Equivalent Generator Properties of Acute Ischemic Lesions in the Isolated Rabbit Heart

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SUMMARY Equivalent generator properties of the electrical field produced by ischemic myocardium were studied in 25 isolated rabbit heart preparations. Electrocardiograms from 32 electrodes deployed about a spherical tank containing the isolated, perfused heart were recorded before and after suture ligation of the left anterior descending artery. The ligation was high (10 preparations) or low (10 preparations) along the interventricular septum. In a final five hearts, ligatures were placed sequentially in both positions. Signals were processed to quantify the percentage of summed square (SSQ) potential attributable to a centric dipole (CD), to a four-element centric multipole series (CMS) and to a single moving dipole (SMD) during the S-T segment. Fifteen minutes after low ligation, 74 ± 12%, 98 ± 1%, and 96 ± 3% (mean ± 1 SD) of SSQ potential recorded 10 m sec into the S-T segment could be accounted for by the CD, CMS, and SMD models, respectively. The computed SMD was determined to be fixed in location and orientation throughout the S-T segment but to increase in magnitude from early to late S-T. Dipole moment directly correlated with the area of the epicardial lesion (r = 0.82). Results were quantitatively similar after high ligation and after each of the sequential occlusions. Tank surface isopotential maps during the S-T segment uniformly demonstrated a single maximum that was spatially aligned with the ischemic lesion, and with an intensity proportional to both computed dipole moment and epicardial lesion size (r = 0.97). Thus, CMS and SMD cardiac models provide quantitatively accurate descriptions of the experimentally induced electrical fields.

ELECTROCARDIOGRAPHIC patterns due to myocardial ischemia, injury, and infarction have been of interest to investigators since the early studies of Eppinger and Rothberger,1 Pardee,2 and Wilson and associates.3 Specific interest in S-T segment abnormalities evolved because these "injury currents" generally reflect acute rather than chronic aberrations of myocardial electrophysiology. As such, they have been studied as a means of quantitating the area and severity of myocardial damage4-6 and of following the natural7 and unnatural8 course of acute myocardial infarction.

Prior studies have described the transmembrane potential changes responsible for S-T elevation,9 the biochemical10,11 and coronary blood flow12 correlates of these abnormalities, and the possible clinical significance of variations in magnitude of the injury currents recorded at myocardial and body surface positions.13-14 Most recently, a biophysical approach using the solid angle theorem has been developed to explore the distant effects of changes in lesion boundaries.15-17 In the studies to be presented, the characteristics of electrical fields generated during the S-T segment by coronary occlusion were studied using a system permitting quantitation of the components of equivalent cardiac generator models.15-17 Results demonstrate that injury currents can be adequately represented by a single moving dipole model of the heart's electrical activity.

Methods

Experimental Preparation

Twenty-five New Zealand white rabbits were studied, using a previously reported isolated heart perfusion system.15-17 After systemic heparinization, the rabbit was stunned by a heavy occipital blow, a left thoracotomy was performed, and the heart was rapidly excised. Perfusion through the cut end of the aortic root was immediately instituted with Krebs-Henseleit electrolyte solution warmed to 37°C and oxygenated with 95% O2-5% CO2. The heart was enclosed within a precision-machined, cast epoxy sphere, 6.25 cm in diameter, filled with additional electrolyte solution. The perfusion medium contained oxygen and carbon dioxide at partial pressures of 525 mm Hg and 39 mm Hg, respectively. Perfusion pressure was 70 cm H2O. The mitral valve was disabled through the left atrium to provide an exit route for fluid in the left ventricular chamber.

Electrocardiographic signals were recorded from 32 silver-silver chloride electrodes exactly deployed on the inner surface of the test chamber at points corresponding to the 20 vertices and the 12 centroids of the facets of an underlying regular icosahedral reference figure. Electrodes were paired to form 32 bipolar leads, signals from which were amplified by a bank of low noise (4-μV, peak-to-peak) differential amplifiers. Analog signals were converted to digital form at a sampling rate of 2500 samples/channel per second.

Experimental Protocol

Eighteen seconds of data were recorded initially. Subsequently, the lower hemisphere of the test chamber was removed and replaced with an accessory section containing a plane glass surface. Photographs of the suspended...
heart, taken through this "picture window" were used to locate points on the epicardial surface. The perfusion cannula and the attached heart were rotated 72° between serial, QRS-triggered photographs such that a series of five pictures provided a complete pictorial representation of the specimen (Fig. 1).

Hearts were next divided into three experimental subgroups. In 10 hearts, a single 5-0 nylon ligature was placed about the left anterior descending artery halfway between the heart's base and the apex (Fig. 1, panel A). In the other 10, the ligature was placed high along the interventricular groove (Fig. 1, panel B). In a final five, an initial low ligation was followed in 15 minutes by a high ligation (Fig. 1, panel C). The chamber was reassembled and refilled with electrolyte.

Electrocardiographic signals were recorded 5, 10, and 15 minutes after the single ligation in the first two subsets and at 5, 10, and 15 minutes after each ligation in the final subgroup. After the final recording session, a second set of five photographs was taken, and the location of the ligature(s) determined by triangulation.

The hearts were then perfused with a 0.5% solution of methylene blue. After 2-4 minutes of perfusion with this dye, the heart was removed from the perfusion cannula. The zone of epicardial surface not perfused with methylene blue, approximating the zone of myocardium supplied by the occluded vessel, was traced and its area measured. The heart was then serially sectioned parallel to the base to determine the cross-sectional distribution of the perfusion defect.

Data Analysis

Only data from preparations with stable electrocardiographic patterns, with isoelectric S-T segments prior to coronary ligation, and with definite evidence of a perfusion defect after methylene blue staining are included in this report.

A series of, typically, 16 beats from each lead that were similar in morphology as determined by an automated autocorrelation routine were averaged to reduce random noise and converted to unipolar form. Onsets and offsets of the QRS complex and ST-T intervals were then determined manually.

Parameters of a four-element centric multipole series and the single moving dipole's equivalent cardiac generator models were determined at 2-msec intervals during the S-T segment and T wave. The former model consists of 24 terms defining the characteristics of a centric, fixed location dipole, quadrupole, octapole, and hexadecapole. The six parameters of the latter model correspond to the three moment and three location terms of the single moving dipole best reproducing the observed surface potentials.

Results were expressed as the summed-square (SSQ) potential generated on the surface of the sphere by a specific generator. SSQ levels were chosen to provide a correlate to signal energy content. Percent fit of the electrical field by a given generator was computed from the ratio of SSQ potential due to that generator model to the total SSQ potential recorded at that instant. Residual potential was defined as the SSQ surface potential not attributable to the equivalent generator, and the percentage residual was computed as 100 - % fit.

Data points occurring during the S-T segment and T wave from hearts within each experimental subgroup were normalized to a common time interval. The initial two-thirds of this period was considered to represent S-T segment and the terminal one-third to correspond to T wave. Means and confidence limits (±35%) were computed after logarithmic transformation of individual SSQ values to avoid physically untenable negative potential values as lower confidence limits. All statistical values are given as mean ± 1 standard deviation, unless specifically stated otherwise.

Isopotential maps of the electrical potential on the surface of the test chamber were constructed using the computed centric multipole series as an interpolation routine.

Because the amplification system was capacitor-coupled, it was not possible to differentiate between primary S-T elevation and secondary S-T elevation due to T-Q segment depression. It was therefore determined that, in accord with clinical practice, S-T elevation would be considered as a primary phenomenon, resulting in an epicardial injury vector directed outward from the epicardial surface during the S-T segment.

Results

Prior to coronary ligation, all preparations demonstrated isoelectric S-T segments. Equivalent generator
fitting to these control data yielded results similar to that previously reported from this laboratory.16 A single moving dipole accounted for 89 ± 10%, 91 ± 9%, and 93 ± 7% of recorded surface potential 10, 20, and 40 msec, respectively, into the S-T segment in the 25 studies. In contrast, a centric dipole fit 74 ± 12%, 72 ± 13%, and 71 ± 9% of the electrical potential at these points, whereas the four-element centric multipole series accounted for over 99% of observed activity at all time points during the S-T segment.

After ligation, S-T elevation evolved in unipolar records from electrodes overlying the lesion, with reciprocal S-T depression being recorded from leads facing the opposed cardiac surface. Additionally, R waves increased in magnitude, or developed in records from leads previously exhibiting predominant negative deflections, after coronary occlusion. Typical changes in unipolar electrocardiograms recorded in two leads from a preparation before and after a high ligation are presented in Figure 2. In each heart studied, heightening of the R wave was maximal in leads recording the greatest S-T segment elevation.

Heart rate after ligation remained within ±10% of control values. All preparations remained in normal sinus rhythm, without ventricular ectopy, significant QRS prolongation, or atrioventricular block.

Low Ligations

An example of the results of fitting a four-element centric multipole series and a single moving dipole cardiac model to potentials sensed 15 minutes after low left anterior descending artery ligation (Fig. 1A) is presented in Figure 3. The root mean square (RMS) potential plot in panel A demonstrates significant S-T segment elevation. Amplitudes of the four elements of the centric multipole series and the residual potential (panel B) demonstrate that most of the observed S-T elevation occurred in the dipole term, with lesser contributions by quadripole, octapole, and hexadecapole elements. During depolarization, non-dipole terms were of greater importance, as previously described.16 Similarly, results of applying the single moving dipole model (panel C) indicate that most of the observed injury current may be attributed to the dipole, with only minimal elevation of the S-T segment occurring in the residual plot.

Results of fitting recorded potentials from all 10 preparations to a four-element centric multipole series are displayed in Figure 4. In panel A (left), time-dependent plots of the percentage of SSQ potential attributable to a centric dipole throughout the ST-T waves for each of the 10 preparations are superimposed. Apparent is the range of adequacies of fit during the S-T segment (53-92%) and the consistent tendency to lower dipolarity near the T wave. Group mean and plus-minus 35% ranges of these data are shown on the right of panel A. The entire series, however, fit over 98% of SST potential during the S-T segment, as demonstrated on superimposed plots of percentage of residual potential and in group mean data (panel B). Again, residual was greatest near the end of repolarization.

Data documenting the adequacy of a single moving dipole model are presented in Figure 5. Plots of percentage of SSQ potential attributable to the moving dipole demonstrate that, during the S-T segment, dipolarity exceeded 87% in all cases (panel A) and that mean values exceeded 95% at all points during the S-T segment (panel B). Dipolarity decreased and residual increased (panel C) during the T wave.

Similarly, unnormalized data document high dipolarity. At points 10, 20, 40, and 60 msec into the S-T segment,
A single moving dipole accounted for 96 ± 3%, 96 ± 3%, 97 ± 4%, and 97 ± 4% of observed potential 15 minutes after ligation.

The location of the ligature about the coronary artery was determined by triangulation from photographs of the preparation and compared with that of the computed dipole. Results demonstrated the dipole to be 0.4 ± 0.2 cm from the knot, 20 msec into the S-T segment. In all preparations it was located within the zone predicted to be nonperfused as estimated by methylene blue infusion. The unstained area measured 0.81 ± 0.34 cm².

Location, moment, and orientation of the computed moving dipole as a function of time throughout repolarization were also determined. Changes in the coordinates of the dipole and in its moments throughout repolarization from those at the S-T segment onset are plotted in panels A and B of Figure 6. The exact location and orientation of the dipole at the J-point varied widely from preparation to preparation. Hence, referencing all results to these values provided a method to portray the stability, or lack thereof, of the values later in S-T. In panel C, the three-dimensional angle between the dipole computed at 2-msec intervals during repolarization and at the S-T onset is plotted. Results demonstrate that the dipole remained relatively stationary in location (panel A) and orientation (panel C) throughout the early and middle phases of repolarization. Its moment, however, increased from early to mid-S-T (panel B) and then decreased at the end of repolarization.

Comparing data derived from potentials recorded 5, 10, and 15 minutes after ligation revealed no significant change in dipolarity, location, or orientation (P > 0.1, all comparisons). Dipole moment increased from 2748 ± 341 μA-cm/ohm-cm at 5 minutes to 3146 ± 608 μA-cm/ohm-cm at 10 minutes and 3122 ± 663 μA-cm/ohm-cm at 15 minutes (P > 0.1) with a mean translocation of 0.02 cm from 5-minute to 15-minute data (all data, 20 msec into S-T segment).
High Ligations

Injury currents recorded after ligating the left anterior descending artery high along its course (Figs. 1B and 2) were studied as described above.

A centric dipole fit 61-91% of recorded SSQ potential during the S-T segment (Fig. 7A), while the four-element centric multipole series replicated a minimum of 99% (Fig. 7B) 15 minutes after ligation.

The optimally computed single mobile dipole fit 94-99% of recorded electrical activity during the S-T segment (Fig. 7C), 15 minutes after ligation. Percentages of dipolarity in non-normalized data were 97 ± 3%, 97 ± 2%, 98 ± 2%, and 98 ± 2%, at points 10, 20, 40, and 60 msec into the S-T segment, respectively.

As with low ligations, the S-T segment generator remained fixed in location and orientation throughout the S-T segment, but increased in magnitude from early to middle periods of repolarization. At 20 msec into the S-T segment, the dipole was located 0.6 ± 0.3 cm from the
ligature in an apical direction. Unstained areas measured 2.77 ± 0.84 cm².

Dipolarity did not change significantly (P > 0.1) from 5 to 15 minutes after occlusion, although dipole strength increased from 3813 ± 698 μA-cm/ohm-cm 5 minutes, to 4490 ± 1051 μA-cm/ohm-cm 10 minutes, to 6005 ± 1582 μA-cm/ohm-cm 15 minutes after ligation. Dipole location and orientation did not change significantly.

Dual Ligations

The five preparations in which sequential ligations were performed were studied to evaluate the effects of an increase in ischemic area on equivalent generator parameters. Electrical fields 15 minutes after the first ligature was placed were 97 ± 2% dipolar (single moving dipole), 20 msec into the S-T segment, with a dipole moment of 2563 ± 622 μA-cm/ohm-cm. Fifteen minutes after the second, proximal ligation, dipole moment increased to 5231 ± 3036 μA-cm/ohm-cm 20 msec into the S-T segment, with 97 ± 2% dipolarity. The computed dipole migrated basally between these recordings, being located 0.5 ± 0.3 cm from the site of the distal ligature after placement of the distal suture and 0.7 ± 0.3 cm from the proximal suture after the second occlusion was introduced. The changes in dipolarity were statistically insignificant (P > 0.1).

Dipolarity was not statistically correlated with dipole moment (P > 0.1) as computed in all 25 preparations.

Chamber Isopotential Mapping

Isopotential maps were constructed for selected points during repolarization for all three experimental groups. During the S-T segments, a single maximum was observed in all preparations, in a position spatially aligned with the epicardial location of the nonperfused areas (Fig. 8). A single minimum was located on the opposed face of the tank, with an intensity uniformly less than that of the maximum, i.e., a pattern typical of an eccentric dipole.

The intensity of the maximum increased in maps corresponding to sequentially later points during the S-T seg-

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**Figure 7** Percent of SSQ potential, recorded 15 minutes after high left anterior descending artery ligation, attributable to a centric dipole (panel A) and a single moving dipole (panel C). Potentials not attributable to a four-element centric multipole series and single moving dipole models are portrayed in panels B and D, respectively. In each panel, means and ±35 confidence limits are plotted as a function of time during a standardized ST-T interval.
FIGURE 8  Isopotential distribution on the surface of the experimental chamber, superimposed upon tracings of the cardiac silhouette. Positive potential lines are solid, negative lines are marked, and the line of zero potential is dashed. The five maps in each panel correspond to the five photographic views of the heart. In map 1, the anterior interventricular groove bisect the view; subsequent views correspond to serial 72° rotations of the heart to the observer's right from view 1. Location of the ligature is identified by the dark bullet on the heart tracing. Panel A: Isopotential distribution 20 msec into the S-T segment, 15 minutes after low coronary ligation. The single maximum is best seen in view 1. Contour lines are at 25-µV intervals. Panel B: Isopotential distribution 20 msec into the segment, 15 minutes after high coronary occlusion. A single maximum (view 1) and a single minimum (views 4 and 5) are observed. Contour lines are at 50-µV intervals.

FIGURE 9  Isopotential distribution in one preparation with dual arterial occlusions. Markings are as in Figure 8. Contour lines are drawn at 25-µV intervals. Panel A: Patterns 20 msec into the S-T segment, 15 minutes after the initial low ligation. Panel B: Distribution 20 msec into the S-T segment, 15 minutes after the second proximal ligation. Both ligation sites are depicted in the silhouette in view 1. The single maximum, best seen in view 1 of each panel, increased in strength and migrated from a position aligned with the low lesion to one related to the high ligation.
tion and to the presumed movement in center of mass of the ischemic lesion.

Intensities of both the maxima and the minima recorded 20 msec into the S-T segment were directly correlated with the computed dipole moment (r = 0.97, P < 0.01).

**Pathological Data**

Examination of cross-sections of the methylene blue-perfused hearts demonstrated transmural zones of nonperfusion. In all cases, regions of both the interventricular septum and free wall were affected.

In the preparations with single ligations, the area of the epicardial lesion was related to computed dipole moment 40 msec into the S-T segment, 15 minutes after ligation. A calculated correlation coefficient of 0.82 was statistically significant (P < 0.01) (Fig. 10).

**Discussion**

The described experimental system provided a controlled environment in which to explore the electrogenesis of injury currents produced by myocardial ischemia. Precise geometries of the test chamber and electrodes, the small size of the sphere in relation to that of the heart, and the elimination of irregular boundaries and phase inhomogeneities permitted quantitation of generator characteristics. Although such determinations have been reported from intact animals, computational complexities limit widespread application. Finally, the transparency of the chamber and perfusate permitted photographic documentation of epicardial lesion location, permitting confirmation of computed dipole location.

Certain limitations are apparent, however. The hearts under consideration were both artificially perfused with an electrolyte solution rather than blood and were surrounded on both endocardial and epicardial surface by the oxygenated medium. Furthermore, the contracting heart performed little mechanical work, an important factor determining oxygen consumption and hence severity of ischemia in other preparations and in man. Thus, extrapolation of these data to clinical situations must be done only with great caution at present.

One finding of the present investigation was the failure of a centric dipole to account for much of the recorded surface activity. Because the lesion was eccentric, attempting to replicate the electrical field of even a pure dipolar source by a centric generator would require the operation of higher order multipole terms in accordance with the dipole "shift equations". In contrast, the single moving dipole admirably reproduced the experimentally generated field (Figs. 5 and 7) during the S-T segment. During the T wave, however, dipolarity decreased below that observed earlier in the S-T segment, a phenomenon observed in normal hearts and presumably related to the increasing asynchrony of myocardial potential patterns as recovery is completed. Similarly, early after the QRS, i.e., near the J-point, nondipolarity was also high; this may be attributed to overlapping of terminal depolarization and early repolarization creating multiple, nonuniform, simultaneously active electromotive surfaces.

The operative dipole was further determined to be located in the region of the ligature placed about the coronary artery, and to remain stationary during the dipolar phases of recovery. A more exact determination of dipole location relative to the center of the lesion, as reported for epicardial burns, was not possible because the borders of the ischemic zone were not visible in the beating, unstained preparation. Dipole orientation likewise remained fixed (Fig. 7), but its moment increased as recovery proceeded. Thus, the upsloping S-T segment characteristic of injury may be reasonably attributed to a fixed location, fixed orientation dipole whose strength increases progressively during the S-T segment.

Although it may be expected that an injured area would generate a dipolar field, because of unidirectional intracellular current flow toward the injured area during systole or in the opposite direction in diastole, the complex geometries of such lesions suggest cause for nondipolarity. Basic principles of electromotive surface modeling demonstrate that a single, relatively small, electrically active layer with a circular, planar rim may be accurately replaced by a single dipole oriented normal to the rim and located at its center. The presence of nonplanar bounds or of multiple separate rims generates nondipolar terms or multiple dipoles. In the latter case, a nondipolar field would result, except under specific conditions of strength, orientation, and eccentricity. One may reasonably apply these principles to fields expected of myocardial ischemic lesions.
lesions. The occurrence of transmural free-wall lesions may result in two electromotive surfaces, one on the endocardial surface and the second on the epicardial border. Further complexities of geometry, such as septal involvement, as shown here, would further detract from the expected adequacy of a single double layer, single dipole model.14

In this context, then, the experimentally demonstrated dipolarity is somewhat unexpected. First, however, it must be recognized that the fractional dipolarity of ischemic lesions reported is significantly less statistically than that of epicardial burns (96 ± 3% vs. 99 ± 2%, P < 0.01, unpaired t-test) of similar size previously described.22 This may reflect the presence of an endocardial layer and/or septal injury in addition to free wall, epicardial damage. The high dipolarity may also be partially explained by larger epicardial than endocardial surface areas13 and by more severe ischemia in subepicardial than in subendocardial zones after supercritical coronary stenosis.11

Regardless of the true explanation, certain implications are suggested. First, currently available equivalent cardiac generator models are adequate to describe the potential fields emanating from ischemic myocardium. One aspect of interest is that both normal and ischemic S-T segment potentials may be fit by a single mobile dipole.16 The reasons for these fits differ, however. In the case of normal recovery, it is the diffuseness and symmetry of the event that is putatively responsible, whereas with injury currents it is the localization of activity that is implicated.

The exquisite performance of the centric multipole series may also have specific relevance with the development of leads sensitive to multipolar information.27 These would provide a concise, nonredundant, and complete description of the cardiac field. Indeed, appropriate rotation and translocation of this set of singularities provide the theoretical basis for quantitation of the geometry, including planarity and size, of the rim of the double layer.24 Low amplitude octapole terms, yielding unfavorable signal-to-noise ratios, may limit application of this intuitively important corollary, as it is these that are primarily determined by boundary dimensions.

Second, the dipolarity directly influences the type of electrocardiographic lead system needed to totally sample the electrical field. As noted by Taccardi,28 a dipolar field may be characterized by three appropriately designed leads, whereas a nondipolar one would require total body potential recordings to completely define the electrical activity. Thus, current data suggest that lead systems based on a single dipole, e.g., vectorcardiographic schemes,4 may be adequate to quantitate the properties of the field.

Furthermore, a dipolar electrical field is characterized by a single maximum and a single minimum.15 Thus, an electrode array covering only the single zone or maximal positive or negative potential would sense the essence of that field. If, in contrast, a second pair of extrema existed distant from the first, or if the area of high voltage gradients was not blanketed by the electrode grid, significant and possibly critically important information might be disregarded.

Application of these thoughts to the problem of clinically applied lead systems with electrodes limited to the left anterior precordium7, 8, 29, 30 remains speculative. Such a design may be adequate in that only one maximum and one minimum would be expected on the body surface if the current data may be extrapolated to man. Furthermore, the standard left anterior precordial location of the grid also corresponds to the area of outward bulging on the electrocardiographic image torso, corresponding to zones of high potential gradient that require high electrode densities for adequate sampling.21

The possibility that nondipolar patterns may exist in man or that the presumed dipole may project high potentials to regions beyond the borders of a limited grid cannot be ignored. If present, the lost information may be of importance. Whereas some investigators8, 29 have described single maxima in man after myocardial infarctions, others30 have reported multiple extrema in a significant proportion of subjects. Confirmation of either pattern awaits full thoracic body surface mapping of injury potentials in patients with acute myocardial infarction.

Finally, correlations of computed dipole parameters and surface patterns with epicardial lesion patterns provide experimental support for pursuing clinical body surface mapping as a noninvasive method for quantifying "infarct size." Over 94% of the variance of surface extrema strengths about their means were attributable to differences in generator intensities which, in turn, were dependent upon the areas of nonperfused tissue. The positions of these extrema were spatially aligned with the epicardial geometries and remained fixed in location, or shifted in dual ligation protocols, in a manner consistent with movement of the operative generator. These latter features would not be detectable with current summation4 methods that convey intensity but not distribution of potential. Such direct quantitative and qualitative correlations may not, however, be observed in studies on intact animals in which differences in lesion location in the volume conductor and in electrical and physiological inhomogeneities of bodily tissues are less controlled than in these studies on the isolated heart.

References
9. Samson WE, Scher AM: Mechanism of ST segment alteration during


Equivalent generator properties of acute ischemic lesions in the isolated rabbit heart.
D M Mirvis, F W Keller, R E Ideker, D G Zettergren and R F Dowdie

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