thickness. A storage oscilloscope (Tektronix T912) was used to obtain instantaneous plots of LVP vs. LVID, i.e., pressure-diameter (P-D) loops for the global ischemia experiments. Similarly, LVP vs. LVSL, i.e., pressure-segment length (P-L) loops, were obtained for the experiments on regional myocardial ischemia (Fig. 1). The pressure signal was connected to the y axis and the dimension signal (ID or SL) to the x axis. In prior studies the area of the P-D loop has been used to provide an index of total LV stroke work16 and the area of the P-L loop to provide an index of regional myocardial work.16-18 Obviously, stroke work is dependent on several factors, e.g., heart rate, preload, and afterload, and thus its use as the sole indicator of myocardial performance is limited. However, the areas of P-L loops have been shown to correlate well with regional myocardial performance,14 particularly during ischemia.15 The areas of the pressure-dimension loops were calculated with a digital planimeter from photographs taken during the control state and at selected intervals through the periods of ischemia and reperfusion. Five to seven beats were superimposed and averaged, except during the very rapid changes occurring with induction of ischemia and early reperfusion when values from single beats were used. In addition to examining the relation between pressure and dimension, we studied the relation between systolic shortening and its first derivative (i.e., dD/dt or dL/dt) by connecting the dimension signal during ejection to the x axis and its velocity to the y axis of the oscilloscope (Fig. 1). It was possible in this manner to analyze simultaneously the effects of ischemia and reperfusion on myocardial work, and on the extent and rate of change of dimensions. Control and response values in the same animals were compared by the paired t-test.16

**Protocol**

Experiments were performed 3-4 weeks postoperatively, when the dogs were apparently well and had recovered from operation. LVP, LV end-diastolic P (LVEDP), the rate of change of LVP (dP/dt), and heart rate were measured in both groups of dogs. LVID and its rate of change (dD/dt) were recorded in the experiments on global ischemia, and SL and its rate of change (dL/dt) were recorded for the experiments on regional myocardial ischemia. In five experiments, LV wall thickness of the ischemic zone was measured as well. These variables were recorded continuously during the control state, when the trained, conscious, unsedated dogs rested quietly, and throughout the development of global or regional ischemia and subsequent reperfusion, until all variables had returned to the preocclusion control values. Global myocardial ischemia was induced by partially constricting the left main coronary artery by inflating the cuff occluder for 100 seconds. Regional myocardial ischemia was induced by totally occluding the left circumflex or anterior
FIGURE 1. Recordings of pressure-length loops at the top and length-velocity relations (phase-plane plot) at the bottom for one LV segment before occlusion (outer loop), and at 5, 10, and 15 seconds into the induction of regional myocardial ischemia. Note the marked disparity between the reduction in extent and rate of shortening during the onset of ischemia.

descending coronary artery for a similar period. Occlusion and reperfusion were confirmed by measurements of coronary blood flow in all experiments with regional ischemia. In seven dogs, the experiment with regional ischemia was repeated, and reperfusion was instituted in two steps. After the ischemic period, the occluder was partially released to restore mean coronary flow precisely to the preocclusion control value for a period of 3-10 minutes, which was found to be adequate for an almost complete recovery of function. The occluder then was fully released.

The extent of global ischemia was determined in six experiments in three dogs, by injecting radioactive microspheres before and during global ischemia. The extent of regional ischemia has been determined previously in our laboratory by the radioactive microsphere technique; in severely ischemic zones, flow falls by an average of 82 ± 2.7% (mean ± SE). The radioactive microsphere technique, as used in our laboratory, has been described in detail previously. After the end of the experiments the dogs were killed, the hearts excised, and 1-g samples of cardiac muscle taken from the normal as well as the ischemic areas. They were taken from every area of the LV in the case of global ischemia. The samples were placed in a γ well counter with appropriately selected energy windows. Raw count values were corrected for background activity and energy cross-over. Flow was expressed in ml/min per g of tissue.

Possible mechanisms contributing to the observed overshoot in function with reperfusion were examined by repeating the standard protocol after β-adrenergic blockade with propranolol, 2 mg/kg, iv (15 dogs), depletion of endogenous catecholamine stores with reserpine, 0.5 mg/kg, im, for 4 days (two dogs), and verapamil, 0.2 mg/kg, iv, followed by a constant infusion of 5 μg/kg per min (three dogs) and general anesthesia with sodium pentobarbital, 30 mg/kg, iv (two dogs).

Results

Global Left Ventricular Ischemia

The control values for the hemodynamic variables are shown in Table 1. Constriction of the left main coronary artery induced a prompt and marked depression of overall LV myocardial blood flow and LV function (Fig. 2). At the end of the ischemic period, there was a relatively homogeneous reduction in LV myocardial blood flow, ranging from 77 ± 1 to 89 ± 2% in the various regions of the LV (Table 2). LV systolic pressure (LVSP) and dP/dt (Fig. 3), the extent of systolic shortening, and the rate of shortening of LVID (Fig. 4) were reduced significantly. The area of the P-L loop, i.e., stroke work, was reduced by 89 ± 4% (P < 0.001), while LVEDP rose by 13 ± 3 mm Hg (P < 0.01) and heart rate by 84 ± 12% (P < 0.001).

LV end-diastolic ID rose slightly (4 ± 2%) but not significantly.

The almost immediate reduction in the extent of systolic shortening preceded the decline in the velocity of shortening (Figs. 2 and 4). In fact, while LV stroke shortening was already reduced by 10 ± 3% (P < 0.02), 10 seconds after the onset of ischemia, velocity began to

### Table 1. Maximal Effects of Ischemia

<table>
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<tr>
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<th>Global studies</th>
<th>Regional studies</th>
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<tbody>
<tr>
<td></td>
<td>Preocclusion control values (n = 9)</td>
<td>Peak effects</td>
</tr>
<tr>
<td>Work (mm Hg-mm)</td>
<td>1010 ± 64</td>
<td>113 ± 4*</td>
</tr>
<tr>
<td>Systolic shortening (mm)</td>
<td>10.3 ± 0.4</td>
<td>2.8 ± 0.1*</td>
</tr>
<tr>
<td>Velocity of shortening (mm/sec)</td>
<td>88.7 ± 3.6</td>
<td>3.8 ± 2.5*</td>
</tr>
<tr>
<td>LV pressure (mm Hg)</td>
<td>125 ± 3</td>
<td>82 ± 6*</td>
</tr>
<tr>
<td>dP/dt (mm Hg/sec)</td>
<td>3004 ± 261</td>
<td>1231 ± 180*</td>
</tr>
<tr>
<td>End-diastolic dimension (mm)</td>
<td>37.4 ± 2.2</td>
<td>38.8 ± 0.7</td>
</tr>
<tr>
<td>End-diastolic pressure (mm Hg)</td>
<td>11 ± 0.6</td>
<td>24 ± 3*</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>100 ± 6</td>
<td>184 ± 12*</td>
</tr>
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</table>

* Values significantly different from control: P < 0.01.
FIGURE 2  A typical recording of left ventricular (LV) pressure, end-diastolic pressure, \(dP/dt\), internal diameter, \(dD/dt\) (velocity), and heart rate in a conscious dog is shown for an experiment of global LV ischemia. The period of constriction of the left main coronary artery is indicated by the arrows. Note the dissociation between the extent and rate of shortening early during ischemia and the overshoot in function upon reperfusion.

decline only after a time lag of 10–20 seconds (Figs. 2 and 4), to be significantly reduced only by 30 seconds (23 ± 8%, \(P < 0.02\)).

Upon reperfusion, heart rate and end-diastolic diameter promptly returned toward control, while LV systolic \(P\) and \(dP/dt\) exhibited an overshoot rising significantly above preischemic control levels (Figs. 2 and 3). In spite of the pressure rise, the extent and velocity of shortening of LVID also increased significantly above the preischemic control levels (Fig. 3), while the area of the LVP-D loop rose by 60 ± 12% \((P = 0.01)\). This overshoot of overall LV function was transient, reaching a peak between 30 and 60 seconds after reperfusion, and rapidly returning to control in 3–5 minutes. These dynamic changes in LV function were consistent and reproducible in three consecutive episodes of global ischemia as long as complete recovery had been attained following the preceding period of ischemia. The overshoot in LV function was coincident with the reactive hyperemic response.

The extent of reactive hyperemia was determined in dogs in which left circumflex coronary flow was measured by an electromagnetic flowmeter. The average of results in three dogs indicated that left circumflex flow rose to a peak averaging 296 ± 25% of control during reactive hyperemia.

Regional Myocardial Ischemia

The effects of brief episodes of regional ischemia were similar, although overall LV function was well maintained throughout the ischemic episode with only a slight increase in heart rate of 24 ± 7% \((P < 0.01)\) and depression of LV \(dP/dt\) of 13 ± 3% \((P < 0.01)\) from the preischemic control levels (Fig. 3). Regional function in the ischemic zone, however, was depressed strikingly (Fig. 4). As observed in prior experiments,10,12 no significant difference in mechanical10 and flow changes12 in the ischemic segment were found between experiments in which the circumflex or the left anterior descending (LAD) coronary artery were occluded. Therefore, data obtained from LAD and circumflex coronary artery occlusions were pooled. At the end of the period of occlusion, regional myocardial blood flow had fallen by 82 ± 3% from 0.95 ± 0.03 ml/min per g and end-diastolic SL was only slightly above the preischemic control level \((3 ± 1%, P < 0.05)\), whereas systolic shortening was abolished almost completely, falling by 82 ± 3% \((P < 0.001)\), and the area of the P-L loop fell by 96 ± 5% \((P < 0.01)\). Velocity of SL shortening, dL/dt, was likewise reduced by 70 ± 5% \((P < 0.001)\) although, similar to dD/dt in the experiments on global ischemia, it began to decline only after a reduction in

### TABLE 2  Effects of Constriction of the Left Main Coronary Artery on Distribution of Blood Flow to the Left Ventricle

<table>
<thead>
<tr>
<th>Description</th>
<th>Flow (ml/min per g)</th>
<th>Constriction</th>
<th>% Δ</th>
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<tbody>
<tr>
<td>Septum (base)</td>
<td>1.02 ± 0.12</td>
<td>0.13 ± 0.03</td>
<td>-87.9 ± 2.28</td>
</tr>
<tr>
<td>Septum (mid)</td>
<td>1.07 ± 0.12</td>
<td>0.15 ± 0.04</td>
<td>-86.4 ± 3.68</td>
</tr>
<tr>
<td>Septum (apex)</td>
<td>1.03 ± 0.11</td>
<td>0.13 ± 0.02</td>
<td>-87.3 ± 2.04</td>
</tr>
<tr>
<td>Posterior papillary muscle</td>
<td>0.96 ± 0.04</td>
<td>0.11 ± 0.02</td>
<td>-89.1 ± 1.71</td>
</tr>
<tr>
<td>Posterior free wall</td>
<td>1.00 ± 0.05</td>
<td>0.17 ± 0.03</td>
<td>-83.2 ± 3.65</td>
</tr>
<tr>
<td>Anterior papillary muscle</td>
<td>1.07 ± 0.08</td>
<td>0.19 ± 0.06</td>
<td>-80.4 ± 7.03</td>
</tr>
<tr>
<td>Anterior free wall</td>
<td>1.03 ± 0.07</td>
<td>0.24 ± 0.02</td>
<td>-76.6 ± 1.44</td>
</tr>
</tbody>
</table>
Figure 3. The mean ± SEM changes from control are shown for left ventricular (LV) systolic pressure, dP/dt, end-diastolic dimensions, and heart rate for nine conscious dogs in which global LV ischemia and its relief (circles), and 14 conscious dogs in which regional myocardial ischemia and its relief, were studied (triangles). Systolic shortening was already apparent. By 5 seconds after the onset of ischemia, segment shortening had declined by 14 ± 3% (P < 0.01) from control, while velocity of segment shortening started to decline after a distinct time lag of several seconds (Fig. 1). In several individual experiments, velocity was maintained for periods of time, up to 10-15 seconds, when shortening was already markedly reduced (Fig. 1).

Figure 4. The mean ± SEM changes from control are shown for left ventricular work (circles), extent of systolic shortening (squares), and velocity of shortening (triangles) for the experiments in which global ischemia was induced and followed by reperfusion (upper left), for the experiments where regional ischemia and reperfusion were induced before (upper right) and after (bottom) pretreatment with propranolol, 2 mg/kg, iv. The instant of reperfusion is shown by the broken vertical lines.
In contrast to the observations with global left ventricular ischemia, regional ischemia induced not only marked reductions in the area of the P-L loop, but also striking changes in its shape (Fig. 5). Early during the ischemic episode, at a time when systolic shortening had declined only slightly, the area of the P-L loop (regional work already was markedly reduced due to transient lengthening of SL during the decline of ventricular pressure, which occurred several cycles after the occlusion and lasted for about 15–20 seconds, i.e., until active systolic shortening had become markedly reduced. This expansion, which in some instances was equal to the extent of the initial systolic shortening, was followed by a late secondary shortening of the ischemic segment; therefore, the ischemic segment would transiently reach its end-diastolic length immediately after closure of the aortic valve, only to shorten again later when ventricular pressure had fallen. Simultaneous transient changes (but opposite in direction) in the wall thickness of the ischemic zone were observed.

Upon reperfusion, segment function was rapidly restored while coronary blood flow in the previously occluded coronary artery rose from a preischemic control of $42 \pm 5$ ml/min to a peak of $152 \pm 7$ ml/min. By 30–45 seconds, at a time when SL at end-diastole and heart rate were no longer significantly different from their preischemic control levels, the extent of shortening of SL had risen significantly above its preischemic control level (18 ± 4%, $P < 0.01$) and the area of the P-L loop rose by 28 ± 4% ($P < 0.01$) above preischemic control levels. Velocity of shortening became slightly, but on the average not significantly, elevated above the preocclusion value. This overshoot in segmental function during reperfusion was transient and subsided after 3–5 minutes at a time when coronary blood flow was no longer significantly elevated from the prior control. When subsequent episodes of regional ischemia were induced after complete recovery, the responses were characterized by changes in coronary flow and segmental function which were essentially identical to those observed during the first episode.

Mechanisms of the Functional Rebound during Reperfusion

Adrenergic Blockade

The possible role of adrenergic mechanisms in mediating the overshoot of myocardial function which occurred during reperfusion was studied by repeating the coronary occlusion after pretreatment with propranolol, 2 mg/kg, iv. Although, as anticipated, $\beta$-blockade depressed overall as well as regional myocardial function (Table 3), it did not alter the response to ischemia nor did it block the overshoot (Fig. 6). In the three dogs studied after propranolol, recovery from global left ventricular ischemia was associated with an increase in LV stroke work averaging 40% above the preocclusion control values, compared to an average overshoot of 46% prior to propranolol. A similar overshoot also was observed in one of the dogs after pretreatment with reserpine, 0.5 mg/kg, im, × 4 days plus propranolol, 2 mg/kg, iv, immediately preceding the occlusion (Fig. 6). Beta-adrenergic blockade also did not substantially modify the manner in which regional function is lost during myocardial ischemia or regained following its relief. In particular the dissociation between work and the extent of shortening on the one hand and of the velocity of shortening on the other, as well as the overshoot following reperfusion, still were present. Indeed, the latter tended to be even more pronounced than in the absence of $\beta$-blockade (Fig. 7). In 12 experiments, LV segment work increased by $66 \pm 12\% \ (P < 0.001)$, SL shortening by $48 \pm 12\% \ (P < 0.01)$, and velocity of shortening of SL by $16 \pm 4\% \ (P < 0.01)$ above the preocclusion control levels. These changes all were significantly greater ($P < 0.05$) than those observed prior to $\beta$-blockade in the same dogs. A similar overshoot in regional function was observed in one dog after pretreatment with reserpine, 0.5 mg/kg, im × 4 days.

General Anesthesia

Five separate myocardial segments were studied in two dogs. After a control occlusion and release, the dogs were anesthetized with pentobarbital sodium, 30 mg/kg, iv, and the chest was opened. This procedure greatly reduced regional myocardial performance: segment work in the
TABLE 3  Maximal Effects of Ischemia after Propranolol

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<th>Global studies</th>
<th>Regional studies</th>
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<tr>
<td></td>
<td>Preocclusion</td>
<td>Preocclusion</td>
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<tr>
<td></td>
<td>control values</td>
<td>control values</td>
</tr>
<tr>
<td></td>
<td>(n = 3)</td>
<td>(n = 12)</td>
</tr>
<tr>
<td>Work (mm Hg mm)</td>
<td>905</td>
<td>146 ± 31*</td>
</tr>
<tr>
<td></td>
<td>72</td>
<td>-2 ± 12(\dagger)</td>
</tr>
<tr>
<td>Systolic shortening (mm)</td>
<td>8.5</td>
<td>1.9 ± 0.3*</td>
</tr>
<tr>
<td></td>
<td>1.6</td>
<td>0.6 ± 0.1(\dagger)</td>
</tr>
<tr>
<td>Velocity of shortening (mm/sec)</td>
<td>71.1</td>
<td>16.5 ± 2.5*</td>
</tr>
<tr>
<td></td>
<td>24.1</td>
<td>4.5 ± 1.1(\dagger)</td>
</tr>
<tr>
<td>LV pressure (mm Hg)</td>
<td>125</td>
<td>117 ± 3</td>
</tr>
<tr>
<td></td>
<td>68</td>
<td>111 ± 1(\ddagger)</td>
</tr>
<tr>
<td>dP/dt (mm Hg/sec)</td>
<td>2900</td>
<td>2018 ± 440*</td>
</tr>
<tr>
<td></td>
<td>1595</td>
<td>1763 ± 46(\ddagger)</td>
</tr>
<tr>
<td>End-diastolic dimen (mm)</td>
<td>40.1</td>
<td>14.6 ± 1.3</td>
</tr>
<tr>
<td></td>
<td>40.9</td>
<td>15.0 ± 0.1(\ddagger)</td>
</tr>
<tr>
<td>End-diastolic pressure (mm Hg)</td>
<td>14</td>
<td>12 ± 0.9*</td>
</tr>
<tr>
<td></td>
<td>21</td>
<td>16 ± 1(\ddagger)</td>
</tr>
<tr>
<td>Heart rate      (beats/min)</td>
<td>86</td>
<td>90 ± 2(\dagger)</td>
</tr>
<tr>
<td></td>
<td>124</td>
<td>102 ± 4</td>
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Values significantly different after \(\beta\)-blockade: \(\ast P < 0.01, \ddagger P < 0.02\), for regional ischemia only, since the small number of experiments on global ischemia did not allow statistical evaluation.

Values significantly different from preocclusion control: \(\ddagger P < 0.01\); \(\ddagger P < 0.05\).

Verapamil

In experiments on three separate segments carried out in three dogs, verapamil (0.2 mg/kg), administered as an intravenous bolus, followed by continuous infusion, depressed regional as well as overall myocardial function. Compared to pre-verapamil levels, regional function was depressed by 46 ± 5\% (\(P < 0.001\)), shortening by 32 ± 5\% (\(P < 0.001\)), and velocity by 35 ± 5\% (\(P < 0.01\)). Following the transient period of regional ischemia, segment function was significantly improved during reperfusion. Stroke work exhibited an overshoot to 69 ± 10\% (\(P < 0.001\)), shortening to 52 ± 11\% (\(P < 0.01\)), and velocity to 16 ± 3\% (\(P < 0.01\)) above the respective preocclusion values.

Verapamil in experiments on six separate segments carried out in three dogs, verapamil (0.2 mg/kg), administered as an intravenous bolus followed by a continuous infusion, depressed regional as well as overall myocardial function. Compared to pre-verapamil levels, segment work was depressed by 46 ± 5\% (\(P < 0.001\)), shortening by 32 ± 5\% (\(P < 0.001\)), and velocity by 35 ± 5\% (\(P < 0.01\)). Following the transient period of regional ischemia, segment function was significantly improved during reperfusion. Stroke work exhibited an overshoot to 69 ± 10\% (\(P < 0.001\)), shortening to 52 ± 11\% (\(P < 0.01\)), and velocity to 16 ± 3\% (\(P < 0.01\)) above the respective preocclusion values.

Figure 6  Left ventricular pressure-internal diameter relations induced with global LV ischemia are shown. The continuous tracing is a control beat prior to ischemia. The dotted line was obtained during reperfusion, when end-diastolic diameter and heart rate were at or near control levels, but the area of the loop, work, was enhanced. Neither iv propranolol, 2 mg/kg (center), nor 4 days of reserpine, 0.5 mg/kg, im (right), prevented the increase in work that was observed early during reperfusion.

Figure 7  Peak changes from control preocclusion levels during reperfusion in 14 segments with regional myocardial ischemia before and in 12 segments after treatment with propranolol, 2 mg/kg, iv, are shown along with those from eight segments at the end of a 3-minute period of reperfusion with coronary flow restricted to the preocclusion control level. Significant changes from preocclusion control are indicated by the symbols.
Reactive Hyperemia (Fig. 8)

The importance of the reactive hyperemia in mediating the overshoot in function was tested in eight segments in five dogs. In these dogs after the 100-second period of regional ischemia, the coronary occlusion was released only partially and mean coronary flow was allowed to return to the preocclusion level and was maintained at that level for 3–5 minutes (Fig. 8). During this period, regional function recovered almost completely but no overshoot was observed (Figs. 7 and 8).

When the occlusion was completely released and a delayed reactive hyperemia allowed to occur, a clear overshoot in function was observed (Fig. 8). Segment work rose 57 ± 12% (P < 0.01), and shortening 52 ± 12% (P < 0.01) above the preischemic control levels as blood flow rose 270 ± 15% (P < 0.001) above the preischemic control. When partial release was maintained for 10 minutes, neither reactive hyperemia nor the overshoot in function were observed either during the 10-minute period of partial release or after full release had occurred at 10 minutes.

Discussion

This study shows that brief episodes of acute myocardial ischemia and its relief induce complex dynamic changes in myocardial performance. The loss of function during the development of global or regional LV ischemia is characterized by a dissociation between LV work and shortening on the one hand and the velocity of shortening on the other. In the absence of changes in preload, afterload, and contraction frequency, the velocity of shortening is dependent on the inotropic state. It has been proposed from studies of isolated cardiac muscle that the maximum velocity of shortening of unloaded muscle (V_{max}) on the one hand and the force generated by the cardiac muscle on the other may be dependent upon different mechanisms with different time constants. Indeed, Tyberg et al. found, in the isolated papillary muscle contracting isometrically, that the rate of force generated was less sensitive to hypoxia than the actual amount of force generated and proposed that early ischemia might shorten the duration of the active state, while affecting its intensity only slightly. Similarly, in anesthetized animals, hemorrhagic shock depressed cardiac pump performance as reflected by cardiac output and left ventricular diastolic pressure more than it affected V_{max}.

In an isolated ventricular septum preparation and in the intact isovolumic heart, ischemia depressed the tension or pressure generated more than their time derivatives, i.e., dT/dt of dP/dt. Finally dL/dt in the anesthetized dog, as well as contractile element velocity (V_e) in patients, were less sensitive to ischemia than shortening.

Left ventricular pressure-dimension and pressure-length relations have been used to analyze global and regional myocardial function and have proven particularly useful in the analysis of myocardial ischemia. The area of these loops has been used to provide indices of total or segmental ventricular work because changes in left ventricular internal diameter have been shown to be proportional to changes in LV volume as long as contraction remains homogeneous. Regarding this point, it is of interest to contrast the effects of global and regional ischemia. When the ischemic stimulus was applied to the entire left ventricle by constriction of the left main coronary artery, the reduction in total left ventricular work was proportional to the reduction in shortening and pressure and the general shape of the pressure-diameter loop was unaltered. However, when the ischemic stimulus was localized, the reduction in the area of the pressure-length loop, i.e., of regional work, was significantly greater than that expected from the reduction in shortening (Fig. 5). This resulted from the transient lengthening of the ischemic segment which occurred late in systole. This was one of the earliest and most prominent effects of regional myocardial ischemia. A similar change in ischemic segment dynamics and in the shape of the pressure-segment loop as a consequence of acute myocardial ischemia recently was observed in anesthetized open-chest animals. However, in that study, P-L loops were obtained from experiments in which epicardial
segment length was measured by means of a mercury-in-rubber gauge.25 Thus the higher heart rate and smaller cardiac size associated with general anesthesia and the open chest and the difference in the method of measuring cardiac dimensions probably account for these investigators’ finding of substantial increases in epicardial segment length during the isovolumic pressure rise13 both in control conditions and during the early phases of ischemia. Indeed, in one series of our experiments, regional myocardial ischemia was produced in the anesthetized animal with open chest and a similar early increase in enddiastolic segment length also was noted.

Recovery from brief episodes of ischemia was associated with a transient overshoot of function. Similar results were observed during recovery from global and regional ischemia. The transient overshoot was characterized by increases in left ventricular stroke work, as reflected by the areas of the pressure-diameter and pressure-length loops, as well as the extent and velocity of shortening. The mechanism by which reactive hyperemia induced the overshoot in function was not elucidated. However, several conceivable mechanisms can be eliminated. First, changes in preload, afterload, and heart rate, important determinants of myocardial performance, obviously were not playing a major role, since with regional ischemia, afterload, as reflected in left ventricular systolic pressure, preload, as reflected in end-diastolic dimensions, and heart rate were at or near control values at the time of the peak rebound. Second, it did not appear to have been mediated by adrenergic mechanisms, since a large dose of propranolol, 2 mg/kg, or combined propranolol and reserpine, failed to abolish the overshoot. Verapamil, a drug which blocks the slow inward Ca²⁺ current during the plateau phase of depolarization, also did not prevent the overshoot. Moreover, it still was present after general anesthesia with pentobarbital and thoracotomy. In earlier studies in anesthetized open-chest animals, in which regional myocardial force was measured with a strain gauge arch, a transient overshoot of measured force was observed during recovery from brief regional ischemia.26,27 The prevention of reactive hyperemia, i.e., restriction of coronary blood flow during reperfusion to the preischemic control value, was the only intervention studied which prevented the overshoot. During the period of restricted reperfusion, myocardial function recovered almost but not quite completely to normal. It has been shown that some subendocardial underperfusion still is present during this period even though total coronary flow is normal.29 On the other hand, when this restriction to perfusion was eliminated, the delayed reactive hyperemia was accompanied by a delayed overshoot in function. One possible mechanism that might explain the overshoot involves a metabolic or ionic change, which was induced by the ischemia and overcompensated for by the reactive hyperemia. It is also interesting to note that recovery from ischemia and brief periods of myocardial hypoxia has been associated with a prolonged time-course of ventricular relaxation.30,31 It is of further relevance that this posthypoxic lengthening of the relaxation phase was prevented in the isolated papillary muscle by partial reoxygenation.32 Moreover, others have observed that following relief of anoxia of the isometrically contracting isolated papillary muscle, a lengthening of the relaxation phase was observed, i.e., the period during which the heart muscle is producing tension became prolonged.19 Similar observations also have been made on isolated heart muscle21 and isolated heart preparations22 following ischemia.

In conclusion, in the conscious dog, myocardial ischemia induces a dissociation between the extent and rate of myocardial fiber shortening; velocity declines later in time and to a lesser degree than both shortening and work. Subsequent reperfusion induces a transient overshoot in myocardial function that is not mediated by β-adrenergic mechanisms, but which appears dependent upon the associated reactive hyperemia.

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References

Diastolic Coronary Artery Pressure-Flow Relations in the Dog

RONALD F. BELLAMY

SUMMARY Conscious dogs were used to investigate the relations between aortic (P_a) pressure and coronary flow (F) during individual diastoles. When the dogs were in a semibasal state, coronary pressure-flow relations were described by a family of lines, and diastolic flow was a linear function of aortic pressure. For a given perfusion pressure, higher flows were associated with lines of progressively greater slope and lower zero flow pressure intercept (P_o). Zero flow pressure intercepts were estimated by extrapolation and found to vary between 20 and 50 mm Hg, depending on the magnitude of flow. The zero flow pressure may represent the height of a vascular waterfall caused by vasomotor tone with the resistance-controlling coronary flow being (P_a-P_o)*F. Interventions that decrease vasomotor tone increase coronary flow by both decreasing vascular resistance and increasing the perfusion pressure gradient. The gradient increases because the effective coronary back pressure is the height of the vascular waterfall and the latter is reduced when vasomotor tone falls. Passive changes in vessel dimensions, arterial recruitment, and autoregulation appear to be of little importance during individual diastoles.

THE RELATIONSHIP between pressure and flow is of fundamental importance in understanding the hemodynamics of a vascular bed. In comparison with other vascular beds, the relationship between pressure and flow in the coronary circulation is modified by two factors: (1) throttling of flow during systole and (2) predominant local control manifested as rapid autoregulation of flow with changing pressure.

Prior reports of coronary pressure-flow relations have not entirely clarified the effects of these factors. Nonphasic pressure flow data were used and thus the effect of systole on the overall relation has not been distinguished. Although the time-dependent nature of autoregulation has been recognized in some studies by differentiating between instantaneous and steady state pressure-flow relations, the point in time following an experimental perturbation at which an instantaneous relation begins to be modified by autoregulation is not known. Previous studies have used data from experiments on dogs with the chest open and thus are subject to the distortion introduced by anesthesia, surgical trauma, and drugs. The conscious instrumented dog, in a semibasal state with a slow resting heart rate, offers a unique opportunity to study diastolic coronary pressure-flow relations in a more physiological state than previously reported. In this study, coronary pressure-flow relations were measured during the diastoles of individual beats in the resting state and when flow was increased by reactive hyperemia and infusion of adenosine.

Methods

The data presented in the paper are from analyses of unpublished records prepared in the course of several
Initial myocardial adjustments to brief periods of ischemia and reperfusion in the conscious dog.
M Pagani, S F Vatner, H Baig and E Braunwald

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