A Mechanism for the Electrocardiogram Response to Left Ventricular Hypertrophy and Acute Ischemia

By Pierre S. Thiry, Reinhardt M. Rosenberg, and Joseph A. Abbott

ABSTRACT

A proposed mechanism for explaining the electrocardiographic response in left ventricular hypertrophy and in subendocardial and epicardial acute ischemia was incorporated in a mathematical model of electrical heart activity. The model of hypertrophy was simply an increase in cell size, and the principal effect on the computer-generated 12-lead electrocardiograms (ECGs) was an increase in R-wave amplitude and ventricular activation time and a flattening or polarity reversal of the T wave. The model of acute ischemia was a reduction between plateau and resting potential of the transmembrane action potential. The principal effect on the computer-generated 12-lead ECGs was an S-T segment displacement up or down depending on the location of the lesion. This shift was linearly proportional to the severity of the ischemia, i.e., the reduction in electrical activity of the ischemic cell, and for a lesion of given severity the S-T segment shift was a measure of the area, not the volume, of ischemic tissue. Therefore, this model suggests that a direct correlation does not necessarily exist between volume-measuring tests such as serum enzyme values in the case of necrosis and S-T segment shifts.

KEY WORDS
S-T segment shift  computer model  electrical heart activity
T-wave polarity  ventricular activation time

In a recent paper, a mathematical model of electrical heart activity has been described and used to compute surface potentials that resemble in detail the 12-lead electrocardiograms (ECGs) of a normal heart of intermediate (45°) orientation (1). In the present paper, we have shown that, when the changes associated with left ventricular hypertrophy are introduced into this model, the surface potentials generated by it resemble the ECGs frequently seen in left ventricular hypertrophy and that, when the electrophysiological changes associated with acute ischemia are incorporated in the model, the type of S-T segment distortion associated with acute ischemia occurs in the computer-generated ECGs. Therefore, our model suggests a mechanism for the ECG patterns seen in these cases. Moreover, a mathematical model always allows quantitative relations to be established between cause and effect. Thus, the amount of R-wave amplitude increase typical of left ventricular hypertrophy can be connected quantitatively with the degree of hypertrophy modeled, and the amount of S-T segment shift can be correlated with the extent of ischemic damage introduced in the model.

As is frequently the case in the mathematical modeling of complex, real systems, simplifying assumptions must be made. These assumptions are usually introduced to benefit the tractability of the problem, but they can also give insight into the process being modeled. For instance, if a considerable simplification of a complicated circumstance still permits the desired process to be successfully duplicated by the model, the inference exists that the element so simplified may not have a primary function in the process being modeled.

Our model is of the distributed dipole type in which the dipole strength is deduced from the electrophysiological behavior of myocardial cells; the computation of the skin surface potentials utilizes classical quasi-static theory of time-varying dipoles embedded in a volume conductor.

Distributed dipole models in a volume conductor are well known. Among the most successful are those of Selvester and his group (2-5), which have become successively more sophisticated with regard to modeling of the heart and the body; they have also been

From the Department of Mechanical Engineering, University of California, Berkeley, California 94720, the Cardiopulmonary Unit, University of California Service, San Francisco General Hospital, and the Department of Medicine, University of California, San Francisco, California 94143.

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utilized to simulate infarction (4, 5) and hypertrophy (2). Direct comparison of their results with ours is difficult, because Selvester and his group have concentrated their efforts on ventricular depolarization and the QRS complex and our interest has been centered on repolarization and the S-T, T effects as well.

Our model duplicates correctly the T-wave polarity seen in clinical ECGs (1), and the mechanism used to generate it is based on experimental observations of the ventricular recovery sequence published by van Dam and Durrer (6). However, this explanation of the T-wave polarity is not new. It was already anticipated by Wilson et al. (7) in 1934; it was suggested by van Dam and Durrer themselves (6), and it was expressed in an impressive series of papers associated with the names of Burgess, Harumi and Abildskov (8, 9) and summarized by Burgess (10) in 1972. In that description, which we shall refer to as the Burgess model, electrical cardiac activity was treated as a traveling wave phenomenon, resulting in a particularly elegant formulation of the problem.

Although our model also utilizes the experimental results of van Dam and Durrer (6), it is so different from the Burgess model as to hardly resemble it. We decomposed the heart into components to retain our model of conduction block (11) and also because highly localized conditions in the myocardium can probably be dealt with more easily when the heart is divided into components than when it is treated in its entirety.

**Methods**

To model the heart, we divide it into eleven components and assign to each a dipole of fixed location and direction but of variable strength. The location is that of the centroid of the component, and the direction is that of signal propagation at the location in question. “Direction of signal propagation at a location” is understood to mean the direction normal to the wave front of the depolarization wave at that location, pointing in the direction of wave-front advance. The dipole strength is modeled on the resultant dipole of a single myocardial cell as the transmembrane action potential spreads over the cell membrane. The basis for choosing the cell as a model of the electrical behavior of a myocardial component is the generally accepted view that, insofar as electrical activity is concerned, “the heart muscle behaves in many ways as if it were a single cell” (12). In particular, the signal spread through a myocardial component produces a resultant dipole whose strength as a function of time resembles that produced by the signal spread over the surface of a myocardial cell except that its magnitude depends on the volume of the component, i.e., the number of normal cells contained in it.

Where contiguous cells along the conduction path, i.e., in the direction of signal propagation, have different action potentials, additional dipoles arise whose effects are added to those of the dipoles modeling the heart components (1). This effect has been called the contiguity effect and will be discussed later in this paper in more detail.

The electrode locations are identified by their Cartesian coordinates in a body-fixed coordinate system, and the surface potentials induced by the dipoles at these locations are computed by regarding the body as a volume conductor. These potentials are then plotted by the computer, resulting in the computer-generated ECGs.

**THE MYOCARDIAL CELL**

The reason for considering a model of the electrophysiological behavior of the single cell is in part that it, in turn, furnishes the model for the electrical behavior of the myocardial components and in part that we wish to introduce the effects of cellular hypertrophy into our heart model. Thus, we must compute the resultant dipole which arises from the spread of depolarization and repolarization over the membrane of our cell model. This computation requires a mathematical representation of the transmembrane action potential as a function of time and cell geometry.

It is well known that the nonpacemaker ventricular cells are the major contributors to the skin surface potentials; therefore, a mathematical representation of the transmembrane action potential was chosen which is more or less typical of these cells. It is shown in Figure 1, and its mathe-
mathematical formulation is similar to that in the earlier paper (1). Our results are not highly sensitive to this particular choice of mathematical representation so long as the action potential has a depolarization and a repolarization phase and resembles in a general way the curve shown in Figure 1; we chose the particular form shown because it is both representative and mathematically convenient.

The cell geometry chosen for the model of normal electrical heart activity in our earlier paper was spherical (1). That choice is not a literal image of a myocardial cell, which is elongated and shaped more nearly like a cylinder, but, as will be shown, the sphere turns out to be the most suitable choice from the standpoint of the conduction process in the heart. Moreover, it can be demonstrated that the results for the spherical cell are very similar to those obtained when the cell is modeled as an elongated cylinder.  

Although the mechanism of the activation process in the heart is not yet fully understood in many of its details (13), it is clear from the studies of Durrer et al. (14) and Scher (15) that the direction of signal propagation (as defined earlier in the present paper) does not generally proceed in the direction of the cell cylinder axis. For instance, in the left ventricular wall the direction is more nearly in a plane normal to the cylinder axis, and in the right ventricle and the septum it appears in some locations to be neither normal to nor along the axis. But, if the direction of signal propagation in the heart bears no clear relation to that of the cell axis, then it is reasonable to choose for a model of the myocardium a shape which does not possess a preferred direction; the only such shape is the sphere.

If the speed of signal propagation over the cell surface is assumed to be uniform, then the resultant dipole generated by the action potential propagation over the surface can be readily calculated (1); its strength is the diphasic curve in Figure 2a. As expected, this curve consists of a sharply peaked positive wave which we will call a QRS wave in analogy to the ECG (although it should, perhaps, more precisely be called an R wave), a horizontal portion at zero potential which we will call an S-T segment, and a broad wave of negative polarity which we will denote as a T wave.

When the spherical model of the cell is replaced by a cylinder of length / closed off at the ends by equal hemispheres having the same radius as the cylinder, the resultant dipole is readily calculated; the dipole strength for that cell is shown in Figure 2b. Clearly, the two curves are quite similar, and either can serve as a model of the electrical activity of a myocardial component.

In analogy to the ventricular gradient of Wilson et al. (7), i.e., the algebraic sum of the area under the QRS complex and the T wave in the clinical ECG, we will denote the algebraic sum of the QRS wave and the T wave in the diphasic curve of the single cell as the cell gradient.

THE CONTIGUITY EFFECT

Activity initiated at a cell in the myocardium spreads in the direction of signal propagation to neighboring cells by a mechanism which is not fully understood (15). The preponderant evidence favors the view that the intercalated disks, low-resistance components compared with the high-resistance cell membranes, form the electrical connection between adjacent cells in the myocardium, but other mechanisms may exist as well (12). Inasmuch as our model is concerned with the advance of the depolarization wave through the myocardium and not with the details of intra- or intercellular conduction mechanisms, we simply postulate the existence of a low-resistance element in the myocardium which forms the electrical connection between neighboring cells.

If the spherical models of two cells, say cell 1 and cell 2, are contiguous and if the line connecting their centers coincides with the direction of signal propagation, then cell 2 will become activated very shortly after the spread of activation over cell 1 reaches the contact point with cell 2. Now, the intercellular gap is only on the order of 200 Å, and the electrical nexus between adjacent cells is a low-resistance element of approximately 1-3 ohm cm² (15). Therefore, it seems reasonable to postulate zero time for the signal travel from cell 1 to cell 2. Under this assumption, the onset of depolarization occurs simultaneously at the contact points in the two cells.

Now, if the transmembrane action potentials in these two cells are different, that difference gives rise to a dipole which would be absent if the two cells were not contiguous (1); it is for this reason that this effect has been called the contiguity effect.
ECG RESPONSE TO HYPERTROPHY AND ISCHEMIA

effect. It is not a new effect, and its existence has been utilized before by several authors to explain the observed T-wave polarity in clinical ECGs. In these explanations, attention was focused on the difference in transmembrane action potentials, and the need for contiguity between these cells was perhaps recognized but not verbalized.

There are at least two interesting examples in which the contiguity effect has a profound effect on the computer-generated ECGs. One of these deals with the recovery process in the myocardium.

In an important experimental study published 13 years ago, van Dam and Durrer (6) examined the temporal relations of the recovery process at different depths of the left ventricular wall in the dog heart in situ. The actual quantity measured was the functional refractory period, because this period is the only feature of the recovery process which lends itself readily to quantitative determination. They found that "in most cases, recovery of excitability was more advanced in the middle layers than in the subendocardial and outer wall." Their experimental data show an increase of approximately 15 msec in recovery time of the endocardial layer over that of the middle layer.

These observations were greatly extended and in part confirmed in a relatively recent study by Burgess et al. (16), who also found the difference in functional refractory periods between endocardial and middle layers reported by van Dam and Durrer (6), but they could not document the difference in functional refractory periods between middle and epicardial layers. In addition, Burgess et al. (16) found significant differences in the durations of functional refractory periods in the apicobasal direction; they concluded that, in general, the areas activated early have the longer functional refractory periods. These authors also state, based on observations by Hoffman and Cranefield (17), that "there is reasonably good evidence that functional recovery periods reflect action potential duration of ventricular muscle." In any event, in the absence of firm evidence to the contrary, one can probably do no better than to assume that the durations of transmembrane action potentials vary as do the functional refractory periods. This assumption is one of those utilized by Burgess et al. (8-10, 16) and by us.

It appears from the studies of Burgess et al. (16) and in general also from those of van Dam and Durrer (6) that the activation sequence proceeds from myocardial layers composed of cells with longer transmembrane action potential durations to layers of cells with shorter transmembrane action potential durations. If cell 1 belongs to the former layer and cell 2 to the latter and these cells are contiguous, the transmembrane action potentials at the contact points of the two cells will look like those shown in Figure 3a. Thus, there exists a potential difference between the cells during the repolarization phase when the potential of cell 2 at the contact point is lower than that of cell 1. This difference means that the contiguity effect adds a positive contribution to the diphasic curve of these two cells (1). If the potential in cell 2 had been longer than that in cell 1, then the contiguity effect between them would have made a negative contribution.

Another example of the importance of the contiguity effect appears in the model of acute ischemia.

Prinzmetal et al. (18) have found as a result of very sophisticated experiments that in acute ischemia the membrane resting potential "decreases in negativity" and the amplitude of the membrane action potential decreases. Similar results have been obtained by Samson and Scher (19). The term "amplitude" as used in the present paper refers to the potential difference between the depolarized and the resting states (1). Hence, both effects observed by Prinzmetal et al. (18) in acute ischemia produce amplitude reductions in our sense. Thus, we model acute ischemia in a cell by a reduction in amplitude of the transmembrane action potential of that cell. Suppose cell 1

\[ f(t) \]

\[ \text{CELL I} \]

\[ \text{CELL II} \]

FIGURE 3

a: Transmembrane action potentials of two contiguous cells at their contact point when cell 1 (CELL I) has a longer transmembrane action potential duration than does cell 2 (CELL II). b: Transmembrane action potentials of two contiguous cells at their contact point when cell 2 has a lesser transmembrane action potential amplitude than does cell 1 due to acute ischemia.
frontal plane is the x,y-plane with x-axis positive right-to-left and y-axis positive head-to-foot. The sagittal plane is the y,z-plane with z-axis positive in the anteroposterior direction.

Each sublayer is represented by a dipole whose strength as a function of time is given by a diphasic curve resembling in shape that of a single cell (see Fig. 2) but with an amplitude proportional to the volume of the sublayer, i.e., proportional to the number of myocardial cells of normal size in it. The dipole of the component is the sum of the dipoles of the sublayers.

FIGURE 4

Resultant dipole strength from the spread of activation over two contiguous cells when cell 1 is normal and cell 2 has a transmembrane action potential amplitude reduced by 20% due to acute ischemia.

Belongs to normal tissue, cell 2 belongs to ischemic tissue, the two cells are contiguous, and the direction of signal propagation is from cell 1 to cell 2. Let us denote by B and C the contact points on cell 1 and cell 2, respectively. Then the two transmembrane action potentials at B and C in proper time relation to each other look like those shown in Figure 3b. It is easy to see that during the entire depolarized state as well as during repolarization the potential in cell 1 is larger than that in cell 2; thus, the contiguity effect makes a positive contribution to the diphasic curve during the entire cycle beginning with the end of the depolarization phase of cell 1. This effect produces an S-T segment elevation and also tends to raise the T wave. The resultant diphasic curve of the two cells now looks like that shown in Figure 4. Similarly, if the amplitude of the transmembrane action potential of cell 2 were larger than that of cell 1, the S-T segment would be depressed.

THE HEART MODEL

The heart model used in this study is described elsewhere (1). It consists of eleven components; two of these are the atria and nine more represent the ventricular septum and the ventricles in the manner shown in Figure 5. The decomposition of the left ventricle is shown schematically in greater detail in Figure 6. Every component in the model is decomposed into electrically homogeneous layers whose boundaries are normal to the direction of signal propagation, and every layer is decomposed into sublayers (1). In this way, it is possible to follow the progress of the depolarization and repolarization waves through the component and also to introduce local malfunctions in preassigned portions of every component.

In our model of electrical heart activity, the location and direction of a number of dipoles must be defined. In general, the dipole location is identified with that of the centroid of the myocardial tissue represented by the dipole and the dipole direction with that of signal propagation at the location in question. Location and direction are given relative to a coordinate system with the origin at the electrical centroid of the heart. In conformity with normal practice in cardiology, the

FIGURE 5


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Schematic presentation of the details of the decomposition of the left ventricle. See Figure 5 for definition of abbreviations.

of the sublayer dipoles, each displaced in time with respect to its neighbor in accordance with the signal propagation velocity and the thickness of the sublayer. The activation of the diphasic action potential of each component occurs at the arrival time of the depolarization wave at the component represented by that dipole. The data regarding the progress of the depolarization wave through the human heart utilized by us were obtained in a delicate series of observations by Durrer et al. (14). Similar results in the dog heart have been reported by Scher (15); these data were utilized in the Burgess model, because the performance of that model was compared with experiments on the dog heart. It would have been possible to incorporate the wave propagation simulation of Solomon and Selvester (20, 21) in our mathematical model. However, this procedure would have considerably enlarged our computer program and, thus, the cost of this study, which was carried out without extramural support; it was rejected for this reason.

THE SKIN SURFACE POTENTIALS

The twelve leads of a standard ECG are obtained from the skin surface potentials at nine points on the body. As an integral part of the multiple dipole hypothesis, it is assumed that these potentials are induced by the dipoles which model the heart. The body can be regarded as a volume conductor, and its boundaries and local conduction properties can be determined by measurement. Therefore, it is possible, in principle at least, to compute the skin surface potentials at given points on the conductor boundary induced by dipoles of known location, direction, and moment. However, the required properties of the body are difficult to ascertain, they differ from individual to individual, and once they are known the computation of the skin surface potentials leads to an elaborate and computationally difficult boundary-value problem. Gelernter and Swihart (22) have examined the problem of the boundedness of the volume conductor, Selvester and his group have taken into account boundary and distance effects (2, 3) and inhomogeneity within the body (3), a critical study of this problem has been made by Scher et al. (23), and important contributions to the effect of volume conductor inhomogeneity have been made by Geselowitz (24, 25) in his studies of electrical and magnetic fields generated by dipoles in inhomogeneous, bounded volume conductors.

The difficulties just alluded to disappear when the body is regarded as a portion of a homogeneous volume conductor of infinite extent. Partly to keep the problem computationally tractable but mostly because the basic problems treated by us are present in bounded or unbounded and in homogeneous or inhomogeneous volume conductors, we postulate the existence of an equivalent, electrically homogeneous body immersed in an infinite, electrically homogeneous medium having the same coefficient of conductivity as the equivalent body. Equivalence is established when the skin surface potentials at the nine points on the body induced by the same dipole are equal in the actual and the equivalent body.

In computing the skin surface potentials, we use the classical, quasi-static approximation, i.e., although the electrical sources in the heart are considered to be time varying, the induced potentials are calculated as though steady-state conditions exist at every instant.

A COMPUTER MODEL OF HYPERTROPHY

The microscopic evidence of myocardial hypertrophy is an increase in the size of the muscle fibers but no increase in the number of these fibers (26-28). Uhley has shown (29) that the transmembrane action potential of hypertrophied myocardial cells remains normal.

The contiguity effect produced by adjacent layers having different transmembrane action potentials depends only on the difference in transmembrane potential between contiguous cells belonging to different layers and the total number of contacts between such unlike cells. Therefore, the contiguity effect of these adjacent layers remains unchanged by hypertrophy, because the number of cells and the transmembrane action potentials are unchanged.

It follows that the model of hypertrophy consists in increasing the cell radius of the affected component of the heart without changing the contiguity effect of adjacent layers.

The example of left ventricular hypertrophy considered in this paper is hypertrophy of the
entire left ventricle as evidenced by an increase in cell radius of 15%. This value produces a volume increase of the left ventricular myocardium of 52%. No heart rotation due to hypertrophy is included in the example.

**A COMPUTER MODEL OF ACUTE ISCHEMIA**

Since this paper deals exclusively with modeling of electrical heart activity, coronary system insufficiency is only considered to the extent that it affects transmembrane action potentials. In general, we regard a component of the myocardium as ischemic if its electrical activity is impaired but has not ceased altogether.

With respect to ischemic lesions, a good deal of experimental evidence (18, 19) shows that acute ischemia reduces the amplitude of the transmembrane action potential, i.e., the voltage spread between the plateau (or the depolarized state) and the resting potential. This reduction is brought about by both an increase in the resting potential and a decrease in the potential in the depolarized state (18).

The cases included in the present paper are high anterior and posterior-inferior acute ischemia of the left ventricle. The high anterior ischemia affects all of the left anterior ventricle and approximately 25% of the middle left anterior ventricle, and the posterior-inferior ischemia affects the left posterior ventricle (see Fig. 6). The areas involved are the cross-hatched areas shown schematically in Figure 7.

We model only subendocardial and epicardial ischemia; transmural lesions have not been considered. The component of the ventricular wall affected by ischemia has been divided into an epicardial and a subendocardial layer as shown in Figure 8. The epicardial portion comprises the epicardial and intermediate layers considered by van Dam and Durrer (6) and one sublayer of the endocardial layer; this portion is cross-hatched in Figure 8. The endocardial portion includes the remainder of the ventricular wall and is shown as the open portion of Figure 8.

To model acute ischemia, we have reduced the action potential amplitude of the ischemic tissue by 20% but we have retained the normal duration of the action potential. Thus, our model of the transmembrane action potentials of a normal and an ischemic cell looks like those shown in Figure 3b. The amplitude reduction of 20% was chosen arbitrarily.

**Results and Discussion**

The heart model described in the present paper was used to obtain computer-generated 12-lead ECGs of a heart of intermediate (45°) orientation. Particular attention was paid to the ventricular gradient and to the modeling of left ventricular hypertrophy and left ventricular acute ischemia.

**T-WAVE POLARITY AND VENTRICULAR GRADIENT**

The problem of T-wave polarity is intimately linked with the notion of the ventricular gradient first suggested as a diagnostic indicator by Wilson et al. (7). They showed by a remarkably simple and appealing argument that the algebraic sum of the total area under the diphasic action potential of a one-dimensional muscle strip must be zero. It has also been shown (1) that the cell gradient of a three-dimensional spherical cell model is zero, and it can be shown that the same result holds for the cylindrical cell. It can be concluded that, if a myocardial component were composed of cells having identical transmembrane action potentials, then the gradient of that component would be zero. Similarly, if the ventricles were composed entirely of such components, then the ventricular gradient would be zero regardless of the three-dimensional character of the prob-

*Readers interested in this demonstration should write to the authors.*

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lem or the direction of the component dipoles. It is an immediate consequence of this observation that contiguity effects render the gradients nonzero.

The fact that the interface between layers having different transmembrane action potential durations can explain the clinically observed T-wave polarity is readily demonstrated in a mathematical model because, in such a model, the effects which contribute to the computed skin surface potentials can be separated. In Figure 9, we show the computer-generated 12-lead ECGs of the model of a normal heart with the contiguity effects included on the left and deleted on the right. It should be realized that in the latter case, the difference in transmembrane action potential durations was retained; only the effect of the contiguity of the layers having different durations was deleted. As a result, all leads in Figure 9b have zero ventricular gradients.

In comparing Figure 9a with Figure 9b, it is evident that the contiguity effect reverses the T-wave polarity in all leads except V₁. In that lead, the T wave is actually more positive without the effect than it is with the contiguity effect, although the difference is not large. It may be concluded that, for the heart orientation modeled, the ventricular gradient in V₁ normally is nearly zero. Since V₁ is the only lead with an electrode position in the sagittal plane, it is implied thereby that the dipoles of components having layers of different transmembrane action potential durations lie nearly in the frontal plane.

The existence of layers having different transmembrane action potential durations was already suspected 40 years ago by Wilson et al. (7) in a paper which shows a very deep insight into the genesis of the ECG. We should like to quote their remarkable statement: "... if adjacent elements of a muscle fiber differ in their state of activity, one being nearer to or farther from the resting state than the other, there must be an electromotive force across and normal to the plane that separates them." In fact, Wilson et al. (7) postulated "... local variations in the excitatory process ... due solely to a gradient affecting the duration of the excited state; in other words, to a difference between the velocity of the wave of depolarization and the velocity of the wave of repolarization." This statement leads us to believe that these authors would have, in fact, explained the positive ventricular gradient precisely by the contiguity effect of cells having different transmembrane action potential durations had they not invoked a velocity difference between depolarization and repolarization waves. To our knowledge, experimental results have not uncovered such a velocity difference, and we believe that none need be postulated to explain the positive ventricular gradient of clinical ECGs.

The expectation that a gradient in transmembrane action potential duration across the ventricular wall might well explain the nonzero ventricular gradient was clearly recognized by van Dam and Durrer (6) who undertook their study "... to correlate these [their] findings with the polarity of the T-wave." It was explicitly stated by Burgess (10) when she wrote that "... the concordance of QRS and T-waves must be due to the inhomogeneity of ventricular action potential
form,” and the same suggestion occurs several times in a very instructive survey article by Surawicz (30).

LEFT VENTRICULAR HYPERTROPHY

The computer-generated 12-lead ECGs of our example of left ventricular hypertrophy are shown in Figure 10. In general they show an average increase in R-wave amplitude of 36% except in V1 and V5 where deep S waves are seen. In addition, the ventricular activation time is increased by an average of approximately 14%. These configurations correspond to clinical experience (31).

The computer results are not unexpected. Our analytical results (1) show that the QRS and T-wave amplitudes are proportional to the square of the cell radius and that their durations are linearly proportional to the cell radius. It can easily be shown that the first result also holds for the cylindrical cell and that the durations are equal to the sum of two terms; one of these terms is directly proportional to the cell radius and the other to the cylinder length. Therefore, an increase in cell radius (radius and length in the cylindrical cell) increases the amplitude of the cellular diphasic action potential as well as the duration of the waves. In fact, an increase of 15% results theoretically in an amplitude increase of the diphasic cell action potential of exactly 32.25%. This increase is of the same order of magnitude as that of the R wave but does not agree with it precisely, because the R wave results from the complex electrical activity of the entire heart not only that of the left ventricle.

The flattening or reversal of the T wave in left ventricular hypertrophy is due to the fact that the contribution to its negativeness is increased by more than 30%, but the contiguity effect of adjacent layers of different transmembrane action potential durations, which tends to erect the T wave, is unaffected by hypertrophy; thus, flattened or inverted T waves can be expected in left ventricular hypertrophy.

In the literature, the increased R-wave amplitude in left ventricular hypertrophy is frequently regarded as puzzling in view of the unchanged transmembrane potentials and the lack of an increase in the number of myocardial cells, and the inverted T wave is ascribed to unknown repolarization changes (31). However, the former can be explained by the relation between the monophasic and the diphasic action potentials of the single cell, and the latter by the contiguity effect of adjacent layers having different transmembrane action potential durations, thereby lending further support to the explanation of the upright T wave resulting from these layers.

VENTRICULAR ACUTE ISCHEMIA

The computer-generated 12-lead ECGs of four cases of acute ventricular ischemia modeled by us are shown in Figure 11b-e; Figure 11a shows the normal ECG for easy comparison.

A broad summary of our theoretical study coincides completely with the general conclusions reached by Prinzmetal et al. (18) in an experimental study of 89 experiments on 34 dogs. There exists a quantitative linear relation between surface and intracellular electrograms, and S–T segment displacement in the computer-generated ECGs is the most
significant change produced by our model of acute myocardial ischemia.

As a general observation, it is seen from Figure 11 that, when subendocardial and epicardial ischemia is considered in the same part of the ventricle, the S-T segment displacements in these two cases are in opposite directions. This result is expected, because the contiguity effect for signal propagation from normal to ischemic cells is opposite to that from ischemic to normal cells; the former occurs in epicardial ischemia, the latter in subendocardial ischemia.

Similarly, the S-T segment shifts due to posterior ischemia are generally in opposite directions to those due to anterior ischemia when lesions in the same layers are compared. Again, this result is expected, because the dipoles of the affected components point approximately in opposite directions in these two cases.

Both results coincide with clinical observations in which tracings taken directly over the injured areas show S-T segment elevation. However, if normal muscle lies between the injured muscle and the electrode, S-T segment depression is expected (31).

It may seem surprising that, in our example, the amount of S-T segment displacement is nearly the same for subendocardial and epicardial ischemia even though twice as much tissue volume is ischemic in the epicardial case. To understand the reason for this finding, it must be realized that a dual electrical effect is produced by ischemia: one effect is a reduction in transmembrane potential amplitude and the other is the contiguity effect produced on the boundary between normal and ischemic tissue. The first effect is proportional to the volume of the ischemic tissue, the other is an area effect.

Assume that Figure 8 shows the portion of

![Computer-generated 12-lead ECGs of acute ischemia. a: Normal. b: High anterior subendocardial ischemia. c: High anterior epicardial ischemia. d: Inferior posterior subendocardial ischemia. e: Inferior posterior epicardial ischemia.](image-url)
the ventricular wall that is involved in ischemic changes. Then, it is evident that in the case of epicardial ischemia, slightly more than twice as much myocardial tissue is ischemic than in the subendocardial case. However, the area normal to the conduction path separating normal from ischemic tissue is the same in both cases. Therefore, the S-T segment shift is equal in amount in both cases, although it is opposite in direction.

The ischemic tissue volume effect due to a reduction in electrical activity results in reduced amplitudes in the QRS complex and the T wave; however, we will now show that this effect is too small in our example to be readily evident from an examination of the ECGs. In the example, approximately 20% of the ventricular wall is involved in ischemia. In the subendocardial case, one third or approximately 7% of the ventricular myocardium is regarded as ischemic, and in the epicardial case 14% of the ventricular myocardium is ischemic. Hence, only 7% more ventricular tissue is ischemic in the latter case than in the former. Now the reduction in transmembrane potential is 20% in our example. Therefore, the amplitude difference of the QRS complex and the T waves in these two cases cannot exceed 20% of 7% i.e., 1.4%. This difference is too small to be easily seen even though careful measurements show a very small difference.

To study this question further we have examined the numerical data of the computer output. For the case of anterior ischemia, we have calculated in each lead the coefficient

\[ C_R = \frac{(R_n - R_p)(R_p - R_s)}{R_n}, \]

where \( R_n \) is the R-wave amplitude in the normal case, \( R_p \) is the R-wave amplitude in the epicardial case, and \( R_s \) is the R-wave amplitude in the subendocardial case. When these coefficients are averaged over all 12 leads, it is found that \( C_{R_{ave}} = 1.45 \), which means that the R-wave change, even though very small, is 45% larger in the epicardial case than it is in the subendocardial case. This value is very nearly in accord with the difference in diseased tissue volume involved in these two cases.

Based on our proposed mechanism of the S-T segment shift, we believe that the most obvious effect of acute ischemia, the S-T segment shift, is not a quantitative measure of the volume of ischemic tissue present but rather of the cross-sectional area of such tissue normal to the direction of signal propagation. Thus, a direct correlation should not necessarily be expected between S-T segment shift and the result of methods of evaluating ischemia which depend on the volume of the ischemic lesion (such as enzyme tests in the case of tissue necrosis). For instance, if the reduction in electrical activity doubles and the ischemic area remains constant, the S-T segment shift also doubles. However, when ischemic lesions are in equal locations, have equal reductions of electrical activity, and involve equal volumes of ischemic tissue, but one occupies twice as large an area as the other, then that lesion with the larger area will have double the S-T segment shift. Finally, in many cases, an increase in the area of a lesion will involve an equal increase in its volume; in these cases a direct correlation between S-T segment shift and volume-measuring tests should be readily demonstrable.

It can be seen from Figure 11 that, in the model, acute ischemia produces R-, S-, and T-wave changes in addition to the S-T segment displacement. In general, the peaks of the R, S, and T waves are shifted in the same direction as the S-T segment. In the case of the T wave, this result would be expected, because the reduction of 20% in the transmembrane potential occurs during the plateau as well as the repolarization phase, and the latter is responsible for the T-wave formation. In the case of the R and S waves, the reason is that the QRS-complex formation is not yet completed when the depolarization wave encounters the interface between normal and ischemic tissue; hence, the shift produced by the ischemia starts prior to the beginning of the S-T segment formation.

Our computer model has produced a quantitative correspondence between the severity of ischemia on the one hand and the ECG response on the other, where the term severity is understood to mean diminution of electrical signal output. This correspondence may eventually find its way into the diagnostic area, and it may become useful in monitoring during treatment and in other clinical applications.

SOME SIMPLIFYING ASSUMPTIONS

Many assumptions were made in the con-
struction of our model, and many of these were significant simplifications of very complex, real situations. One is our procedure of replacing the human body by an equivalent body that can be treated as an infinite, homogeneous volume conductor. We believe that making this assumption is justified on several grounds. Foremost, we wished to examine a mechanism which leads to R-wave amplitude increase and T-wave amplitude reduction or inversion in left ventricular hypertrophy and to S-T segment shift in acute ischemia. Although the details of the volume conductor properties probably have quantitative effects on these ECG configurations, they will neither create nor destroy a mechanism for producing them. In fact, we believe on the basis of our results that the detailed volume conductor properties have only a secondary effect on these ECG distortions. Moreover, it is well known (23) that the volume conductor properties in question show considerable individual differences so that a norm would have had to be established for body configuration. Actually, the procedure of replacing a complex system or component by an equivalent one is widely practiced and has proven valuable in many classical problems, provided the notion of equivalence is properly defined. Finally, with the highly successful work of many investigators in the area of the body as a volume conductor (2-5, 22-25), the principles involved in accounting for more realistic body conductor properties are quite well in hand, and their incorporation in our model is merely a matter of a considerable expansion of our present computer program.

Another assumption that may appear unrealistic is the transmembrane action potential configuration of Figure 4 selected to model acute ischemia. The following observations can be readily demonstrated. If the plateau phase of the transmembrane action potential had been given some negative slope rather than zero slope, the effect on the computer-generated ECGs would have been slight, because the diphasic action potential is not highly sensitive to the detailed transmembrane action potential configuration so long as the latter has the general form shown. Then, if the transmembrane action potential configuration of acute ischemia were simply a constant percent reduction of the action potential (with the resting potential as the datum), the S-T effect would be the same as that shown. On the other hand, if the ischemic transmembrane action potential had a somewhat steeper negative slope during the plateau phase than it does in the normal case, then the S-T segment would not only be displaced in translation, but it would be somewhat tilted as well. Although the transmembrane action potential configuration chosen for this study may not be highly realistic in its details, it harbors the essential elements of potentials characteristic of acute ischemia, and it has proven useful in suggesting a mechanism for the S-T segment displacement produced by acute ischemia.

References

5. SELVESTER RH, WAGNER JO, RUBIN HB: Quantitation of myocardial infarct size and location by electrocardiogram and vectorcardiogram. In Quantitation in Cardiology. Baltimore, William & Wilkins Company, 1972, pp 31-44
6. VAN DAM RTh, DURREN D: Experimental study on the intramural distribution of the excitability cycle and on the form of the epicardial T-wave in the dog heart in situ. Am Heart J 61:537-542, 1961
7. WILSON FN, MACLEOD AG, BARKER PS, JOHNSTON FD: Determination and significance of the areas of ventricular deflections of the electrocardiogram. Am Heart J 10:46-61, 1934
27. Lowe TE, Bate EW: Diameter of cardiac muscle fibers: Study of the diameter of muscle fibers in the left ventricle in normal hearts and in the left ventricular enlargement of simple hypertension. Med J Aust 1:461–469, 1948
A mechanism for the electrocardiogram response to left ventricular hypertrophy and acute ischemia.

P S Thiry, R M Rosenberg and J A Abbott

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