Expansion of Extracellular Space in the Nonischemic Zone of the Infarcted Heart and Concomitant Changes in Tissue Electrolyte Contents in the Rat

By Philip I. Polimeni and Jafar Al-Sadir

ABSTRACT

The alterations in electrolyte content that occur in an infarcted zone of the heart have also been reported to occur in a similar manner, although to a far less degree, in the distant, apparently normal zones of the heart. These alterations in the nonischemic myocardium have usually been tabulated without comment, presumably because their magnitudes approach values of statistical dispersion. Our measurements of electrolyte content in the normal zone of the infarcted rat heart confirmed that all of the electrolyte contents were slightly modified. There was a rise in sodium, calcium, and chloride and a decline in potassium and magnesium. In addition, the extracellular space (14C)sucrose in this zone was elevated by nearly 15%. We have postulated a mechanism for this elevation based on an increase in the net filtration rate through myocardial capillaries. The expansion of the extracellular space can account for all of the electrolyte changes in the normal zone with the exception of the alteration in calcium. Therefore, there is no basis for assuming that these myocardial alterations reflect general movements of electrolytes down their electrochemical gradients. We suggest that the increment in the nominal concentration of cellular calcium is related to a compensatory mechanism that allows the reduced mass of functional myocardium to contract more vigorously.

It is well known that the electrolyte contents and distributions of myocardial tissue are markedly altered after severe ischemia or injury: the tissue becomes edematous, it gains sodium, chloride, and calcium, and it loses potassium and magnesium. Presumably, these changes are confined to the damaged zone of the myocardium and reflect the movements of ions and water down their electrochemical gradients. Surprisingly, several investigators have found that the electrolyte contents of noninfarcted zones of infarcted human and canine hearts are intermediate between those of infarcted tissues and comparable tissue obtained from hearts of normal humans (1-4) or sham-operated dogs (5-7). The electrolyte contents found in the noninfarcted zones are never much different from the limits of statistical dispersion associated with normal or control values, so that the alterations are small and demonstrable only with fastidious analytical techniques. For this reason, negative findings in the literature need not necessarily rule out the possibility that electrolyte distribution in the apparently normal zone of the infarcted heart is subtly affected by distant ischemia.

Since the electrolyte changes in the functional zone of the infarcted heart are all in the same directions as those in the injured zone, it is reasonable to speculate that a common, nonspecific phenomenon may underlie the alterations in both zones. The most obvious mechanism is an increment in membrane permeability and a diminution of the active processes responsible for the maintenance of the transmembrane electrochemical gradients. This mechanism appears to have been implicitly assumed by those authors who have commented on the significance of the intermediate electrolyte values which they have found. Calculations show, however, that the alterations in the electrolytes in noninjured muscle of the infarcted heart can be just as plausibly explained by a small expansion of the muscle's extracellular compartment. With this possibility in mind, we reexamined the electrolyte composition of ischemic and nonischemic samples from experimentally infarcted hearts, particularly focusing on quantifying the extracellular volumes of these samples. We attempted to answer two questions. Do the electrolyte contents and distributions within the appar-
ently normal myocardial muscle of the infarcted heart change? If they do change, do the changes reflect alterations in the cellular contents or alterations in the size of the extracellular compartment?

Methods

Female Sprague-Dawley rats weighing 200-250 g were divided into two groups; each group consisted of 12 rats. The first group was subjected to myocardial infarction induced by ligating the descending branches of the left coronary artery and its accompanying vein, and the second group underwent sham-operations and served as controls. The procedure used to provoke the infarct was based on techniques developed by Bajusz and his colleagues and described by him in detail (8). We modified the procedure slightly for our convenience. The rat was anesthetized with ether, the heart was exposed and exteriorized through an incision between the fourth and sixth ribs on the left side, and the left descending coronary artery and vein were ligated together with 5-0 Ethicon cardiovascular silk approximately midway between the base and the ventricular apex. The heart was reinserted into the thorax, and the wound was rapidly closed with stainless steel clips. The entire operation generally required about 3 minutes, of which some 80-120 seconds were expended during the open-chest phase. Artificial respiration was not required, since surviving rats began breathing and regained consciousness within a few minutes. It must be noted that the minute diameter of the artery made it virtually impossible to visualize the vessel during the operation. However, in preliminary experiments, the artery was visualized after the injection of opaque materials and observed to run next to the vein in the interventricular groove. Notwithstanding these landmarks, some variation in the level and the amount of tissue ligated was unavoidable because of the rapid movement of the heart and the brief period allowed for the ligation. The sham-operated rats were treated similarly except that the coronary vessels were not ligated.

The rats rested until the next day with food and water available ad libitum; they were then anesthetized with ether, bilaterally nephrectomized, and injected with approximately 100 µl of [14C]sucrose via an exposed femoral vein. After allowing the extracellular tracer to equilibrate (36-123 minutes), each rat was anesthetized again, the thorax was opened by a sternal incision, about 5 ml of blood was withdrawn from the inferior vena cava, and the heart was excised. After trimming and discarding all of the atrial tissue, the ventricular mass was divided into basal and apical halves above the site of the coronary occlusion. Since the borders of the infarct were poorly delineated, the apical tissue undoubtedly contained a substantial amount of noninfarcted tissue. For this and other reasons cited later, the electrolyte contents and distributions within the apical samples cannot be taken to be quantitatively representative of infarcted tissue. However, care was taken to avoid any infarcted or ischemic tissue in the basal sample. Pieces of tissue were taken from the basal and apical samples for wet and dry weighing to determine their water contents. The tissues were dried overnight in quartz crucibles at 95°C in vacuo. The mean weights of comparable sets of samples did not differ by more than 11%. The samples were then extracted for 2 days in 0.1N nitric acid. The blood samples were centrifuged immediately after they were drawn; the serum was then separated and refrigerated for later analysis.

Tissue extracts and serum samples were analyzed for sodium and potassium by emission spectrophotometry, for chloride by coulometric-amperometric titration with silver ions, for calcium and magnesium by atomic absorption spectrophotometry, and for radioactivity due to [14C]sucrose by liquid scintillation counting. The analytical procedures, the determination of the extracellular space, and the calculation of intracellular electrolyte concentrations used in this paper have been described in detail in a previous communication (9).

Experiments were also performed on two healthy male mongrel dogs of comparable weight (24 and 28 kg). After induction of anesthesia with a small intravenous injection of sodium thiopental, the dogs were anesthetized with an intravenous infusion of a warm solution of alpha-chloralose. Alpha-chloralose anesthesia has been shown to have only minimal, transient effects on cardiovascular dynamics (10). Supplementary doses of chloralose were given to maintain a relatively uniform state of anesthesia throughout the experiment. Respiration was controlled by a Harvard volume respirator connected to a tracheotomy tube. Systemic arterial blood pressure was measured through a short 14-T-gauge semirigid Teflon catheter inserted into the right carotid artery and connected to a Statham P23De pressure transducer and recorded on a Hewlett-Packard ink-recording system. The heart was exposed by a midsternal thoracotomy; a pericardiotomy was performed, and a pericardial cradle was created to support the exposed heart. The left anterior descending coronary artery was identified, and a small portion was dissected and freed at the junction of its middle and lower third. A small wedge-shaped myocardial biopsy was obtained from the apical segment supplied by the terminal left anterior descending coronary artery. Ligation of the coronary artery with a silk snare was then performed in one dog; the other dog served as a control (sham-operated). Six hours later, myocardial biopsies were obtained in both dogs from the apical segment and a distant area supplied by the left circumflex coronary artery at the base of the left ventricle. Both dogs maintained normal, stable blood pressures throughout the experiment, received comparable amounts of fluids, and were free of major dysrhythmia. Technical procedures and hemodynamic data have been reported in greater detail elsewhere for a similar porcine preparation (11). The volume of the extracellular compartment was determined in the biopsy sample by a morphometric technique (9).

Results

Data obtained from rat hearts with experimental infarctions and from their controls are referred to as myocardial infarct (MI) and sham-operated (SO) data, respectively. Each group consisted of 12 individuals. The data are given as means ± SE, and their significance was evaluated by application of Student’s t-test for paired or unpaired data.
SERUM ELECTROLYTE CONCENTRATIONS

The serum electrolyte concentrations (mmoles/liter serum) of sham-operated rats and rats with myocardial infarction are shown in Table 1. The values were similar in both groups, except for slightly but significantly lower ($P < 0.05$) concentrations of Mg and Cl in MI samples. Comparisons of serum concentrations found in sham-operated rats with plasma concentrations in normal rats of comparable weight (9) indicate a 6% decline in Na and a 28% rise in Mg, presumably associated with surgical trauma (12–14).

MYOCARDIAL ELECTROLYTE CONTENTS

The electrolyte contents of SO and MI tissue samples is given in mmoles/kg dry tissue in Table 2. The values for the SO samples were close to the values obtained in normal rats (9) when allowance was made for the changes in serum electrolyte concentrations. It is noteworthy that the small differences between the contents of the basal and apical zones of the SO heart showed a consistent pattern: there was slightly more of each of the predominantly extracellular electrolytes (Na, Ca, and Cl) in the basal zone and slightly less of both of the predominantly intracellular electrolytes (K and Mg). This pattern could be fortuitous, but it could also suggest subtle differences along the longitudinal axis of the heart in membrane permeability, active transport, or the volume density of myocardial cells compared with extracellular tissue.

The electrolyte contents of the apical samples of the MI hearts clearly showed the effects of myocardial infarction, namely, myocardial loss of K and Mg and gain of Na, Ca, and Cl. The values should not be considered an accurate representation of the electrolyte content of infarcted tissue, for as we have already noted, each sample undoubtedly contained a noninfarcted zone of unknown and probably variable size. Thus, the alterations in the electrolyte content of infarcted tissue are surely greater than those indicated by these data.

Comparison of the electrolyte contents of basal samples from MI hearts with those of SO hearts was interesting in that it clearly confirmed the observations that the contents in the apparently healthy zone of the infarcted heart were intermediate between those of normal (or control) and infarcted tissue. With the exception of Ca, the differences were small and not statistically significant, which probably accounts for the doubts displayed by other workers who have commented on this phenomenon (1–4, 6, 7).

MYOCARDIAL EXTRACELLULAR SPACE

The mean volume of the extracellular ([14C]sucrose) compartment in SO hearts was 0.229 ± 0.003 kg water/kg tissue water (Table 3, values of base and apex combined), a value close to that of normal rats (0.230 ± 0.002 kg water/kg tissue water) reported elsewhere (9). Tissue water content (Table 3) was almost identical in both zones of the SO heart and nearly the same as that in the normal rat ventricle (3.32 ± 0.02 kg water/kg dry tissue, $n = 24$).

In the apical zone of the MI heart, the tissue water content rose markedly (Table 3) as expected.

### Table 1

<table>
<thead>
<tr>
<th>Electrolyte</th>
<th>Sham-operated</th>
<th>Myocardial infarct</th>
</tr>
</thead>
<tbody>
<tr>
<td>Na</td>
<td>134 ± 1</td>
<td>134 ± 1</td>
</tr>
<tr>
<td>K</td>
<td>4.6 ± 0.2</td>
<td>4.8 ± 0.2</td>
</tr>
<tr>
<td>Cl</td>
<td>106 ± 1</td>
<td>102 ± 1</td>
</tr>
<tr>
<td>Ca</td>
<td>2.58 ± 0.07</td>
<td>2.63 ± 0.06</td>
</tr>
<tr>
<td>Mg</td>
<td>1.35 ± 0.06</td>
<td>1.21 ± 0.04</td>
</tr>
</tbody>
</table>

All values are means ±SE.

* Circulation Research, Vol. 37, December 1975

### Table 2

<table>
<thead>
<tr>
<th>Electrolyte</th>
<th>Sham-operated</th>
<th>Myocardial infarct</th>
</tr>
</thead>
<tbody>
<tr>
<td>Na</td>
<td>169 ± 4</td>
<td>183 ± 6</td>
</tr>
<tr>
<td>K</td>
<td>384 ± 8</td>
<td>383 ± 6</td>
</tr>
<tr>
<td>Cl</td>
<td>122 ± 4</td>
<td>132 ± 5</td>
</tr>
<tr>
<td>Ca</td>
<td>4.2 ± 0.1</td>
<td>5.1 ± 0.2</td>
</tr>
<tr>
<td>Mg</td>
<td>45.8 ± 0.6</td>
<td>44.7 ± 0.6</td>
</tr>
</tbody>
</table>

The apical samples from the infarcted hearts contained the infarct, whereas the basal samples were presumably free of necrotic tissue. All values listed in parentheses in this and all subsequent tables are considered to be nominal for reasons given in the text.
for tissue that is largely infarcted, and the extracellular space also appeared to expand enormously. This increase in extracellular space is probably erroneously high, because the calculated intracellular water content was less than that in the noninfarcted zone—a most improbable situation (15, 16). Furthermore, it is well known that molecules much larger than sucrose readily permeate the plasma membranes of cells in ischemic tissue. The nonspecific breakdown in membrane permeability subsequent to ischemia not only accounts for the redistributions of tissue electrolytes but also for the obviously exaggerated values of extracellular space obtained in infarcted tissue.

Comparison of extracellular space or (H2O)0 in the basal samples of SO and MI hearts indicates that the extracellular compartment of functional and apparently still normal ventricular muscle had expanded (P < 0.001) by about 15% 1 day after a myocardial infarct. The intracellular water content seemed to have declined somewhat, but the sensitivity of the methodology was insufficient to permit an unequivocal conclusion on this point.

**Intracellular Electrolyte Concentrations**

The cellular electrolyte concentrations (Table 4) of the two zones in the SO hearts were well within the range of values previously measured in other sets of normal or control ventricular samples (9, 17, 18). The differences associated with basal and apical samples were statistically significant (P < 0.01) for Na, Ca, and Cl. However, the inaccuracies that can easily emerge (with relatively small errors in the extracellular space measurements) when the intracellular concentrations of predominantly extracellular electrolytes (Na and Cl) are calculated preclude our attributing a physiological significance to these data. The predominantly intracellular electrolytes, whose cellular concentrations can be far more accurately determined, were not statistically different in the two zones.

Comparison between the basal samples of SO and MI hearts showed a remarkable constancy in the intracellular concentrations with the exception of Ca in which basal [Ca]j increased 24% (P < 0.05).

**Table 4**

<table>
<thead>
<tr>
<th>Electrolyte concentration (mmoles/liter cell water)</th>
<th>Sham-operated</th>
<th>Myocardial infarct</th>
</tr>
</thead>
<tbody>
<tr>
<td>Na</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Base</td>
<td>23 ± 1</td>
<td>22 ± 1</td>
</tr>
<tr>
<td>Apex</td>
<td>20 ± 1</td>
<td>(26 ± 1)</td>
</tr>
<tr>
<td>K</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Base</td>
<td>148 ± 3</td>
<td>150 ± 3</td>
</tr>
<tr>
<td>Apex</td>
<td>150 ± 3</td>
<td>(158 ± 4)</td>
</tr>
<tr>
<td>Cl</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Base</td>
<td>14 ± 1</td>
<td>13 ± 1</td>
</tr>
<tr>
<td>Apex</td>
<td>9 ± 1</td>
<td>(19 ± 2)</td>
</tr>
<tr>
<td>Ca</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Base</td>
<td>0.83 ± 0.04</td>
<td>1.03 ± 0.08</td>
</tr>
<tr>
<td>Apex</td>
<td>0.67 ± 0.03</td>
<td>(2.11 ± 0.24)</td>
</tr>
<tr>
<td>Mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Base</td>
<td>17.3 ± 0.2</td>
<td>17.3 ± 0.3</td>
</tr>
<tr>
<td>Apex</td>
<td>17.7 ± 0.3</td>
<td>(15.3 ± 0.5)</td>
</tr>
</tbody>
</table>

For the calculation of intracellular concentrations, the serum electrolyte concentrations were converted to the unit of mmoles/kg serum water by dividing the serum values in Table 1 by 0.946.
The apparent intracellular concentrations of the electrolytes in the infarcted samples are unreliable for the reasons discussed earlier. The values for Na, Ca, and Cl all showed the expected increases, but they were undoubtedly understated because of the erroneously large extracellular space values determined in injured tissue. For the same reasons, cellular K and Mg appeared to be more concentrated than they were in actuality. Although the errors cannot be corrected, it is instructive to recalculate the intracellular electrolyte concentrations from the data in Tables 1–4 on the assumption that the ischemic cells are swollen. Such calculations showed that $[\text{Na}]_i > 40$, $[\text{K}]_i < 137$, $[\text{Cl}]_i > 30$, $[\text{Ca}]_i > 2.1$, and $[\text{Mg}]_i < 13.8$ mmol/liter cell water. For each electrolyte, then, the electrochemical gradient had diminished as would be expected in injured tissue.

**Morphometric Measurement of Extracellular Space in the Dog Heart**

Although the evidence convincingly indicates some swelling of the extracellular space in apparently normal tissue of infarcted rat hearts, it was considered useful to examine this phenomenon in the in situ dog heart by a morphometric method. This method is not subject to the criticism that the observed swelling of the extracellular space is due to an abnormal penetration of extracellular tracer into the cellular compartment; the method has been found to be consistently sensitive to extracellular space increments (17) of the magnitude observed with the tracer method in the experiments reported in this paper. This experiment was meant to support the results derived from the rat experiments; it was not intended to provide additional quantitative data. For this reason and also because the morphometric method is particularly time consuming and laborious, the experiment was limited to two dogs. The canine preparation has two major advantages: (1) the volume of the infarct can be better controlled and defined and (2) the pre- and postinfarction samples of apparently normal tissue can be obtained from the same heart.

The main disadvantage is that fluid and drugs must be administered to the dogs during the 6 hours between the times when the two biopsies are obtained.

The results are shown in Table 5 (extracellular space is expressed as cm$^3$ extracellular volume/cm$^3$ ventricle in the table). The apical extracellular spaces in the SO and MI hearts differed initially, but they were within the range of values that has been observed in the rat ventricle using the same technique. More importantly, 6 hours after the heart was infarcted in the apical zone by ligating the left anterior descending coronary artery, the extracellular space of the distant nonischemic myocardium supplied by the circumflex coronary artery increased markedly. The phenomenon was not observed in the sham-operated dog.

**Discussion**

It is well established that the ischemic myocardium takes up large amounts of sodium, calcium, and chloride while it simultaneously loses potassium and magnesium (1, 2, 5, 6, 19, 20). Presumably these electrolytes run down their electrochemical gradients across a plasma membrane rendered abnormally permeable to ions. Several authors have also commented on the peculiar finding that the myocardial contents of various electrolytes within the nonischemic zone of the infarcted hearts of both men (1–4) and dogs (6, 7) are intermediate between the contents of normal heart muscle and ischemic or infarcted heart muscle. In general, the differences between the contents in apparently normal myocardial samples from infarcted and noninfarcted hearts are not large, but the pattern suggests that the electrolyte alterations occurring

<table>
<thead>
<tr>
<th>Sham-operated</th>
<th>Myocardial infarct</th>
</tr>
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<tbody>
<tr>
<td><strong>Before</strong></td>
<td><strong>After</strong></td>
</tr>
<tr>
<td>Extracellular space (cm$^3$/cm$^3$ ventricle)</td>
<td>0.204 ± 0.007</td>
</tr>
<tr>
<td>Change in extracellular space (%)</td>
<td>+4 ± 5</td>
</tr>
<tr>
<td>$P$</td>
<td>NS</td>
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</table>

The extracellular spaces of the nonischemic zones are expressed as cm$^3$ extracellular volume/cm$^3$ ventricle. All values are means ± SE. NS = not significant.
in an infarct are also occurring to a lesser degree in distant nonischemic zones of the same heart. The most direct interpretation of this pattern probably is that the electrochemical gradients for the ionic distributions decrease in the functional myocardium as they do in the ischemic zones, but not as strikingly. This interpretation is plausible when it is considered that in an infarcted heart the energetics of mechanically functional fibers must cope with an augmented work load per unit mass of muscle. However, calculations have shown that the same pattern of change can be just as plausibly explained by an expansion of the extracellular space. Therefore, our experiments were designed to distinguish between these two possibilities.

Our results, applying two independent methods for measuring extracellular space, indicate that the subtle electrolyte changes found within the distant nonischemic zone of infarcted hearts are almost completely explicable by a 15% increment in the extracellular compartment. With the exception of calcium, the nominal cellular concentrations of the electrolytes remained constant within this zone. This constancy is not surprising, for it has been previously observed under other markedly abnormal conditions such as hypothyroidism (17) and severe, nonischemic hypoxia (18).

The mechanism responsible for the expansion of the extracellular compartment in apparently normal ventricular tissue following myocardial infarction is obscure. Its onset must be relatively rapid, for it was observed 6 hours after coronary artery ligation in our dog experiments. Chemical analysis of ischemic canine hearts in another study (6) may be interpreted as suggesting that the onset occurs much earlier. Although several possible mechanisms of extracellular expansion can be suggested, we are inclined toward the possibility of a passive expansion secondary to the altered hemodynamics of the injured heart.

It has been frequently reported that occlusion of a major branch of the canine left coronary artery results in an increased blood flow through the remaining arteries (21-26). Venous outflow from the great cardiac vein is increased after ligation of the left anterior descending coronary artery, whereas oxygen saturation of venous blood from nonischemic muscle declines (26). This result is compatible with the concept that the work load of the functional myocardial cells in the injured heart is augmented under the control of reflexes directed toward maintaining cardiac output. Since the aortic blood pressure is not increased after occlusion of the coronary artery, the increased coronary blood flow must reflect a reduction in the resistance of the coronary arteries, presumably due to vasodilation. Such a response would enlarge the vascular compartment, but it seems unlikely that the increment could account for more than a fraction of the extracellular space expansion. However, if the blood flow is increased by precapillary vasodilation, then the subsequent rise in capillary hydrostatic pressure might well account for the increment in extracellular space on the basis of Starling's mechanism of transcapillary fluid flow. The rise in capillary hydrostatic pressure would also be reinforced by neurogenic vasoconstriction under the influence of augmented sympathetic tone. Hydrostatic pressure in myocardial tissue might be expected to rise under these conditions, an expectation at variance with the findings of Herzberg et al. (25) using the needle technique. However, since the methodology used for the measurement of tissue pressure is presently controversial even when the measurements are made in quiescent tissues under optimal conditions (27, 28) and since expansion mechanisms other than those considered by us are possible, it remains to be seen whether the discrepancy is real or only apparent.

It is perhaps noteworthy that, whereas the extracellular compartment expands in the functional zone of the infarcted heart, in the injured zone this compartment may be diminished by the expansion of the cellular compartment. Although the extracellular volume in the infarcted zone appears to rise, if the sucrose space is taken to be representative of the extracellular compartment in ischemic tissue, there are several reasons for considering that an expansion of this compartment is improbable. First, it is well known that ischemic cells become hypertonic during the degradative metabolism of ischemic conditions. Second, since even large molecules diffuse nonselectively across the plasma membrane of the ischemic cell, it would be highly unlikely that this membrane would remain impermeable to sucrose carried by patent collateral vessels. Eventually these collateral vessels might also become obstructed subsequent to severe cellular swelling (29). That collateral vessels do indeed perfuse the infarcted zone is suggested by the data, since without collateral perfusion the tissue electrolyte contents within this zone would remain unchanged after coronary ligation. Third, the calculated concentrations of cellular electrolytes all show the expected diffusion down their respective electrochemical gradients only if it is assumed that the extracellular space determined in the infarcted zone is grossly overestimated. For these reasons,
none of the data obtained with infarcted tissue, and otherwise indicative of tissue distributions of electrolytes and water, can be taken at face value.

The expansion of the extracellular compartment in the well-perfused zone of the infarcted heart quantitatively accounts for the small changes in the cellular contents of sodium, potassium, magnesium, and chloride that are suggested by the data from several laboratories and confirmed in the present paper. This constancy is encouraging, because, together with the alterations in tissue contents, it lends support to the evidence for extracellular space expansion in the nonischemic zone of the infarcted myocardium.

In contrast to the alterations of myocardial magnesium and monovalent ions, the alteration in calcium appears to reflect a change in intracellular as well as extracellular calcium. Unless an increase in the affinity for calcium occurred at extracellular sites, the calcium concentration of cells within the functional zone rose to 124 ± 11% (P < 0.05) of the control concentration. The meaning of the 24% increment is unclear, but it might be speculated that the increment is due to a net uptake of calcium by myocardial cells obliged to maintain cardiac output despite a diminution of functional myocardium. The increment could have been mediated by an elevation in heart rate and catecholamine levels during the experiment, when the rat was subject to thoracotomy, myocardial infarction, and nephrectomy. It is well known that calcium influx into myocardial cells is markedly augmented by increases in the rate of depolarization and by catecholamines. An augmented calcium concentration in the various cellular compartments in dynamic equilibrium with myoplasmic calcium would presumably heighten contractile tension. Such a mechanism has been previously postulated to explain an apparent elevation of cellular calcium in ventricular muscle from the hypertensive rat (30), in which myocardial fibers also must perform at higher levels of mechanical work to maintain cardiac output.

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