Myocardial protection during ischemic cardiac arrest

The importance of magnesium in cardioplegic infusates

The increasing use of coronary infusates for the protection of the human heart during ischemic cardiac arrest has placed great emphasis on the need for a rational and safe formulation of any infusion solution. Using a rat heart model of cardiopulmonary bypass and ischemic cardiac arrest, we have found magnesium to be a highly effective component of protective infusates which can be additive to hypothermia and other protective agents. However, the concentration of magnesium bears a complex relationship to the degree of protection, a fact which stresses the need for the establishment of the correct concentration for optimal protection.

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The current growth of interest in the use of various cardioplegic and protective infusates during open-heart surgery has resulted in the development of a number of different solutions.1–10 These solutions are infused into the coronary arteries for a few minutes immediately following aortic cross-clamping. Although the composition of currently used solutions varies, the basic principles underlying their use are similar.1 First, cardioplegic agents are included in the solution to induce arrest rapidly. Second, protective agents may be included to combat one or more of the deleterious effects of ischemia.

With the rapid development of new infusion solutions and our current inadequate knowledge of the complex interrelationship between various ions and molecules in such infusates, we5, 11 have become increasingly concerned about the potential hazards associated with the omission (e.g., calcium) or the inclusion (e.g., lactate) of various compounds in any infusate. In this connection we3 have advocated that the composition of any coronary infusate should deviate as little as possible from the composition of normal extracellular fluid.

Extracellular fluid contains magnesium. In a recent assessment of a number of cardioplegic or protective agents, we1 reported that magnesium represented the
single most effective component of any infusate tested. In these studies, magnesium was included at a concentration of 16 mM per liter. In some solutions magnesium has been used at concentrations as high as 160 mM per liter, whereas in others it has been completely absent. Since the normal plasma magnesium concentration is 0.5 to 1.5 mM per liter, we considered it important to ascertain the optimal concentration for its use in coronary infusates. For this study we used an isolated, working rat heart model which had previously proved to be valuable in the assessment of myocardial protection.

Materials and methods

Hearts. Hearts were obtained from male rats (280 to 320 grams of body weight) of the Wistar strain.

The experimental model. The isolated, perfused, working heart model, which has already been described in detail, is a left heart preparation in which the oxygenated perfusion medium (at 37°C) enters the cannulated left atrium at a pressure of 20 cm. H₂O and is passed to the ventricle, from which it is spontaneously ejected (electrical pacing was not used in this study) at a rate of 40 to 55 ml per minute, via an aortic cannula, against a hydrostatic pressure of 100 cm. H₂O. Coronary effluent can be sampled for biochemical analysis or pooled and recirculated with the aortic outflow.

Total cardiopulmonary bypass with maintained coronary perfusion may be simulated by clamping the left atrial cannula and introducing perfusion fluid at 37°C into the aorta from a reservoir located 100 cm. above the heart. This preparation, which is essentially that described by Langendorff, will continue to beat but does not perform any external work. Ischemic cardiac arrest may be induced in this preparation by clamping the aortic cannula. Short periods of preischemic coronary infusion (at 37°C or any desired degree of hypothermia) of protective or cardioplegic solutions may be achieved by use of a reservoir (located 60 cm.

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**Fig. 2A.** The postischemic recovery of hearts from 30 minutes of ischemia at 37°C. The recovery of aortic flow rate is shown as a percent of the preischemic control value. Each heart was subjected to preischemic coronary infusion (2 minutes) with solutions containing various concentrations of magnesium: (○) 0 mM per liter; (●) 1.2 mM per liter; (●) 2.4 mM per liter; (●) 3.6 mM per liter; (△) 5.0 mM per liter; (▲) 7.5 mM per liter; (○) 10.0 mM per liter; (●) 12.5 mM per liter; (x) 15.0 mM per liter. Each point represents the mean values of six hearts, and the standard error of the mean is indicated by the bars.
Myocardial protection during ischemic arrest

John Doe

The experimental time course (Fig. 1). Immediately after excision of the heart, the aorta was connected to the aortic cannula and Langendorff perfusion was initiated for a 5 minute washout and equilibration period. During this 5 minute period, left atrial cannulation was completed. During this and subsequent perfusion periods, the circulating fluid was Krebs-Henseleit bicarbonate buffer, \( pH \) 7.4, containing 11.1 mM of glucose per liter and gassed with 95 percent oxygen and 5 percent carbon dioxide. The heart was then converted to a working preparation by terminating the retrograde aortic perfusion and initiating left atrial perfusion. During a 15 minute period, control values for aortic and coronary flow rates, peak aortic pressure, and heart rate were recorded. At the end of this control period, the atrial and aortic cannulas were clamped and the heart was subjected to a 2 minute period of coronary infusion with the protective solution under study. Infusion was then terminated and the entire heart was maintained in an ischemic state for a fixed period of time. Although the hearts were perfused above the heart) attached to a side arm of the aortic cannula.

Table 1. Composition of the coronary infusate*

<table>
<thead>
<tr>
<th></th>
<th>Grams per liter</th>
<th>Millimoles per liter</th>
</tr>
</thead>
<tbody>
<tr>
<td>NaCl</td>
<td>6.36-7.74</td>
<td>108.8-58.8</td>
</tr>
<tr>
<td>NaHCO₃</td>
<td>2.10</td>
<td>25.0</td>
</tr>
<tr>
<td>KCl</td>
<td>1.10</td>
<td>14.8</td>
</tr>
<tr>
<td>MgSO₄·7H₂O</td>
<td>0.0-12.32</td>
<td>0.0-50.0</td>
</tr>
<tr>
<td>KH₂PO₄</td>
<td>0.16</td>
<td>1.2</td>
</tr>
<tr>
<td>CaCl₂·2H₂O</td>
<td>0.18</td>
<td>1.2</td>
</tr>
<tr>
<td>pH 7.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Osmolality</td>
<td>300 mOsm./Kg. H₂O</td>
<td></td>
</tr>
</tbody>
</table>

*For clarity, the composition is expressed in both grams per liter and millimoles per liter, degrees of hydration are stated, and all reagents are of the highest grade of purity. The pH at 37° C. is indicated, as is the osmolality measured by a conventional depression of freezing-point method.

at 37° C. during the control and subsequent recovery periods, the use of dual temperature circuits permitted the infusion of cardioplegic or protective solutions at 37° C. or at any desired degree of hypothermia. Similarly, the hearts could be maintained at any desired temperature throughout the period of ischemia.

After a suitable period of ischemia, the hearts were subjected to reperfusion at 37° C. Initially, reperfusion...
was in the Langendorff mode for 10 seconds, during which nonrecirculating perfusion allowed washout and elimination of the residual cardioplegic infusate. Left atrial perfusion was then reinstated for a 30 minute period, and the recovery of various parameters of cardiac function was recorded.

**Infusion solution.** The solution used in these studies is shown in Table I. The composition of the magnesium concentration was varied in the range of 0 to 50 mM per liter. So that a constant osmolality (300 mOsm. per kilogram of water) would be maintained, the concentration of sodium was adjusted to compensate for changes in the magnesium concentration.

Precautions were taken to prevent the precipitation of calcium, and all infusates and perfusion fluids were filtered through a cellulose acetate membrane (pore size 5 $\mu$.)

**Expression of results.** The absolute recovery values for various parameters of cardiac function in individual hearts were compared and expressed in terms of a percentage of those values obtained during the preischemic control period. In addition to eliminating any inherent variability between individual hearts, this method allowed the recovery of each parameter of function to be expressed as a percentage and to be related to the nature of the coronary infusate and the duration of ischemic arrest. At least six hearts were used for each condition studied, and all data were expressed as the mean ± standard error. Comparison between groups was by Student’s t test.

### Table II. Recovery of aortic flow, aortic pressure and heart rate after 30 minutes of ischemia at 37° C.

<table>
<thead>
<tr>
<th>Infusate magnesium (mM/L)</th>
<th>Aortic flow</th>
<th>Aortic pressure</th>
<th>Heart rate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control (mllmin)</td>
<td>Recovery after 30 min. of reperfusion (percent)</td>
<td>Control (cm. H2O)</td>
</tr>
<tr>
<td>0</td>
<td>52.6 ± 3.6</td>
<td>6.1 ± 4.9</td>
<td>182 ± 3</td>
</tr>
<tr>
<td>1.2</td>
<td>47.9 ± 3.5</td>
<td>27.2 ± 10.8</td>
<td>180 ± 4</td>
</tr>
<tr>
<td>2.4</td>
<td>51.5 ± 4.2</td>
<td>57.6 ± 11.8</td>
<td>183 ± 3</td>
</tr>
<tr>
<td>3.6</td>
<td>49.7 ± 3.8</td>
<td>56.5 ± 9.8</td>
<td>183 ± 3</td>
</tr>
<tr>
<td>5.0</td>
<td>55.4 ± 2.4</td>
<td>61.6 ± 5.5</td>
<td>185 ± 3</td>
</tr>
<tr>
<td>7.5</td>
<td>58.0 ± 1.9</td>
<td>63.3 ± 6.7</td>
<td>185 ± 4</td>
</tr>
<tr>
<td>10.0</td>
<td>59.7 ± 1.8</td>
<td>63.9 ± 8.8</td>
<td>187 ± 2</td>
</tr>
<tr>
<td>12.5</td>
<td>46.9 ± 1.5</td>
<td>82.6 ± 3.1</td>
<td>183 ± 4</td>
</tr>
<tr>
<td>15.0</td>
<td>46.6 ± 1.6</td>
<td>90.6 ± 5.1</td>
<td>180 ± 5</td>
</tr>
<tr>
<td>20.0</td>
<td>42.1 ± 1.1</td>
<td>85.5 ± 3.1</td>
<td>169 ± 4</td>
</tr>
<tr>
<td>30.0</td>
<td>44.6 ± 1.5</td>
<td>70.0 ± 5.4</td>
<td>174 ± 4</td>
</tr>
<tr>
<td>50.0</td>
<td>45.7 ± 2.3</td>
<td>42.1 ± 10.8</td>
<td>176 ± 3</td>
</tr>
</tbody>
</table>

*The recovery of aortic flow, aortic pressure, and heart rate are expressed as a percent of the preischemic control. Values for all groups are the mean of six hearts, and the standard error of the mean is indicated.

### Results

**Dose-response curves.** In the initial series of experiments, hearts ($n = six for each group) were subjected to a 2 minute period preischemic infusion with solutions containing the following concentrations of magnesium: 0, 1.2, 2.4, 3.6, 5.0, 7.5, 10.0, 12.5, 15.0, 20.0, 30.0 and 50.0 mM per liter. In each instance the solution induced almost instantaneous diastolic arrest. Hearts were subjected to 30 minutes of ischemia at 37° C. and then to reperfusion for 30 minutes. During the reperfusion period, the recovery of parameters of cardiac function was monitored; the results for aortic flow are shown in Fig. 2 and those for heart rate, aortic flow, and aortic pressure are given in Table II.

The results clearly indicate that increasing the magnesium concentration of the infusate from 0 to 15.0 mM per liter produces a progressive and significant improvement in the recovery of function during the reperfusion phase (aortic flow improving from 6.1 ± 4.9 percent to 90.6 ± 5.1 percent, $p < 0.00001$). However, as the infusate magnesium concentration increases from 15.0 to 50.0 mM per liter, there is a progressive decline in functional recovery (aortic flow falling from 90.6 ± 4.9 percent to 42.1 ± 10.8 percent, $p < 0.001$).

Fig. 3 shows the precise relationship between the postischemic recovery of aortic flow measured 30 minutes after the onset of reperfusion (an index of the degree of protection afforded by the infusate) and the magnesium concentration of the infusate. The relationship is not a simple one. There is a linear and
striking increase in protection as the magnesium concentration is increased from 0 to 2.4 mM per liter ($p < 0.001$). Between 2.4 and 10.0 mM per liter, there is little increase in protection for a major increase in magnesium concentration. However, between 10.0 and 15.0 mM per liter, there is a secondary striking increase in protection ($p < 0.01$). Beyond 15.0 mM per liter there is a progressive decline in protection and recovery.

**Applicability under different conditions.**

**Temperature and duration of ischemia.** The preceding experiments were carried out with a 30 minute period of normothermic ischemia. Since the temperature and duration of ischemia affects tissue damage and functional recovery, the experiments were repeated under conditions of extended (60 minutes) hypothermic (28°C) ischemia. The results (Fig. 4) reveal a similar dose-response relationship to that found with shorter periods of normothermic ischemic arrest (Fig. 2). Thus, with a concentration between 0 and 2.4 mM of magnesium per liter in the infusate, there is a striking improvement ($p < 0.01$) in protection and recovery of aortic flow. This improvement is followed by a plateau and a secondary rise, which again suggests that 15 mM per liter is the optimal concentration. Protection then declines with increasing concentrations of magnesium. Although the dose-response profile for 30 minutes of normothermic arrest is similar to that for 60 minutes of hypothermic arrest, the absolute recovery is higher in the hypothermic group at any single concentration. This observation is readily explained by the fact that 60 minutes of ischemic arrest at 28°C in the rat heart is less damaging than 30 minutes of arrest at 37°C. This observation illustrates the protective properties of hypothermia and the fact that this protection is additive to that conferred by magnesium.

**Possible contribution of changes in the sulfate concentration.** Since the adjustments in magnesium concentration were affected by altering the amount of magnesium sulfate dissolved in the coronary infusate, it was important to ascertain whether the observed effects were attributable to the magnesium or its sulfate counter ion. Experiments were therefore undertaken in which, at certain selected points in the dose-response
Fig. 4. The relationship between the concentration of magnesium in the preischemic coronary infusate and the postischemic recovery of aortic flow. Hearts were subjected to a 2 minute period of coronary infusion with solutions containing the following concentrations of magnesium: 0, 1.2, 2.4, 5.0, 10.0, 15.0, 30.0, and 50.0 mM per liter. A 60 minute period of hypothermic (28°C.) ischemic arrest followed. Hearts were then reperfused, and the recovery of aortic flow was measured after 30 minutes of reperfusion and expressed as a percent of the preischemic control value. Each point represents the mean of six hearts, and the standard error of the mean is indicated by the bars.

Table III. The effect of sulfate and chloride counter ions upon the recovery of aortic flow rate*

<table>
<thead>
<tr>
<th>Magnesium salt (mM/L.)</th>
<th>Postischemic recovery of aortic flow (percent)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sulfate</td>
</tr>
<tr>
<td>5.0</td>
<td>61.6 ± 5.5</td>
</tr>
<tr>
<td>10.0</td>
<td>63.9 ± 8.8</td>
</tr>
<tr>
<td>15.0</td>
<td>90.6 ± 5.1</td>
</tr>
<tr>
<td>20.0</td>
<td>85.5 ± 3.1</td>
</tr>
<tr>
<td>50.0</td>
<td>42.1 ± 10.8</td>
</tr>
</tbody>
</table>

*Hearts were subjected to a 2 minute period of preischemic coronary infusion with the various solutions under study. This was followed by a 30 minute period of ischemic arrest at 37°C and a 30 minute period of reperfusion. The recovery of aortic flow at the end of the reperfusion period is expressed as a percent of the preischemic control value. Each result is the mean of six hearts, and the standard error of the mean is indicated.

The recoveries of aortic flow at the end of the reperfusion periods, given in Table III, show that with the exception of a small decrease, at 20.0 mM per liter, there was no difference when magnesium chloride was used instead of magnesium sulfate. This would indicate that the observed protection may be attributed solely to the inclusion of the magnesium ion and not to its counter ion.

Possible contribution of compensatory changes in sodium concentration. So that a constant osmolality in the dose-response studies could be maintained, any increase in magnesium concentration was compensated for by appropriate reductions in the sodium content of the infusate. To ascertain that these changes in sodium content were not responsible for the observed results, the following experiments were carried out. Hearts were subjected to preischemic coronary infusion with solutions containing 0, 1.2, 2.4, 3.6, 5.0, and 15.0 mM of magnesium per liter. However, these solutions were not corrected (sodium reduction) for osmolality. The hearts were then subjected to 30 minutes of ischemic arrest at 37°C and 30 minutes of reperfusion. The recoveries of aortic flow at the end of the reperfusion period were compared to those in the previous sodium-corrected group and the results are illustrated in
Table IV. The effect of compensatory changes in the sodium concentration upon the protection afforded by magnesium*

<table>
<thead>
<tr>
<th>Magnesium (mM/L.)</th>
<th>Sodium corrected</th>
<th>Non-sodium corrected</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sodium (mM/L.)</td>
<td>Recovery of aortic flow (percent)</td>
</tr>
<tr>
<td>0.0</td>
<td>108.8</td>
<td>6.1 ± 4.9</td>
</tr>
<tr>
<td>1.2</td>
<td>107.6</td>
<td>27.1 ± 10.8</td>
</tr>
<tr>
<td>2.4</td>
<td>106.4</td>
<td>57.6 ± 11.8</td>
</tr>
<tr>
<td>3.6</td>
<td>105.2</td>
<td>56.5 ± 9.8</td>
</tr>
<tr>
<td>5.0</td>
<td>103.8</td>
<td>61.6 ± 5.5</td>
</tr>
<tr>
<td>15.0</td>
<td>93.8</td>
<td>90.6 ± 5.1</td>
</tr>
</tbody>
</table>

*Hearts were subjected to a 2 minute period of preischemic coronary infusion with the various solutions under study. This was followed by a 30 minute period of ischemic arrest at 37°C and a 30 minute period of reperfusion. The recovery of aortic flow at the end of the reperfusion period is expressed as a percent of the pre-ischemic control value. Each result is the mean of six hearts, and the standard error of the mean is indicated.

Table IV. It is apparent that the small changes in sodium have no significant effect upon recovery; although there would be small differences in osmolality in the non-sodium-corrected group, these would be too minute to account for the striking differences in recovery, especially in the range 0 to 5.0 mM of magnesium per liter. These results again indicate that the improvements in recovery can be directly attributable to the magnesium ion.

Discussion

The results of this study reveal that magnesium is able to exert, in a complex dose-related manner, a marked protective effect upon the ischemic rat myocardium. The interpretation of these results necessitates a brief review of the role of magnesium in myocardial cell function and survival.

Except for potassium, magnesium is the most abundant intracellular cation in the heart: In the ventricular muscle of the rat, an intracellular concentration of 17.3 ± 0.2 mM per kilogram of cell water has been reported. Magnesium exists intracellularly as a complex with adenosine triphosphate (ATP) and other adenine nucleotides and also as free ionized magnesium. The distribution between these two forms is uncertain, as is the extent to which magnesium exists in the various intracellular compartments.

Magnesium is involved in a multitude of critical cellular reactions. Thus ATP complexed to magnesium is the substrate for the enzymatic reactions underlying muscle contraction and relaxation; magnesium may be a critical modulator of muscle tension. In reviewing studies of the role of magnesium in the cell, we found that fluctuations within fairly narrow limits in the concentrations of ionized magnesium and magnesium-adenine nucleotide complexes can profoundly affect the contractile performance of the muscle cell. Magnesium is also involved as a cofactor in all energy-transferring reactions of the cell and in many reactions of oxidation, synthesis, and transport. The plasma membrane of the ventricular cell is the locus of a transport mechanism by which about 98 percent of cellular magnesium exchanges at a slow rate and which probably involves a carrier-mediated transport mechanism. Although the exact relationship between magnesium transport and the transport of calcium, potassium, and sodium remains unclear, it is known that extracellular magnesium can reduce potassium efflux and calcium influx.

Hypomagnesemia is severely detrimental to cellular function and survival; for example, it has been associated with increased incidence of ischemic heart disease and a greater tendency to cardiac dysrhythmias. Depletion of cellular magnesium is often observed in injured myocardial tissue and Shen and Jennings have demonstrated a significant loss of tissue magnesium following the onset of ischemia.

There are several mechanisms which could be proposed to explain our observed pattern of myocardial protection following preischemic coronary infusion with solutions containing elevated concentrations of magnesium. Following the onset of myocardial ischemia there is an abrupt reduction of oxidative metabolism and ATP production. Continued ATP utilization in the face of severely restricted production results in a sharp fall in myocardial energy reserves. The fall in ATP effectively results in a dechelation of intracellular magnesium leading to a transient rise in the concentration of ionized magnesium. Although under normal conditions the sarcolemma has a very low passive permeability to magnesium, myocardial ischemia causes major changes in membrane permeability and permits the loss of substantial amounts of intracellular magnesium and potassium to the extracellular space. This loss of magnesium will be facilitated by the tran-
sient rise in intracellular magnesium and possibly by
the increasing concentrations of cytoplasmic ionized
calcium. If the loss of intracellular magnesium is large
enough, it may lead to an impairment of various reac-
tions which require magnesium as a cofactor.

In addition to contributing to tissue damage during
ischemia, magnesium depletion may be detrimental
during posts ischemic reperfusion. The recovery of
myocardial function requires the re-establishment of
oxidative metabolism and the replenishment of high-
energy phosphate stores. In normal tissue, ATP and
total adenine nucleotide content are in the range 15 to
25 mM per liter. Since the bulk of the ATP will be required to exist as a magnesium com-
pound, and the magnesium content is normally very simi-
lar (17 mM per kilogram of cell water) to the ATP
content, then any loss of magnesium during ischemia
may severely restrict energy availability after ischemia.

The ability of extracellular magnesium to protect the
ischemic myocardium probably results from the follow-
ing: (1) the reduction of the trans-sarcolemmal mag-
nesium gradient and thus the reduction of passive mag-
nesium loss, which conserve magnesium for its role as
a vital enzyme cofactor and as a part of the active ATP
molecule; (2) the reduction of potassium efflux and
calcium influx during ischemia, both of which are
known to be detrimental to tissue survival; (3) reduc-
tion of the incidence of dysrhythmias either by some
direct action of magnesium on sodium-potassium ATPases or through its effect upon transmembrane
calcium and potassium fluxes.

The dose-response relationship observed in these
studies (Fig. 3) is of particular interest. It may well be
that the sharp increase in protection observed when the
extracellular concentration of magnesium is increased
from 0 to 15 mM per liter may be related to the preven-
tion of intracellular magnesium loss. It is notable that
the magnesium concentration for optimal protection is
approximately 15 mM per liter, a value which is con-
siderably enhanced by the correct choice of concentra-
tion.

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