Myocardial Protection Through Cold Cardioplegia with Potassium or Diltiazem

Experimental Evidence That Diltiazem Provides Better Protection Even When Coronary Flow is Impaired by a Critical Stenosis

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SUMMARY Intermittent aortic root infusion of a cold solution containing either potassium chloride (KCl) or diltiazem was performed in 32 dogs during a 2-hour aortic clamping. Half of the dogs in each group had a critical stenosis created on the circumflex artery before cardiopulmonary bypass. Global left ventricular (LV) function was determined 1 hour after bypass by means of LV pressure, peak dP/dt, LV end-diastolic pressure, cardiac and stroke work indexes. Regional function was assessed through microcrystals in the areas of the circumflex and left anterior descending coronary arteries. LV pressure decreased in all dogs, but more so with the KCl solution (p = 0.02). The stenosis had no specific effect on LV pressure, but affected peak positive dP/dt (p = 0.007) and LV end-diastolic pressure (p < 0.0001). Cardiac and stroke work indexes decreased more in the KCl group than in the diltiazem group (p < 0.002) with or without stenosis. Both positive and negative dP/dt were affected by the type of solution (a greater decrease with KCl), but the narrowing affected only the positive dP/dt. Regional LV function remained unchanged in the absence of a narrowing and was depressed equally in dogs with a narrowing whether they received KCl or diltiazem. Overall LV function appeared to be better preserved with diltiazem, with or without impairment of circumflex flow.

ALTHOUGH myocardial protection through infusion of a cold hyperkalemic solution during ischemic arrest has gained wide acceptance, there still is considerable debate on the composition of the solution and on its efficacy when coronary flow is impaired by obstructive coronary artery disease. Calcium-channel blockers have been suggested either as an adjunct to the solution to prevent reperfusion injury or as an alternative to potassium as a means of achieving membraneplagia and optimal myocardial protection.

In the present study we compared, in the dog, during prolonged ischemic arrest, the effectiveness of two cold cardioplegic solutions, one that contained potassium chloride and the other diltiazem, a calcium channel blocker. Each solution was used in two experimental settings: In one group of dogs, the coronary anatomy was left intact; in the other, a critical stenosis was created in the circumflex coronary artery (Cx).

Material and Methods

Protocol
Thirty-two mongrel dogs that weighed 20-30 kg were anesthetized with sodium pentobarbital, 30 mg/kg, intubated and ventilated with ambient air. Catheters were inserted in the left carotid artery, the jugular and femoral veins for monitoring pressures, cardiac output and blood sampling. Through a left thoracotomy, the left ventricular (LV) apex was cannulated with a #22F cannula to measure LV pressure (LVP) and for subsequent decompression.

Two pairs of 2-mm ultrasonic crystals were implanted (through a stab wound, 1.5 cm apart, perpendicular to the long LV axis) near the subendocardium in the area of the left anterior descending coronary artery (LAD) and Cx. The crystals were connected to a sonomicrometer apparatus (Schuessler and Associates). The distance between crystals and calibration was calculated by the technique of Théroux et al. Interventricular septal and posterior ventricular temperatures were monitored with a thermoresistant needle and systemic temperature was monitored with a rectal probe.

After systemic heparinization (3 mg/kg), the dogs were placed on cardiopulmonary bypass (CPB) (Travenol pump and bubble oxygenator 5 MO 310) with a catheter inserted in the right femoral artery and one in the right atrium. Hemodilution (hematocrit 24 ± 4) was used. The priming volume, which consisted of two-thirds Ringer's lactate, one-third dextran 6% in dextrose 5% in water and included 44 mEq of sodium bicarbonate, was adjusted according to weight (50 ml/kg). Perfusion flow (75 ml/min/kg) was regulated so as to keep aortic pressure at 50 mm Hg. Arterial pH was kept at 7.40 ± 0.5 by administering sodium bicarbonate.

When the temperature was lowered to 22–24°C and the LV apex decompressed, the ascending aorta was cross-clamped. Immediately after clamping, 200 ml of a 4°C cardioplegic solution were injected in the aortic root under a pressure of 120–130 mm Hg, measured by a Sorensen pressure cuff. (This line pressure usually corresponds to an aortic root pressure of ≥ 60 mm Hg.) The pericardial cavity was filled with cold saline. Every 30 minutes, an additional 100 ml of the same solution were injected and the pericardial cavity again filled with cold saline. This kept septal and...
posterior LV temperatures below 18°C. The posterior temperature was usually higher than the septal temperature in dogs with a Cx narrowing (1.8° average, range 0.5–2.5).

After 2 hours of ischemic arrest, the aorta was unclamped and rewarming begun. During reperfusion, the heart was defibrillated as soon as possible and the ventricles were paced if atrioventricular (AV) block was present. All dogs that received diltiazem and several in the potassium groups had temporary AV block, which disappeared before cessation of CPB. The left ventricle was kept decompressed and systemic pressure maintained around 70 mm Hg. After 30 minutes of reperfusion, CPB was discontinued. No cardiotonic drugs were used during the experiment. After bypass, LV end-diastolic pressure (LVEDP) was maintained between 5 and 12 mm Hg through transfusion of the perfusion fluid.

Experimental Groups

Four groups of eight dogs were studied. In groups 1 and 2, the coronary arteries were not manipulated; in groups 3 and 4, a critical stenosis was created in the proximal Cx with a specially designed constrictor or coronary ring with an internal diameter that is controlled by a micrometric screw. The stenosis was considered critical when the degree of compression of the artery by the constrictor was such that, while basal flow remained constant, there was abolition of the hyperemic response after an 8-second occlusion of the artery. Blood flow was measured with an electromagnetic probe (Carolina Medical Electronics) calibrated according to the hematocrit.

Two cardioplegic solutions were used. In groups 1 and 3, 20 mEq of potassium were added to the solution. In groups 2 and 4, 150 μg/kg of diltiazem were added to the solution (components of the basic solution were ringer’s lactate in 5% dextrose in water, sodium bicarbonate 18 mEq/l, mannitol 22.2 g/l; osmolarity ± 600 mosmol/l; pH 7.7; total amount of cardioplegic solution administered in all dogs, 500 ml). In the diltiazem groups, just before declamping, a small bolus of diltiazem (15 μg/kg or 5 ml at room temperature) was placed in the aortic root so that, with declamping, it would be flushed into the coronary arteries. The rationale for this was, according to the working hypothesis, to diminish calcium influx also during reperfusion. Dogs in the potassium groups did not receive a comparable small dose of potassium, as this ion is not known to affect postsischemic calcium flux. First, the groups with intact coronary arteries were studied, alternating diltiazem and potassium, and subsequently, those with a Cx narrowing, again with the diltiazem-potassium alternation.

Measurements

Preischemic

Values before bypass are summarized in tables 1–4. Creation of a stenosis in groups 3 and 4 led to a slight drop in heart rate (p < 0.05) and in maximal negative dP/dt (p < 0.05). Blood flow in the Cx averaged 24.9 ± 1.9 before and 21.6 ± 1.2 after creation of the stenosis. Other hemodynamic and regional and global LV values were similar to those before the stenosis. Measurements compared with values after bypass were those measured after creation of the stenosis.

Measurements were taken before CPB in all groups. The ECG (standard limb leads) and LVEDP were recorded on a Gould apparatus (Brush 2600 model). Aortic pressure (AP), LVP, dP/dt and the sonomicrometric signals and their derivatives were recorded on a Beckman apparatus (R4111 model). The dP/dt electrical signal was recorded through a nystagmus velocity coupler (Beckman type 9841) adapted to the R4111 apparatus. End-diastolic length (EDL) and end-systolic length (ESL) were measured, allowing for calculation of degree and velocity of fiber shortening. To compensate for the derivator’s inertia and that of the hydraulic system used for the LVP measurement, the EDL was measured 20 msec before

<table>
<thead>
<tr>
<th>TABLE 1.</th>
<th>Hemodynamic Values Before and After 2 Hours of Ischemic Arrest in Groups 1 and 2 (Without Coronary Stenosis)</th>
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<tbody>
<tr>
<td>Determination</td>
<td>Potassium (group 1)</td>
</tr>
<tr>
<td></td>
<td>Before</td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>155 ± 7</td>
</tr>
<tr>
<td>MAP (mm Hg)</td>
<td>111 ± 7</td>
</tr>
<tr>
<td>LVP max (mm Hg)</td>
<td>122 ± 6</td>
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<tr>
<td>LVEDP (mm Hg)</td>
<td>4.4 ± 0.2</td>
</tr>
<tr>
<td>+dP/dt (mm Hg/sec)</td>
<td>1776 ± 122</td>
</tr>
<tr>
<td>−dP/dt (mm Hg/sec)</td>
<td>2455 ± 147</td>
</tr>
<tr>
<td>CI (ml/min/kg)</td>
<td>98.2 ± 5.3</td>
</tr>
<tr>
<td>SV1 (ml/beat/kg)</td>
<td>0.66 ± 0.03</td>
</tr>
<tr>
<td>SW1 (g·m·kg)</td>
<td>0.96 ± 0.07</td>
</tr>
<tr>
<td>SRI (dyn·sec·cm⁻⁵/kg)</td>
<td>87.6 ± 5.7</td>
</tr>
</tbody>
</table>

Values are mean ± SEM.

Abbreviations: HR = heart rate; MAP = mean aortic pressure; LVP max = maximum left ventricular pressure; LVEDP = left ventricular end diastolic pressure; +dP/dt = peak positive first derivative of LVP; −dP/dt = peak negative dP/dt; CI = cardiac index; SV1 = stroke volume index; SW1 = stroke work index; SRI = systemic resistance index.
the positive deflection of the dP/dt and ESL 20 msec before the negative deflection of the dP/dt.\textsuperscript{10} Percentage of systolic shortening (%ΔL) was calculated by dividing ΔL (ΔL = EDL − ESL) by EDL and multiplying the product by 100. Instantaneous velocities or maximal systolic velocity (max S dL/dt) of the sonomicrometric signals were measured.

Cardiac output was measured using the green dye-dilution technique and a cardiac output computer (COR 100A, Waters Instruments). From the cardiac output data, several other variables were extracted, including cardiac index (CI), stroke volume index (SVI), stroke work index (SWI, [mean AP − LVEDP] × [SVI] × 0.0136), and systemic resistance index (SRI, [mean AP − LVEDP] × 80). Since pressure on the right side was monitored in the superior vena cava but not further down, the left atrial (or its equivalent the LVEDP) and not the right atrial pressure was the value subtracted from the mean AP in the calculation of SRI.

**Postischemic Measurements**

The same variables were measured 30 minutes after cessation of CPB, 1 hour after the aortic clamp had been removed. At that point, systemic temperature was 37°C, arterial pH 7.40 and the heart was in sinus rhythm. In group 3 and 4 dogs, the Cx constrictor was
still in place. The degree of stenosis was ascertained again by measuring the flow response to the standard 8-second occlusion of the Cx. Basal flow was comparable to that before CPB and did not change after temporary occlusion of the artery.

Statistical Analysis

Analysis of variance was carried out using a trend analysis design with the assumption that subjects are random, while Cx condition (stenotic or nonstenotic), solution (potassium or diltiazem) and time have fixed effects. This design is a three-factor experiment with repeated measures on one factor — time. Interactions and main effects were judged statistically significant when the probability of an observed F value was less than 0.05 (F value > 4.20, with 1 and 28 degrees of freedom). Care must be exercised when interpreting the significance level of an effect in the presence of a significant higher-degree interaction. These analyses of variances were obtained from the data summarized in tables 1–4 and depicted in figures 1–3.

**FIGURE 1. Recovery of left ventricular performance. Maximum left ventricular pressure (LVP max) dropped significantly in all groups (p < 0.0001), but more so in the potassium-treated groups (p = 0.02). Changes in peak dP/dt (p = 0.02), cardiac index (COI) and stroke work index (SWI) (p < 0.02) were also more marked with potassium. Only the dP/dt was influenced by the presence of circumflex stenosis (p = 0.007). W.St = with stenosis; No St = no stenosis; Dilt = diltiazem.**

**FIGURE 2. Changes in left ventricular end-diastolic pressure (LVEDP) and peak negative dP/dt. LVEDP changes little when the circumflex artery is intact, but changes markedly when it is narrowed (p < 0.0001). Potassium and diltiazem do not affect these measurements. The negative dP/dt decreased in all groups, but more so in the potassium-treated groups (p < 0.02). W.St = with stenosis; No St = without stenosis; Dilt = diltiazem.**

**Results**

Global LV Function (tables 1 and 2, fig. 1)

The LVP max showed a highly significant decrease for the entire population (p < 0.0001); the decrease was greater with the potassium solution (p = 0.02). No significant difference seemed to result from the narrowing of the Cx (fig. 1).

For the peak positive dP/dt, dogs with a narrowed Cx (groups 3 and 4) reacted differently from those without a narrowing (groups 1 and 2). Postischemic values were significantly lower than mean preischemic values (fig. 1) in the presence of a stenosis (p = 0.007). Simultaneously, the reaction of this variable was also significantly different (p = 0.02), depending on the cardioplegic agent used: deterioration in the groups treated with potassium was more severe than in those treated with diltiazem.

CI and SWI showed a similar pattern. The cardioplegic agent had a highly significant effect (p < 0.002): In dogs treated with potassium, CI and SWI dropped considerably, while these measurements did not change in the groups treated with diltiazem (fig. 1).

The choice of cardioplegic solution did not affect LVEDP in groups that had no stenosis of the Cx (fig. 2). The significant interaction of time was with the presence of a stenosis. LVEDP rose significantly in the stenotic groups but did not change in the nonstenotic groups (p < 0.0001). Peak negative dP/dt dropped markedly in all four groups, but the only significant difference related to the type of solution used: Potassium was worse than diltiazem (p < 0.002). Within each cardioplegic solution group, on the other hand, the presence of a narrowing of the Cx had no appreciable effect on negative dP/dt (fig. 2).
The form of the diastolic signals varied considerably from dog to dog so as to preclude interpretation of diastolic velocities. However, EDL showed no significant variations between groups, even in those with a Cx narrowing that displayed a rise in LVEDP (EDL after CPB in Cx: group 1, 9.38 ± 0.58; group 2, 9.94 ± 0.80; group 3, 9.21 ± 1.0; group 4, 10.60 ± 0.94. Before CPB: arbitrarily 10 mm in all groups).

Discussion

Myocardial protection during induced ischemic arrest has been debated in recent years. Recognition of the concept of optimal myocardial protection, especially during coronary artery grafting, has led to reevaluation and important changes in surgical techniques. Myocardial revascularization, which entailed a 15% incidence of perioperative infarction, was falling short of its goal. Similarly, in valve replacements, inadequate intraoperative protection of the myocardium was considered responsible for the postoperative low-output syndrome.

Numerous experimental and clinical studies have shown that cessation of all electrical myocardial activity during clamping through hypothermia and pharmacologic cardioplegia leads to recovery of LV function and minimal cardiac necrosis. Potassium chloride is the most commonly used agent for membranoplegia. It stops membrane depolarization by preventing sodium entry into the cells through the fast channels. However, some investigators have questioned the effectiveness of cold potassium cardioplegia when delivery of the solution is impaired by coronary artery narrowing, for instance, or when the ischemic arrest is prolonged. In the latter situation, despite frequent infusions of the cardioplegic solution, injury to the myocardial cell is reported to occur at the time of unclamping of the aorta, producing the so-called reperfusion injury. These conditions — impairment of flow by obstructive coronary artery disease and the need for prolonged aortic clamping — usually prevail in patients with severe coronary artery disease.

Hilton and colleagues demonstrated in dogs that temporary occlusion of the LAD during ischemic arrest and cold potassium cardioplegia leads to significant dysfunction of the anterior wall. Control dogs in whom perfusion of the cardioplegic solution was uniform retained a normal LV function. Clark et al. reported that reperfusion injury can be abolished by adding nifedipine, a calcium-channel blocker, to the cold hyperkalemic solution.

Inhibitors of calcium flux, such as nifedipine, block the entry of Ca²⁺ in the cytosol through the slow channels. A low intracellular Ca²⁺ decreases ATP dissociation and utilization by the contractile proteins and the cell membranes. Energy is consumed not only during contraction but also in the processes of excretion of Ca²⁺ out of the cell and of sequestration of this ion in the sarcoplasmic reticulum (SR). Blocking calcium entry into smooth muscles causes marked vasodilatation. Thus, by creating a positive balance between supply (t vasodilatation) and demand (t con-
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tractivity, ↓O₂ consumption), calcium-channel blockers are particularly helpful during myocardial ischemia. At high concentrations, blockers of calcium influx, like potassium, can paralyze myocardial activity and be used as cardioplegic agents.⁶-⁸ Diltiazem is effective in preserving LV function during prolonged ischemic arrest in animals⁹ and in man.¹⁰

The present experiment was designed to compare a calcium-channel blocker to potassium as a cardioplegic agent during prolonged ischemic arrest in situations in which delivery of the cardioplegic solution was normal and in which it was impaired by the presence of a critical stenosis. The results suggest that diltiazem, like potassium, is an effective cardioplegic agent that, in addition, may provide good myocardial protection even when delivery of the cardioplegic solu-

FIGURE 4. Sample tracings of global and regional function variables in two dogs in the potassium cardioplegia group before and after a 2-hour aortic clamping. Note effect of narrowing on left ventricular pressure (LVP), its first derivative (dP/dt) and regional fiber length (∆L) in circumflex (Cx) area.

FIGURE 5. Representative tracings of some measurements of regional and global left ventricular (LV) function in two dogs in the diltiazem cardioplegia group before and after a 2-hour aortic clamping. In one (lower), a stenosis had been created in the circumflex artery. Note effect of narrowing on LV pressure (LVP) its first derivative (dP/dt) and fiber length (∆L) in circumflex (Cx) area.
tion in animals with normal coronary arteries and treated with potassium showed deterioration after 2 hours of clamping as significant drops in LVP max, maximum positive dP/dt, CI and SWI were recorded. Under similar conditions, with the use of diltiazem as a cardioplegic agent, those values returned toward normal or rose above normal compared with preclamping values. When a critical stenosis was created, global LV performance returned closer to normal with diltiazem. In contrast, regional myocardial function showed no significant changes after clamping and protection with either agent when coronary flow was unimpaired. When a critical narrowing was present on the Cx, marked changes in regional function were observed in this area, and those changes were of equal magnitude whether protection was with potassium or diltiazem.

Preservation of global LV function with diltiazem is probably the result of a combination of factors. The vasodilatation noted with this agent probably accounts for the increase in CI and SWI and for the drop in SRI. This cannot explain the apparent preservation of peak positive and negative dP/dt and LVP max values with the use of diltiazem. Like other calcium influx blockers, diltiazem is a potent coronary dilator. In the presence of a critical stenosis, marked coronary vasodilation may, through increased intercoronary flow, promote better delivery of the cardioplegic solution to the area subjected to the narrowing. The noncoronary collateral flow, increasing as a result of peripheral vasodilatation, would provide more substrates to the myocardium despite cessation of coronary flow during clamping. However, these local vascular effects could not overcome the deleterious influence that a stenosis of the Cx exerts on delivery of the cardioplegic solution, and thus, on regional myocardial function. Millard observed an increase in flow to ischemic and border zones using diltiazem in porcine myocardium. This increase in flow, also noted in dogs, was not associated with improvement in regional hypofunction. Such lack of improvement of regional function may be misleading. In our experiment, for example, regional variables were measured by microcrystals implanted in the center of the Cx area; that is away from the peripheral zones where most changes induced by the calcium blocker would be expected to occur. Such a difference in function between border and center zones has been demonstrated in experiments using verapamil.

Our experimental design differs from that of others in that the narrowing was incomplete and left in place throughout the experiment. Maintaining the critical stenosis in place may account for some of the deterioration in LV function after CPB. However, creation of the stenosis before bypass did not alter regional or global functions to a significant degree and, after bypass, the flow across the stenosis was comparable to that before bypass. This suggests that the decrease in flow in the Cx, which was probably responsible for the impaired regional function, had taken place during bypass and clamping of the aorta. Total coronary flow was not measured before or after bypass; the stenosis on the Cx could have prevented the secondary increase in flow that follows the first few instants of an ischemic insult and that can provide, theoretically, for some repair from the injury.

Preservation of overall LV function may result also from the effect of diltiazem on calcium movements that take place inside the cells and across its membrane during ischemic arrest and reperfusion. During clamping, depolarization may be stopped by blocking either the fast channels with potassium or the slow channel with diltiazem. However, inward calcium flux, which increases under anoxic conditions, is not altered by potassium. Intracellular accumulation of Ca++ may cause structural damage, particularly to mitochondria, which show a high affinity for this ion. Removal of C++ from the cytosol either by transfer across the membrane or by sequestration in the SR requires energy or ATP. The combination of high calcium and low ATP represents a vicious circle, ultimately lethal to the contractile cell. Blocking the entry of calcium into the cells appears to be a logical step during clamping and at the time of reperfusion.

Of the compounds classified as calcium-channel blockers, some, like diltiazem, may interfere also with the fast sodium channels. All can induce membraneplagia; that is, cessation of electrical depolarization. Pinsky et al. showed that verapamil may not provide sufficient protection during ischemic arrest. In their study, it gave no protection when administered alone during 1 hour of clamping, but provided excellent protection when it was given in combination with potassium, better than that when potassium alone was used. Whether diltiazem used in combination with potassium may achieve greater protection than when given alone is not known.

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