Reduced Myocardial Reflow and Increased Coronary Vascular Resistance following Prolonged Myocardial Ischemia in the Dog

By James T. Willerson, John T. Watson, Ian Hutton, Gordon H. Templeton, and David E. Fixler

ABSTRACT

Studies were performed to determine whether an alteration in coronary vascular resistance and a reduction in the reflow phenomenon occurred in the blood-perfused, heparinized canine heart after various periods of myocardial ischemia. Regional myocardial blood flow was measured with radioactive microspheres. Proximal left anterior descending coronary artery blood flow was measured with a periarterial flow transducer. Reduced reflow to the ischemic portion of the left ventricle and increased resistance in the left anterior descending coronary artery were present after 120 minutes of myocardial ischemia. The reduction in reflow was specific to the subendocardium of the ischemic area. Saline and isosorbide dinitrate (Isordil) did not prevent the increase in coronary vascular resistance or the significant reduction in reflow to the subendocardial portion of the ischemic area. Hypertonic mannitol given so as to increase serum osmolality 40 mosmoles/kg prevented the increase in coronary vascular resistance and modified the reduction in the reflow phenomenon to the subendocardial portion of the ischemic area. Thus, both an increase in coronary vascular resistance and a significant reduction in reflow to the subendocardial portion of the ischemic area occur in the canine heart after 120 minutes of myocardial ischemia. Moreover, the increase in coronary vascular resistance can be prevented and the reduction in reflow to the subendocardial portion of the ischemic area can be modified by the administration of hypertonic mannitol.

KEY WORDS coronary blood flow regional myocardial blood flow radioactive microspheres isosorbide dinitrate hypertonic mannitol serum osmolality and vascular resistance no-reflow phenomenon

The evaluation of reflow patterns following various periods of myocardial ischemia has relevance to current medical and surgical efforts to protect ischemic myocardium and increase coronary blood flow to ischemic and periischemic tissue. Thus far, however, there has been very little investigation of the influence of prolonged myocardial ischemia on subsequent reflow patterns in the heart.

Reduced reflow has been demonstrated in both the brain and the kidney when vascular continuity is restored after prolonged periods of total interruption of blood supply (1–3). Swollen perivascular and endothelial cells that develop as a consequence of ischemia in these organs appear to obstruct capillaries responsible for supplying blood to the ischemic area. Red cell packing of vascular channels has also been described; it probably contributes to a further reduction in reflow under these circumstances (1, 2). Hypertonic mannitol prevents the development or reduces the magnitude of the cell swelling that occurs during reflow in both the brain and the kidney. Recently Kloner et al. (4), using a vascular marker to identify regions of flow, have also described reduced reflow in the canine heart after prolonged myocardial ischemia. In their study, however, no attempt was made to alter the reflow patterns with any intervention.

The present study was performed to determine whether an alteration in coronary vascular resistance and a reduction in the reflow phenomenon occur in the canine heart after various periods of left anterior descending coronary artery occlusion. Experiments were also conducted to determine whether volume expansion with isotonic saline, treatment with a vasodilator such as Isordil, or administration of hypertonic mannitol alters reflow patterns and coronary vascular resistance after prolonged myocardial ischemia.
Methods

ANIMAL PREPARATION

Adult dogs of either sex weighing between 25 and 35 kg were anesthetized with chloralose (60 mg/kg, iv). An endotracheal tube was inserted, and ventilation was provided by a Harvard respirator using 95% O2-5% CO2. The chest was opened through a median sternotomy. Heparin (3 mg/kg, iv) was administered, the superior and inferior vena cavae were cannulated, and the azygous vein was divided. The caval return was directed to a reservoir through a bubble oxygenator and a heat exchanger (37 ± 0.5°C) and then returned through a variable-speed calibrated pump to the main pulmonary artery. The rate of pumping was set to provide a mean systemic arterial blood pressure of at least 65 mm Hg and a left ventricular end-diastolic pressure within the normal range. A ligature was placed around the main pulmonary artery proximal to the catheter to complete the isolation of the right heart which received only coronary venous drainage. Total coronary blood flow minus only the small portion that drained into the left ventricle was led by siphon drainage from the cannulated right atrium and ventricle to the venous reservoir. A reversible ligature was placed around the proximal left anterior descending coronary artery generally just below the first septal branch to provide intermittent myocardial ischemia. Heart rate was kept constant by atrial pacing. The maximum rate of left ventricular pressure rise (maximum left ventricular dP/dt) was measured using a Millar high-fidelity pressure-tip transducer (model PC480) positioned in the left ventricle (frequency response of 0-20 kHz). A catheter was also positioned in the left atrium for the injection of radioactive microspheres to measure regional myocardial blood flow. Catheters were also placed in the femoral arteries to measure arterial blood pressure and obtain a reference sample for the microsphere flow determinations. A Statham periartrial flow transducer (model SP7515-020) was placed around the proximal left anterior descending coronary artery just proximal to the location of the reversible ligature.

EXPERIMENTAL PROCEDURES

Following complete instrumentation, the dog was placed on right heart bypass; when hemodynamic stability had been achieved, left ventricular and systemic arterial pressures were measured and a batch of radioactive microspheres was injected to measure control regional myocardial blood flow. The left anterior descending coronary artery was then ligated for a 10-minute period; after the ligature was released and a stable cardiac rhythm was present, 3 minutes of reflow was provided. Following the 3 minutes of reflow, regional myocardial blood flow was measured again by injecting a different batch of radioactive microspheres into the left atrium. Flow through the proximal left anterior descending coronary artery, which was monitored by the Statham flowmeter throughout the 10 minutes of ligation, was also monitored during the reflow period at 1-minute intervals for at least 10 minutes. Left ventricular and systemic arterial pressures were also measured. After a recovery period of 30 minutes another period of myocardial ischemia lasting either 30, 60, or 120 minutes was provided followed by a 3-minute reflow period. Regional myocardial blood flow, pressures, and flow through the proximal left anterior descending coronary artery were again measured after this reflow period. In the studies in which 120 minutes of myocardial ischemia was provided, either isotonic saline (nine dogs) or hypertonic mannitol (25% solution, seven dogs) was infused intravenously. The infusion was begun 30 minutes before release of the ligature and continued through the reflow period. These agents were infused at 7.6 ml/min for the initial 10 minutes and then at 3.8 ml/min thereafter. In five experiments, 10 mg of isosorbide dinitrate (Isordil) was given intravenously rather than saline or mannitol 35 minutes before release of the occlusion.

An additional six dogs received 10 mg of Isordil intravenously 35 minutes prior to a period of acute myocardial ischemia lasting 10 minutes to determine whether Isordil influenced regional myocardial blood flow during a relatively short period of myocardial ischemia. These experiments served as a control for the drug's use in the reflow studies. In these experiments, an initial period of coronary insufficiency was provided by ligating the proximal left anterior descending coronary artery in dogs anesthetized with chloralose (60 mg/kg, iv). Regional myocardial blood flow and ventricular pressures were measured prior to and following this period of coronary artery occlusion. The ligature was released, and after 45 minutes a second 10-minute period of myocardial ischemia was provided. Isordil was administered 35 minutes before the second period of left anterior descending coronary artery occlusion, and coronary blood flow, ventricular pressure, and arterial blood pressure were measured at the end of the occlusion. As a control for these experiments, seven additional dogs were subjected to two separate 10-minute periods of acute myocardial ischemia without any intervention; regional myocardial blood flow was measured prior to the first occlusion and at the end of both the first and second occlusions.

Regional myocardial blood flow was determined by the method of Rudolph and Heymann (5). Microspheres 9μ in diameter (46Sc, 85Sr, and 141Ce) and 15μ in diameter (125I) suspended in saline were used to measure regional myocardial blood flow by injecting a batch of different nuclide-labeled microspheres into the atrium. During the various reflow periods, 9μ microspheres were used to measure regional myocardial blood flow. Reference blood samples were collected for a 2-minute period from the femoral arteries using a small Holter pump. At the conclusion of the study, the heart was removed and separated into right ventricle, ventricular septum, ischemic portion of the left ventricle (identified by injecting 0.1 ml of India ink just distal to the ligature around the proximal left anterior descending coronary artery), and nonischemic portion of the left ventricle. Each of these areas was subdivided into inner and outer portions (right ventricle, ischemic area of left ventricle, etc) or right and left halves (ventricular septum) and counted separately in a well scintillation detector (Nuclear Chicago). The reference blood samples were also counted. Regional myocardial blood flow was computed from the formula:

\[
\text{Regional myocardial blood flow} = \frac{\text{Regional myocardial counts}}{\text{Reference sample counts}} \times \text{Reference sample pump flow rate}
\]

A paired t-test was used to compare the differences between interventions within any one group of experi-
ments. Specific comparisons of hemodynamic and regional myocardial reflow changes were made (1) during the control period, (2) following the 10-minute period of occlusion, and (3) after the 30-, 60-, and 120-minute periods of occlusion. Alterations in coronary blood flow were recognized by comparing regional myocardial blood flow following the 10-, and the 30-, 60-, and 120-minute periods of occlusion. Results were considered significant when \( P < 0.05 \).

**Results**

**REGIONAL MYOCARDIAL BLOOD FLOW AFTER 10 MINUTES OF MYOCARDIAL ISCHEMIA**

Ten minutes of acute myocardial ischemia followed by 3 minutes of reperfusion resulted in significant increases in regional myocardial blood flow to all regions of the left ventricle (Fig. 1 and Table 1). The largest increase in regional flow was to the ischemic portion of the left ventricle and specifically to the subendocardial portion of the ischemic area of the left ventricle (Fig. 1). The increases in flow were also greater or tended to be greater in the subendocardium of each of the other different regions of the heart and in the left portion of the ventricular septum. Regional flow to the subendocardial portion of the ischemic area of the left ventricle increased \( 263 \pm 99.5\% \) (SE) \( (P < 0.005) \) and that to the outer wall increased \( 105 \pm 55.9\% \) (SE). Regional myocardial blood flow to the subendocardial region of the nonischemic portion of the left ventricle increased \( 33 \pm 11.3\% \) \( (P < 0.02) \) and that to the outer wall increased \( 13 \pm 7.2\% \) (ns). Flow to the inner wall of the right ventricle increased \( 6 \pm 7.3\% \) (ss), but flow to the outer wall actually decreased \( 5 \pm 6.2\% \) (ss). Flow to the right part of the ventricular septum increased \( 21 \pm 8.0\% \) \( (P < 0.05) \) and that to the left part of the septum increased \( 69 \pm 21.4\% \) \( (P < 0.01) \).

**CHANGES IN REGIONAL MYOCARDIAL BLOOD FLOW AFTER 30 AND 60 MINUTES OF MYOCARDIAL ISCHEMIA**

There were no significant changes in coronary blood flow to either the ischemic or the nonischemic regions of the heart after 30 minutes of myocardial ischemia compared with those noted after 10 minutes of myocardial ischemia (Table 1). Nor was there a significant reduction in reflow to the ischemic area after 60 minutes of myocardial ischemia compared with that noted after 10 minutes of ischemia, although in one of the dogs there was a reduction in reperfusion (Table 1).

**CHANGES IN REGIONAL MYOCARDIAL BLOOD FLOW AFTER 120 MINUTES OF MYOCARDIAL ISCHEMIA**

There was a significant reduction in reflow to the ischemic portion of the left ventricle after 120 minutes of myocardial ischemia compared with
### TABLE 1

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* Denotes significant difference.
that present after 10 minutes of myocardial ischemia (Fig. 1 and Table 1). This significant reduction in reflow to the ischemic area was not prevented by the administration of saline in the eight dogs that were studied. The specific site of the significant reduction in reflow to the ischemic area was the subendocardial portion; the reduction in reflow to the outer wall was not statistically significant (Fig. 1). There was a mean decrease in reflow to the subendocardial portion of the ischemic region of 0.75 ml/min g⁻¹ after the 120-minute occlusion compared with that after the 10-minute occlusion. Reflow was 2.28 ± 0.35 ml/min g⁻¹ after the 10-minute occlusion and 1.53 ± 0.42 ml/min g⁻¹ after the 120-minute occlusion.

**Table 1—Continued**

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MBP = mean systemic arterial blood pressure, LVEDP = left ventricular end-diastolic pressure, LADR = proximal left anterior descending coronary artery vascular resistance, RV = regional myocardial blood flow to right ventricle, LVAT = regional myocardial blood flow to ischemic portion of left ventricle, LVCT = regional myocardial blood flow to nonischemic portion of left ventricle, VS = regional myocardial blood flow to ventricular septum, and NM = not measured.

* Isotonic saline was administered.
after the 120-minute occlusion with saline. Regional coronary blood flow increased in the nonischemic regions of the left ventricle and in the right ventricle following 120 minutes of myocardial ischemia (Fig. 1 and Table 1).

There was also a significant increase in proximal left anterior descending coronary artery vascular resistance with reflow after 120 minutes of myocardial ischemia that was not corrected by the administration of saline (Fig. 2 and Table 1). In fact, left anterior descending coronary artery vascular resistance increased 74 ± 12.6% (P < 0.001) during reflow with saline administration after 120 minutes of myocardial ischemia compared with the resistance noted after 10 minutes of myocardial ischemia. The increase in left anterior descending coronary artery vascular resistance presumably reflected the reduction in reflow to the subendocardial portion of the ischemic area, since there was no significant change in flow to the outer wall of the ischemic area and flow to the nonischemic left ventricle and the right ventricle significantly increased after release of the 120-minute occlusion.

A small but significant increase in mean aortic blood pressure occurred (80 ± 3.3 vs. 93 ± 4.9 mm Hg, P < 0.05) between the period immediately following the 10-minute occlusion and that immediately following the 120-minute occlusion (Table 1). There were no significant changes in left ventricular end-diastolic pressure (5 ± 0.7 vs. 6 ± 1.1 cm H2O), heart rate (135 ± 10.9 vs. 141 ± 15.3 beats/min), maximum left ventricular dP/dt (3031 ± 218.8 vs. 3481 ± 412.9 mm Hg/sec), or hematocrit (35 ± 1.7 vs. 36 ± 3.0%) between the two different periods of occlusion (Table 1).

CHANGES IN REGIONAL MYOCARDIAL BLOOD FLOW AFTER 120 MINUTES OF MYOCARDIAL ISCHEMIA ASSOCIATED WITH THE ADMINISTRATION OF ISORDIL

Isordil did not prevent the marked increase in proximal left anterior descending coronary artery vascular resistance that occurred after 120 minutes of myocardial ischemia and subsequent reflow (Fig. 2). Left anterior descending coronary artery vascular resistance increased 54 ± 21.8% in the reflow period after 120 minutes of myocardial ischemia associated with Isordil administration (P < 0.005). Neither did Isordil prevent the significant reduction in reflow to the subendocardial portion of the ischemic area of the left ventricle (Fig. 3). The mean reduction in reflow to the subendocardial portion of the ischemic area in the five dogs after 120 minutes of left anterior descending coronary artery occlusion was 0.57 ml/min g⁻¹ compared with that present after the 10-minute occlusion. Reflow was 1.85 ± 0.19 ml/min g⁻¹ after the 10-minute occlusion and 1.28 ± 0.07 ml/min g⁻¹ after the 120-minute occlusion with Isordil.

In these Isordil experiments, there were no significant changes in mean aortic pressure (75 ± 2.2 vs. 82 ± 2.0 mm Hg), maximum left ventricular dP/dt (2750 ± 194 vs. 2900 ± 232 mm Hg/sec), or left ventricular end-diastolic pressure (4 ± 0.8 vs. 3 ± 0.5 cm H2O) between the 10- and the 120-minute period of occlusion with reflow. Similarly, there were no significant changes in heart rate (144 ± 7.7 vs. 148 ± 3.0 beats/min) or hematocrit (36 ± 2.6 vs. 34 ± 3.4%) between these two different periods of occlusion and subsequent reflow.

THE INFLUENCE OF ISORDIL ON REGIONAL MYOCARDIAL BLOOD FLOW DURING ACUTE MYOCARDIAL ISCHEMIA

Isordil (10 mg, iv) significantly increased regional myocardial blood flow to all areas of the heart during acute myocardial ischemia. It increased coronary blood flow to the ischemic region of the left ventricle 27 ± 9.4% (P < 0.05) compared with the flow present during the control ligation. Isordil also increased flow 31 ± 8.7% (P < 0.02) to the nonischemic portion of the left ventricle and 33 ± 5.6% (P < 0.05) to the ventricular septum during acute myocardial ischemia. The increase in coronary blood flow after Isordil administration during myocardial ischemia included a significant flow increase to the subendocardial portion of the ischemia area (34 ± 12.2%, P < 0.05).

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Isordil did not change any aspect of ventricular performance significantly during acute myocardial ischemia.

There was no significant change in regional coronary blood flow in any area of the heart between the two serial left anterior descending coronary artery ligations in the seven control dogs studied.

Hypertonic mannitol prevented the increase in left anterior descending coronary vascular resistance following 120 minutes of myocardial ischemia and reflow (Fig. 2 and Table 2). Mannitol also modified the reduction in reflow to the subendocardial portion of the ischemic region (Fig. 4 and Table 2). In the seven dogs tested, mannitol prevented the statistically significant reduction in reflow to the subendocardial portion of the ischemic area, although there was still a tendency for flow to decrease in this area (mean reduction of 0.25 ml/min g⁻¹ tissue). Reflow to the subendocardial portion of the ischemic area was 1.95 ± 0.28 ml/min g⁻¹ after the 10-minute occlusion and 1.70 ± 0.21 ml/min g⁻¹ after the 120-minute occlusion with mannitol. Mannitol also significantly increased coronary blood flow to all of the other regions of the heart following 2 hours of myocardial ischemia (Fig. 4 and Table 2).

In these experiments hypertonic mannitol increased serum osmolality by 40 mosmoles/kg from 302 ± 6.4 mosmoles/kg after 10 minutes of myocardial ischemia and reflow to 342 ± 6.9 mosmoles/kg after 120 minutes of myocardial ischemia and reflow. Hematocrit decreased slightly but not significantly from 33 ± 2.3% to 31 ± 2.1% after mannitol administration. There was no significant change in any aspect of ventricular performance after mannitol administration in these experiments (Table 2). Mean aortic pressure, left ventricular end-diastolic pressure, and maximum left ventricular dP/dt were 77 ± 1.9 mm Hg, 3 ± 0.3 cm H₂O, and 2907 ± 425.1 mm Hg/sec, respectively, during the reflow period following 10 minutes of occlusion and 77 ± 1.7 mm Hg, 5 ± 1.6 cm H₂O, and 3264 ± 355 mm Hg/sec, respectively, after the 120-minute period of occlusion and reflow with mannitol. There was no significant change in heart rate between the two different periods of occlusion (135 ± 10 beats/min in the 10-minute occlusion and 143 ± 17.3 beats/min in the 120-minute occlusion with reflow).
TABLE 2
Changes in Hemodynamics and Regional Myocardial Blood Flow with Reflow after Periods of Myocardial Ischemia of 10 and 120 Minutes with Hypertonic Mannitol

<table>
<thead>
<tr>
<th>Dog</th>
<th>Experiment situation</th>
<th>MBP (mm Hg)</th>
<th>Heart rate (beats/min)</th>
<th>LVEDP (cm H₂O)</th>
<th>LV dP/dt (mm Hg/sec)</th>
<th>LADR (units)</th>
<th>RV (ml/min g⁻¹)</th>
<th>LVAT (ml/min g⁻¹)</th>
<th>LVCT (ml/min g⁻¹)</th>
<th>VS (ml/min g⁻¹)</th>
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<td>9.1</td>
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MBP = mean systemic arterial blood pressure, LVEDP = left ventricular end-diastolic pressure, LVCT = regional myocardial blood flow to nonischemic portion of left ventricle, RV = regional myocardial blood flow to right ventricle, VS = regional myocardial blood flow to ventricular septum, LVAT = regional myocardial blood flow to ischemic portion of left ventricle, and LADR = proximal left anterior descending coronary artery vascular resistance.

Discussion

The data obtained in this study demonstrated that there was an increase in proximal left anterior descending coronary artery vascular resistance and a significant reduction in reflow into the ischemic portion of the left ventricle after 120 minutes of myocardial ischemia. The decrease in reflow was specific to the subendocardial portion of the ischemic area. In other portions of the heart, coronary blood flow increased when the occlusion was released after 120 minutes of myocardial ischemia. These changes in regional myocardial blood flow occurred in the absence of any significant changes in inotropic state, cardiac output, heart rate, or left ventricular filling pressure. There was a slight increase in mean arterial blood pressure after 120 minutes of myocardial ischemia, but this change should have increased rather than decreased flow to the ischemic area.

It is of interest that with reperfusion after periods of myocardial ischemia of 10 minutes produced by proximal occlusion of the left anterior descending coronary artery there was a marked hyperemia that occurred in all of the different regions of the left ventricle.
REDUCED REFLOW IN THE CANINE HEART

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Influence of hypertonic mannitol (n = 7) on regional myocardial blood flow to the inner and outer walls of different regions of the heart following release of the left anterior descending coronary artery occlusion after 120 minutes of myocardial ischemia. Mannitol prevented the significant reduction in reflow to the ischemic portion of the left ventricle after 120 minutes of occlusion. The statistical comparisons are the same as those noted for Figures 1 and 3.

The mechanism of the reduction in reflow in the heart after prolonged myocardial ischemia is presently uncertain. Prolonged ischemia in both the brain and the kidney has been previously demonstrated to be followed by reduced reflow (1-3). In these studies, reflow was measured using a vascular marker to identify areas of potential reflow at the time vascular continuity was restored, and reduced reflow was demonstrated when total blood supply was interrupted for prolonged periods of time. In both the brain and the kidney, perivascular and endothelial cell swelling occurs after prolonged ischemia; the swollen cells obstruct small capillaries supplying blood to the ischemic region. Whalen and his associates (8) described "explosive myocardial cell swelling" with increases in tissue water, sodium, chloride, and calcium after periods of myocardial ischemia of at least 40 minutes followed by reflow in anesthetized dogs, but they did not report actual measurements of reflow ability. Kloner et al. (4) have, however, recently identified a reduced reflow phenomenon in the canine heart after 90 minutes of ischemia produced by circumflex artery ligation; reflow ability was measured by a vascular marker (thioflavin S or carbon black). Krug et al. (9) have reported reduced tissue staining with injected markers in the inner wall of the ischemic area after periods of myocardial ischemia of at least 60 minutes produced by ligation of the left anterior descending coronary artery and the adjacent vein followed by reflow in the cat heart. Intracellular and interstitial swelling were also noted. Krug et al. (9) have also observed ruptured capillaries and hemorrhage by light microscopy in the ischemic area in cat myocardium. Hemorrhage and microthrombi have been noted by Lang and his associates (10) following 3 hours of myocardial ischemia and arterial reperfusion in the...
dog. Red cell packing has also been demonstrated during reflow after prolonged ischemia in the kidney and brain (1, 2, 11). Leaf (12) has suggested that prolonged ischemia results in loss of red blood cell flexibility within the ischemic tissue and that consequent red cell packing contributes to vascular obstruction. It has also been suggested that prolonged ischemia results in a reduced ability of the sodium-potassium adenosinetriphosphatase pump to actively extrude sodium from the interior of cells and thereby leads to cell swelling (13). In the previous studies of reflow in the heart just described, no specific attempt was made to keep cardiac output constant, no measurements of reflow were made utilizing anything other than histological techniques and markers, and no attempt was made to determine the reversibility of the reflow pattern after prolonged myocardial ischemia.

The ability of hypertonic mannitol to prevent the increase in proximal left anterior descending coronary artery vascular resistance and to modify the decrease in regional myocardial reflow to the subendocardial portion of the left ventricular ischemic area suggests that reduced reflow after 120 minutes of myocardial ischemia may be potentially modifiable and at least partially reversible. In the present study, hypertonic mannitol prevented the statistically significant reduction in reflow to the subendocardial portion of the ischemic area in all seven dogs considered. There was still a tendency for flow to fall in the subendocardial region, however, but the magnitude of the reduction compared with that noted in different dogs studied with saline or Isordil was modified by mannitol. There was not a statistically significant difference in reflow to the subendocardial portion of the ischemic area after 120 minutes of myocardial ischemia when the different groups of dogs given mannitol, Isordil, and saline were compared possibly because of inter-dog differences in coronary anatomy and reflow capability. One might argue that, because there were no significant differences in reflow to the subendocardial area when the different groups of dogs were compared, hypertonic mannitol’s ability to reduce or prevent ischemic cell swelling does not totally correct the reduced reflow abnormality and that other major alterations in myocardial tissue including necrosis, capillary disruption, or red cell packing are also responsible for the reduction in reflow.

The mechanism by which mannitol prevented the increase in coronary artery vascular resistance and modified the significant reduction in reflow to the subendocardial portion of the ischemic area after prolonged coronary artery occlusion is uncertain, but it might be the result of its ability to reduce ischemic cell swelling (1) or of a direct reduction in vascular smooth muscle resistance. The latter possibility is suggested, because mannitol increased coronary blood flow in both the ischemic and nonischemic areas of the myocardium in this study. It seems particularly possible that mannitol’s ability to prevent the significant increase in coronary artery vascular resistance may be at least partially due to its ability to significantly increase coronary flow to the outer wall of the ischemic region where at least during this time period the reduced reflow phenomenon did not occur. In previous studies, we have found that hypertonic mannitol increases regional myocardial blood flow to all areas of the heart, i.e., both ischemic and nonischemic areas, during acute myocardial ischemia (14). In other studies, mannitol has been demonstrated to increase regional myocardial blood flow to all areas of the heart in experimental animals without myocardial ischemia (15). It might also be that mannitol increases regional myocardial blood flow in nonischemic areas by reducing perivascular cell size and thereby reducing resistance to flow even in nonischemic areas of the heart. The ability of mannitol to increase coronary blood flow after 120 minutes of myocardial ischemia does not appear to be secondary to its ability to influence ventricular performance, since no significant change in performance was documented in this study; thus, the influence of mannitol in these experiments was limited to one on regional myocardial blood flow after prolonged myocardial ischemia.

Isordil influenced but did not prevent the reduced reflow phenomenon in these studies. Isordil is a vasodilator believed to act by reducing smooth muscle vascular resistance. In this study, however, it failed to prevent both the significant increase in left anterior descending coronary artery vascular resistance after 120 minutes of myocardial ischemia and the significant fall in regional myocardial reflow to the subendocardial portion of the ischemic region. Thus, Isordil given in the same dose and at the same time relative to coronary artery occlusion has a different effect on regional coronary blood flow after prolonged coronary artery occlusion and reflow than it does after relatively short periods of coronary artery occlusion. In the Isordil experiments, there was an apparent slight discrepancy between the magnitude of the increase in left anterior descending coronary artery vascular resistance.
resistance after 120 minutes of myocardial ischemia measured by the flowmeter and the degree of reduction in regional myocardial reflow to the ischemic area measured by the microspheres. That is, the increase in resistance was greater than one might have predicted based on the reduction in reflow to the ischemic area. However, despite this discrepancy, both the flowmeter and the microsphere measurements demonstrated that Isordil did not prevent the reduced reflow phenomenon. Whether another coronary vasodilator such as nitroglycerin or an even larger dose of Isordil might possess the ability to prevent the reduction in the reflow phenomenon and the increase in left anterior descending coronary artery vascular resistance in the heart is presently uncertain.

The potential application of this information to clinical settings is currently unknown. The data obtained in this study do identify an increase in left anterior descending coronary artery vascular resistance and a significant reduction in reflow to the subendocardial portion of the ischemic region of the left ventricle after 120 minutes of myocardial ischemia. The increase in coronary artery vascular resistance can be prevented and the reduction in reflow to the subendocardial portion of the ischemic region can be modified by hypertonic mannitol. Whether this same reperfusion abnormality occurs in patients with ischemic heart disease, and, if it does, whether it can be modified by pharmacological or physiological intervention(s) is uncertain, but this subject is one that deserves investigation in the future.

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