Divergent Effects of Inotropic Stimulation on the Ischemic and Severely Depressed Reperfused Myocardium

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SUMMARY Mechanical function remains depressed for hours and days after even brief periods of ischemia. To determine whether the depressed function of the reperfused myocardium could be improved by inotropic stimulation, we studied segmental function during ischemia and after reperfusion using mercury-in-Silastic length gauges in 15 dogs. During coronary artery occlusion, segmental function could not be improved by inotropic stimulation with dopamine. Release of occlusion after 30 minutes of ischemia resulted in only slight improvement in segmental function (systolic shortening at 20% of control). After reperfusion, segmental function could be markedly enhanced by inotropic stimulation. The response to inotropic stimulation was similar after reperfusion after 3 hours of ischemia if the myocardium remained viable (nine dogs). When the myocardium was necrotic (five dogs), there was no improvement after reperfusion, either spontaneously or in response to inotropic stimulation. If applicable to humans, these results suggest that intractable pump failure caused by extensive but reversible ischemia could be effectively treated by reperfusion and inotropic stimulation.

INRACTABLE HEART FAILURE remains the principal cause of in-hospital mortality among patients with myocardial infarction. Because heart failure is usually the consequence of extensive ischemic injury, interventions have been designed to reduce the ischemic injury by reducing myocardial oxygen demand, augmenting collateral blood supply, and by restoring antegrade flow in the occluded coronary artery. In animals, however, restoration of myocardial viability is not immediately followed by restoration of mechanical function. For instance, the myocardium reperfused after only 20 minutes of ischemia remains severely depressed for at least 6 hours. Since the mechanical function of the acutely ischemic myocardium cannot be improved by inotropic stimulation, it seemed important to determine whether the depression of mechanical function could be improved by inotropic stimulation after reperfusion.

Materials and Methods

Mongrel dogs that weighed 20–32 kg were anesthetized with intramuscular morphine sulfate, 1.5 mg/kg, followed by i.v. pentobarbital, 20 mg/kg. Supplemental pentobarbital was administered as required to inhibit the ocular blink reflex. A Harvard respirator was used for artificial ventilation with room air through auffed endotracheal tube. After thoracotomy through the fifth left intercostal space, the heart was suspended in a pericardial cradle; the left anterior descending coronary artery (LAD) was dissected between the first and second diagonal branch and fitted with a snare.

To study regional mechanical function, a mercury-in-Silastic length gauge (0.64-mm o.d. and 0.34-mm i.d.) was sutured to the surface of the left ventricle parallel to the epicardial fibers, in the center of the area supplied by the LAD segment distal to the dissection. Before each experiment, the length gauge was prestretched for 30 minutes and then calibrated by attaching the ends of the gauge to the jaws of a vernier caliper and extending the gauge by fixed increments. In the range of the present study, the gauge calibration was linear. Systolic shortening was measured and expressed in percent of end-diastolic segment length. An ECG was recorded from the center of the ischemic area by an atrumatic epicardial electrode. Aortic pressure was recorded with a saline-filled catheter introduced through the right femoral artery.

Protocol

In 15 dogs, the LAD was occluded for 30 minutes (group 1). Five minutes after occlusion, i.v. dopamine, 8 μg/kg/min in a total of 30 ml of saline, was infused. After 30 minutes of occlusion, the occlusive snare was released. Ten minutes after reperfusion, the dopamine infusion was repeated. Measurements were obtained before and after 2 and 5 minutes of coronary occlusion, after 5 and 10 minutes of dopamine infusion, and 5, 10, and 15 minutes after dopamine infusion. After reperfusion, the measurements were carried out at 1, 3, 5, and 10 minutes, then after 5 and 10 minutes of dopamine infusion, and 5, 10, 15, and 20 minutes after dopamine infusion.

In 14 dogs, the LAD was occluded for 3 hours (group 2). Measurements were obtained 3, 5 and 30 minutes after LAD occlusion, and every 30 minutes thereafter. At 2.5 hours after occlusion, dopamine, 8 μg/min, was infused for 10 minutes. Measurements were obtained after 5 and 10 minutes of dopamine...
infusion and 5, 10, 15 and 20 minutes after the infusion. After 3 hours of occlusion, the occlusive snare was released. Ten minutes after reperfusion the infusion of dopamine was repeated and measurements were made at 5 and 10 minutes of infusion, and 5, 10, 15 and 20 minutes after the infusion.

Four control dogs were subjected to 30 minutes of LAD occlusion. Saline without dopamine was infused at a rate of 3 ml/min with no other change in preparation or protocol.

**Morphologic Studies**

After the experiment, the dog was sacrificed with an overdose of pentobarbital, and the heart immediately removed. The LAD and circumflex coronary arteries were opened and inspected for the presence of thrombi. The left ventricle was cut perpendicular to the surface in the area of the length gauge, and at 1-cm intervals toward the apex and the base. The slices were incubated for 5 minutes in a light-proof container filled with a 37°C solution of triphenyl-tetrazolium chloride (TTC). By this technique, the nonnecrotic myocardium (with dehydrogenase enzyme activity) turned dark red, while the necrotic myocardium (lacking dehydrogenase activity) remained unstained and pale. After incubation, the slices were rinsed with water, fixed in 10% formalin, and examined for the presence of myocardial necrosis.

**Figure 1.** Solid circles indicate segmental function in group 1 dogs during 30 minutes of ischemia, after reperfusion and during infusions of dopamine. SS = systolic shortening; EDL = end-diastolic length. Open circles indicate segmental function during ischemia and after reperfusion in control dogs that did not receive dopamine.

**Figure 2.** Solid circles indicate segmental function during 3 hours of ischemia, after reperfusion and during infusions of dopamine in nine dogs in group 2A. In these dogs, necrosis was limited to the subendocardial one-third of wall thickness. Open circles indicate segmental function in five dogs in group 2B. In these dogs, necrosis in the area of the length gauge was virtually transmural. SS = systolic shortening; EDL = end-diastolic length.

**Figure 3.** Segment length (SL) changes during ischemia, after reperfusion after 30 minutes of ischemia and the effect of infusions of dopamine (DOP) during ischemia and after reperfusion. During ischemia, dopamine increased systolic lengthening. After reperfusion alone, there was only slight systolic shortening. After reperfusion, dopamine administration induced marked systolic shortening. AP = aortic blood pressure.
Statistical Analysis

Data are presented as mean \( \pm SD \). The multiple comparison method of Scheffé was used to compare repeated measurements. Differences were considered significant when \( p < 0.05 \).

Results

Effect of Dopamine on Segmental Function During Coronary Artery Occlusion

Within 2 minutes of coronary artery occlusion, systolic shortening in the ischemic area was replaced by holosystolic lengthening. The infusion of dopamine did not improve the systolic segmental function during ischemia in either group 1 (fig. 1) or group 2 (fig. 2). In some dogs, dopamine actually worsened segmental function in that it induced or increased systolic lengthening (figs. 3 and 4).

Effect of Dopamine on Segmental Function After Reperfusion

After reperfusion, segmental function remained severely depressed. In group 1, systolic shortening recovered after reperfusion to only 20% of the preocclusion level (fig. 1). Infusion of dopamine after reperfusion markedly enhanced systolic shortening, from 2.3 \( \pm \) 3.1% to 12.5 \( \pm \) 7.3% \( (p < 0.05) \) (fig. 1), a value not significantly different from the preocclusion level.

In the control group of dogs not receiving dopamine either during occlusion or after reperfusion, segmental function remained severely depressed and showed no tendency to recover during the 40-minute postreperfusion observation period (fig. 1).

In nine dogs of group 2, systolic shortening recovered slightly, to 10% of control on the average, after untreated reperfusion. Infusion of dopamine to these dogs (group 2A, fig. 2) improved systolic shortening from 0.55 \( \pm \) 1.5% to 10.1 \( \pm \) 6.4% \( (p < 0.05) \), a value not significantly different from that before coronary artery occlusion (10.9 \( \pm \) 3.9%). In these nine dogs, the TTC technique showed either no necrosis or necrosis only in the subendocardial third of the wall thickness (fig. 5A).

In five dogs of group 2, segmental function showed no improvement after reperfusion alone or during infusion of dopamine (group 2B, fig. 2). In these dogs, the TTC technique revealed necrosis involving virtually the entire wall thickness in the area of the length gauge (fig. 5B).

Figure 4. Segment length (SL) changes during ischemia, after reperfusion after 3 hours of ischemia and the effect of dopamine (DOP) infusion during ischemia and after reperfusion in a representative experiment from a group 2 dog with transmural necrosis. During ischemia, dopamine increased systolic lengthening. After reperfusion alone, systolic lengthening continued. During dopamine administration, systolic lengthening was replaced by akinesis. The deep Q wave after reperfusion reflects the extensive myocardial necrosis.

Figure 5. (A) Section of the left ventricle in the area of the length gauge, stained with triphenyl-tetrazolium chloride after a 3-hour occlusion of the left anterior descending coronary artery in a group 2A dog. Necrosis (light area) is limited to the subendocardial region. (B) Similar section from a group 2B dog showing virtually transmural necrosis.
Discussion

Our measurements using length gauges confirmed observations by Puri and Bing and Vatner et al. that inotropic stimulation may not improve the mechanical function of the ischemic myocardium. Reperfusion after 30 minutes of ischemia resulted in only slight return of function, and there was no tendency for improvement during the 40-minute postreperfusion observation period. In contrast to the ischemic myocardium, however, the severely depressed reperfused myocardium responded to inotropic stimulation by marked shortening if reperfusion was performed before the myocardial injury became irreversible.

The striking difference between the responses of the ischemic and the reperfused myocardium to inotropic stimulation can be explained by availability of energy substrates and oxygen, by washout of accumulated products of ischemic myocardial metabolism, and by better access of the inotropic agent.

After reperfusion, the 10-minute infusion of dopamine produced no electrocardiographic signs of a detrimental effect. Hearse et al. could not detect any signs of new myocardial damage or extension of the existing damage after 30 minutes of inotropic stimulation in a rat heart preparation reperfused after 70 minutes of cardiopulmonary bypass and ischemic arrest. These relatively short-term observations cannot rule out the possibility that a sustained period of inotropic stimulation could have some detrimental effects.

If our experimental findings are applicable to the human heart, pump failure that is caused by extensive but reversible myocardial ischemia and is unresponsive to inotropic and other treatment should be manageable by early restoration of blood flow to the ischemic myocardium and inotropic enhancement of function in the reperfused myocardium. Studies showing reversal of cardiogenic shock in patients with myocardial infarction after successful thrombolysis, but not in patients in whom thrombolysis was not successful, seem to support the findings and conclusions of the present study.

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