Experimental Studies

A Quantitative Estimation of Electric Current Due to Myocardial Injury

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SUMMARY
Myocardial injury causes electric current at the border of injured muscle and the surrounding intact region. In order to determine the magnitude of the injury current, experiments were performed with the isolated canine heart perfused with Tyrode’s solution. The anterior descending branch of the left coronary artery was perfused selectively with high potassium (K⁺) solution and the resulting injury current was reflected in the ST shift of the orthogonal electrocardiogram, derived from the surface of a cubic container in which the heart was placed. After measurement of the ST vector with different K⁺ concentrations, the heart has fixed with formalin and the injury zone was delineated with serial sections. The boundaries of the selectively perfused region were reconstructed. The algebraic sum of orthogonal components of boundary surfaces determined the average direction normal to the boundary, which was found to be parallel with the ST vector. With increasing K⁺ concentrations, the ST shift became more marked. However, it was saturated at about 30 mEq/L K⁺. The maximum injury current, calculated from the saturated value of the ST magnitude, amounted to 0.10 mA/cm² per unit area of the boundary surface. Additional experiments were performed with right ventricular papillary muscle preparations. Injuries were caused by a cotton pad containing high K⁺ solution placed in two directions to make the border along and across the long axis of the papillary muscle. The results indicate that the injury current in an anisotropic structure was essentially directed along the fiber orientation. (Jpn Heart J 35: 323-332, 1994)

Key words: Injury current Hyperpotassemia Anisotropy

The injury current has long been known to flow between intact and injured myocardium and to cause ST deviations in the ECG.¹,² It has been interpreted as an expression of the difference in the membrane potential of adjacent myocardial cells.³ Despite its relevance in the estimation of myocardial injury...

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and prediction of arrhythmogenesis after ischemic injury, few studies have analyzed the direct effects of myocardial injury on electric current sources in the heart.4,5)

In this communication, we present experiments in which the injury current was produced in the isolated canine heart by means of selective coronary perfusion with high potassium (K+) solution. Quantitative analysis was made from observations of the remote potentials, utilizing a similar method to our previous studies.6,7) In addition, the direction of the electric current was related to the anisotropic structure of myocardial tissue in experiments with right ventricular papillary muscle preparations.

**METHODS**

Eleven mongrel dogs were used. The heart was isolated and perfused from the aorta with modified Tyrode’s solution at 37°C. The regular solution contains NaCl 147 mM, KCl 3 mM, CaCl2 1.8 mM, MgSO4 0.49 mM, NaH2PO4 4 mM, and Na2HPO4 0.8 mM, bubbled with 100% O2.

The anterior descending branch of the left coronary artery (LAD) was cannulated for selective perfusion at about the midpoint between its origin and the apex of the heart. Solutions with different concentrations of KCl were used for the selective perfusion of the LAD.

The recording system was essentially identical to that described in our previous reports.6,7) The perfused heart was placed in a cubic box filled with Tyrode’s solution with an edge of 9.6 cm. Five silver electrodes were attached to each of the surfaces of the container and orthogonal X, Y, and Z leads were constructed through equal resistors. The position of the heart was adjusted so that X, Y, and Z leads were directed right to left, superior to inferior, and posterior to anterior, respectively. The signal was amplified by a R-C coupled high-gain amplifier with a time constant longer than 2 sec. Separate recordings of systolic and diastolic injury currents were not performed in this study.

In the control condition, the same solution was supplied through the aorta and the LAD cannula, and orthogonal X, Y, and Z leads were recorded. The heart was then removed from the box and selective perfusion with 10 mM K+ solution was started through the cannula in the LAD. This perfusion generated an injury current at the border of the locally perfused region and the remaining portion of the ventricle. During selective perfusion with the high K+ solution, the heart was suspended in air outside the box to avoid contamination of the regular solution in the box by the high K+ perfusate. After 1 min, the perfusion was stopped and the heart was immersed rapidly in the solution in the same position in the box as previously and the electrical activity was recorded. On completion
of the procedure, perfusion with the regular solution was reinstated. After recovery of the control state was confirmed on the ECG, similar procedures were repeated with higher K⁺ solutions containing 15, 20, and 30 mM KCl.

After the series of K⁺ infusion was completed, black ink was infused into the LAD cannula for staining the region of selective perfusion and the whole heart was fixed with formalin. Horizontal sections of the heart with steps of 1 cm were made and the border of the LAD perfused regions was traced to construct the boundary surface three-dimensionally. Separate and curved surfaces were combined and represented by a vector \( \mathbf{S} \), of which three orthogonal components (\( S_x \), \( S_y \), \( S_z \)) were obtained from the algebraic sum of the projectional areas of the surfaces on YZ, ZX, and XY planes, respectively (Figure 1).

The \( \mathbf{S} \) vector and its components were compared with the ST elevation recorded in X, Y, and Z leads (STx, STy, STz), and with the spatial ST vector.

Calibration of the system was made using of an artificial dipole. Bipolar needle electrodes with a known effective interpolar distance were inserted into various locations of the ventricle. The dipole was energized with a constant current of known amperage. The resulting voltage in the three orthogonal leads (\( M_x \), \( M_y \), \( M_z \)) was combined to calculate the magnitude of a spatial vector \( \mathbf{M} \).

\[
\mathbf{M} = \sqrt{M_x^2 + M_y^2 + M_z^2}
\]

The average value of \( \mathbf{M} \) for various locations of the dipole was calculated as the effectiveness of intramural current on the orthogonal leads.

Additional experiments were performed to relate the direction of fibers to the injury current. Right ventricular papillary muscle preparations were made.
Figure 2. Schema of papillary muscle experiment. A high K+ concentration cotton pad was attached to papillary muscle to measure the injury current.

According to the method described previously.7 Right ventricular papillary muscle perfused from the coronary artery was ligated at the attachment to the tricuspid valve and suspended loosely in air. A small cotton pad containing high K+ solution was applied to the papillary muscle in two directions so that the border of the cotton pad was directed along and across the long axis of papillary muscle (Figure 2). The lead between the cotton electrode and the electrode placed at the opposite side of the preparation was utilized for recording, and the injury potentials due to longitudinal and transverse borders were observed. Only qualitative comparisons were made because only the superficial layers contributed to the injury potential in this experimental design.

**Results**

Figure 3 shows an example of tracings obtained in the experiments with perfusion of different K+ concentration solutions. With increasing concentrations of KCl up to 30 mEq/L, the ST displacement became more marked in the orthogonal leads, associated with a larger ST vector. A further increase of K+ to 50 mEq/L generally did not result in additional ST elevation. In some of the experiments, the saturation occurred at 20 mEq/L.

The Table shows the relationship between the ST vector and the boundary surface. The vector S is normal to the sum of the boundary surfaces and is considered to represent the net effect of regions with injury current. The direction of the S vector was expressed by azimuth Sz/Sx and elevation Sx+Sz/Sy and was found to be nearly parallel with the direction of the ST vector. The magnitude of the ST vector was also approximately proportional to the magnitude of S. These results confirm the classical theory on the genesis of ST displacement based on the injury current across the boundary surface.
Figure 3. A representative case of ST deviation caused by the injury current. ST deviation increased during the high K⁺ perfusion.

**Table.** ST Deviation per Boundary Unit

<table>
<thead>
<tr>
<th>K concentration (mEq/L)</th>
<th>ST deviation per unit (mV/cm²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>0.020 ± 0.004</td>
</tr>
<tr>
<td>15</td>
<td>0.043 ± 0.008</td>
</tr>
<tr>
<td>20</td>
<td>0.067 ± 0.010</td>
</tr>
<tr>
<td>30</td>
<td>0.090 ± 0.017</td>
</tr>
<tr>
<td>50</td>
<td>0.090 ± 0.015</td>
</tr>
</tbody>
</table>

Based on the observations above, the magnitude of the injury current on the boundary surface was calculated per unit area of the surface S. From the results with 30 to 50 mEq/L KCl, the average ST voltage from the recording was 0.098 ± 0.016 mV/cm². The relationship of this result to current in the tissue was calibrated with artificial dipoles. A unit dipole of 1 mA·cm inserted into ventricular muscle was found to produce 1.12 ± 0.14 mV in this system. Hence, the absolute magnitude of injury current is calculated as 0.088 mA·cm per unit area of the boundary surface. The ST vector due to 10 and 20 mEq/L KCl was 21% and 69% of the maximum value above.

At the border zone, myocardial fibers are oriented in different directions. A possible relation of the fiber orientation to the current of injury was investigated in the experiments with papillary muscle. Figure 4 shows tracings with bipolar leads along and across the border of the attached cotton pad with high K⁺ solution. With the border along the fiber direction, the ST elevation due to the high K⁺ pad was far less compared to that with across the fiber. The QRS complex was also deformed by application of the cotton pad, which seems to reflect partial inactivation of the muscle and alterations in the activation process. The latter possibly accompanies the secondary T wave changes. A gross change in activation did not seem to occur because the QRS complex was not prolonged. Hence, the secondary changes were not taken into account in the measurement of ST elevation.
The length of the border of the cotton pad was 10 to 18 mm in the case of a longitudinal boundary, and was 10 to 20 mm for a transverse boundary. The surface area was, however, not obtained accurately, so only a qualitative estimation was made.

**DISCUSSION**

The current of injury is known to flow as the result of the potential gradient induced by traumatic, ischemic, and other causes of myocardial injury. Perfusion with a high K⁺ solution directly affects the membrane potential at the border between regions with normal and abnormal environments and constitutes an experimental model for quantitative measurements. A further advantage of this method is that the procedure is reversible and repeated observations are possible.

The results of this study indicated that, with a given K⁺ concentration, the ST displacement was approximately proportional to the area of the boundary surface and that the direction of the ST vector was nearly perpendicular to the boundary. This is in accord with the classical solid angle theory. However, the classical theory ignores both the strength of the double layer and the constant which should be multiplied to the solid angle. One of the main purposes of this study was to obtain the constant as a determinant of the absolute voltage at a given location.

The magnitude of the ST shift depends on the K⁺ concentration of the local...
perfusate. But with concentrations higher than 30 mEq/L (and sometimes 20 mEq/L), the ST elevation was saturated without any further increments. Since ordinary R-C coupled amplifiers were used, the ST shift represented a sum of those due to systolic and diastolic currents of injury. The membrane potential will be higher in systole and lower in diastole on the normal side. When fibers in the high K⁺ region are completely inexcitable, the maximum ST elevation due to the sum of systolic and diastolic potential difference will have a fixed value corresponding to the height of the normal action potential.

Utilizing the maximum value of the ST elevation with 30 to 50 mEq/L potassium, the strength of the double layer was calculated as 0.088 mA·cm per unit area. This figure is remarkably similar to the value obtained in our previous experiment on the activation wave front. Although the activation wave moves rapidly and is concentrated in a small region compared with injury current, both values are based on the local difference of the membrane potential, which was approximately 100 mV, as a source of electric current. The similarity of their electromotive force provides further support for the previous model of the relationship between the strength of the generator and the intracellular axial current. The structure of local current is variable, according to the sharpness of the boundary and the direction of individual fibers. The numerical value expresses the averaged uniform strength of the double layer as a generator for the remote potential. When the K⁺ concentration of the local perfusate was 10 and 20 mEq/L, the current density was 21% and 69% of the maximum value, respectively.

Janse and his associates have made a quantitative estimate of the current source and sink in the ischemic heart and gave a peak value of several mA/mm³ of myocardial tissue. A comparison with the expression in this study seems to be of value in the understanding of the nature of local currents.

Figure 5 shows a simplified estimate of the injury current. Consider a fiber orientated perpendicular to the boundary with a measured length “d”. The current source is located on the intact side of the boundary and the sink on the injured side. Assuming the source and sink densities are roughly uniform, the axial current has a peak value somewhere within the boundary. Since the integral of the axial current is the voltage difference across the boundary, the peak axial current will be approximately proportional to 1/d. Assume an intracellular potential difference of 100 mV across the boundary. If the length d = 2 mm in a tissue with parallel fibers, the source to sink distance is roughly estimated as 1 mm. A current dipole moment of 0.1 mA·cm/cm² is equivalent to a source-sink current of 1 mA in a disk of 1 cm² × 1 mm of the boundary tissue, corresponding to 10 μA/mm³ source-sink density. When the boundary is less sharp with a width of 4 mm, the source current density per volume will be one fourth this value, however, the double layer moment is invariant.
Figure 5. A schema for estimation of the injury current. See text for further discussion.

Local voltage measurements were not performed in this study because they are susceptible to experimental conditions such as the size of electrodes and local variations of tissue injury and resistivity from site to site. The penetration of myocardium by electrodes might cause further injury and superficial electrodes are influenced by exposure of the system to air. The remote potential is insensitive to the local inhomogeneous structures and variations of the recording system, and therefore is reliable for the estimation of the overall effect of the boundary. Thus, it is most appropriate for understanding the electogenesis of the tissue injury current.

Tissue anisotropy is an important factor in myocardial electogenesis during activation.\textsuperscript{12,13} It has been suggested that anisotropy also has an influence on the repolarization wave.\textsuperscript{14} The model of axial current as the source of the external field predicts a similar influence on the injury current. The results of our experiments with papillary muscle preparations show that the injury current appears to be essentially along the fiber. Although the results could not be evaluated quantitatively, the difference between the current flow in longitudinal and transverse boundaries was marked. Fibers in ordinary ventricular muscle are not uniformly directed and complicated patterns of local currents appear to attenuate the effec-
tive double layer strength. The value of double layer moments obtained in this study corresponds to the averaged effective moments of ventricular tissue.

Clinically, myocardial ischemia is the most frequent cause of injury current. In the ischemic heart, the extracellular $K^+$ concentration has been reported to reach 20 mEq/L or more. However, the boundary is not always sharp; it is often indiscrète and widespread over the ventricular tissue. The ST displacement depends on the interstitial $K^+$ concentration, as well as on the geometry of the boundary within the ventricles. Perfusion with a high $K^+$ solution does not necessarily reproduce an ischemic disease process. As long as electrical events are concerned, though, it directly affects membrane potentials to simulate pure electrical events. Sharpness of the boundary may vary from case to case. But on the remote potential, the effect of the boundary is an integral of contributions across the boundary, which is determined only by the condition of both sides.

Arrhythmogenesis of injury current has also been discussed in the literature. Although the sum of maximum systolic and diastolic injury currents is comparable to the current due to the activation wave, the direction of the injury current is opposite in systole and diastole. On the intact side of the boundary, effective depolarizing current is expected in diastole, but its strength depends on the grade of diastolic membrane potential of injured fibers. On the other hand, the current is repolarizing in systole, which may enhance early recovery of fibers in the border zone. Sharpness of the boundary is also essential for determining the local current density.

REFERENCES


15. Katzung BG, Hondeghem LM, Grant AO: Cardiac ventricular automaticity induced by current of injury. Pfugers Arch 360: 193, 1975