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A BIDOMAIN MODEL FOR ANISOTROPIC CARDIAC MUSCLE

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Cardiac muscle is considered to consist of an intracellular domain and an extracellular or interstitial domain. Current passes from one domain to the other through the cell membrane. Electric potentials in interstitial space are shown to be associated with current sources proportional to the spatial gradient of the cellular transmembrane action potential, ϕ_m. Hence, given the distribution of ϕ_m throughout the myocardium, one can calculate the surface electrocardiogram and extracorporeal magnetocardiogram. The problem is considerably complicated when anisotropy is considered. If interstitial space is approximately isotropic, however, the sources are still proportional to $\nabla\phi_m$. It is shown that the effects of intracellular anisotropy on the surface electrocardiogram may be relatively small. The inverse problem is discussed briefly, with consideration of the relationship of the magnetocardiogram to the electrocardiogram. Finally, it is shown that if the heart can be considered to be bounded by a closed surface, then the value of ϕ_m on this surface is uniquely related to the surface electrocardiogram to within a constant, provided there are no internal discontinuities. Such discontinuities, however, would be expected to occur in cases of ischemia and necrosis.

Keywords — *Electrocardiogram, Bidomain model, Heart muscle, Magnetocardiogram, Anisotropy, Model study.*

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INTRODUCTION

It has long been recognized that the heart electrically has properties of a syncytium. Furthermore, strips of heart muscle show cable-like properties when prepared to exhibit propagation either along the fiber axis (25), or transverse to it (4). The electrical properties differ in the two directions. Hence, cardiac muscle exhibits electrical anisotropy (15,18). This result is not unexpected since the heart cells are cylinders, and the cylinders are structurally arranged in parallel arrays in local regions, although the axis of fiber orientation does vary from one region of the heart to the other (23).

Cable theory implies that the heart muscle is well characterized by an intracellular space and an extracellular space separated by a membrane (2). In contrast to the squid axon, which is part of a single cell, the cable properties of heart tissue extend over regions encompassing many cells. Hence, one is led to the picture of an intracellular domain and an extracellular domain, each of which may be pictured as effectively extending throughout the region of the muscle, independent of the cell boundaries.

In this picture, then, the heart may be considered to consist of two syncytia: an intracellular domain and an extracellular domain. Current passes from one domain to the other through the cell membrane. The electrical properties of each domain depend on the passive electrical properties of the intracellular and extracellular fluids, electrical properties of the tight junctions between cells, and the geometrical arrangement of the cells.

Starting from cable theory and generalizing it to two dimensions, Spach and Barr (21) and Spach and co-workers (22) were led to an "extracellular-intracellular" model of the heart's electrical activity in which extracellular potentials could be calculated from a knowledge of intracellular potentials. On the other hand, Miller and Geselowitz (13) developed a model starting from the concept of interpenetrating intracellular and extracellular domains (20). The two models are mathematically equivalent. They have been remarkably successful in accounting for the human electrocardiogram and magnetocardiogram for the normal and ischemic heart (7,13), as well as for potentials in a tissue bath preparation (22). The bisyncytial or bidomain model predicts that the bioelectric sources in the heart are proportional to the gradient of transmembrane potential. The present paper will develop the theory, with emphasis on the bisyncytial or bidomain model, and explore some of its consequences.

MODEL

Let σ_i and σ_e be the effective conductivity of intracellular and extracellular (interstitial) space, respectively, where the intracellular and interstitial compartments are each taken to occupy the entire tissue space. The current density, $\mathbf{J}$, is then

$$\mathbf{J} = -\sigma_i \nabla \phi_i - \sigma_e \nabla \phi_e \ , \tag{1}$$

where $\mathbf{J}$ is a macroscopic current density and ϕ_i and ϕ_e are macroscopic potentials in intracellular and interstitial (extracellular) space, respectively. Macroscopic quantities may be considered to be averages over small volumes of tissue including several cells.

The transmembrane potential, ϕ_m, is

$$\phi_m = \phi_i - \phi_e \ . \tag{2}$$

Hence

$$\mathbf{J} = -\sigma_i \nabla \phi_m - (\sigma_i + \sigma_e) \nabla \phi_e \ . \tag{3}$$

Since the volume conductor problem for electrocardiography is a quasi-static one, the divergence of $\mathbf{J}$ must vanish. Therefore,

$$\nabla \cdot \sigma_i \nabla \phi_m = -\nabla \cdot (\sigma_i + \sigma_e) \nabla \phi_e \ . \tag{4}$$

Both σ_i and σ_e will be larger in the longitudinal direction than in the transverse direction, reflecting the anisotropic nature of the myocardium. Hence, both conductivities are represented by tensors. Initially we will ignore anisotropy. We will also assume that the heart is immersed in a medium of conductivity,

$$\sigma = \sigma_i + \sigma_e = 1/\rho_i + 1/\rho_e = 1/\rho \ , \tag{5}$$

identical to the bulk conductivity of the heart. In other words, we will assume the cardiac sources to be in a homogeneous isotropic volume conductor.

Formally we can represent the sources by impressed currents (5). If $\mathbf{J}^i$ is the impressed current density at a point, then the total current $\mathbf{J}$ is given by

$$\mathbf{J} = \mathbf{J}^i - \sigma \nabla \phi \ . \tag{6}$$

Since the divergence of $\mathbf{J}$ vanishes,

$$\nabla \cdot \sigma \nabla \phi = \nabla \cdot \mathbf{J}^i \ . \tag{7}$$

In an unbounded medium, Eq. 7 has as a solution

$$\phi = -\frac{1}{4\pi\sigma} \int \frac{\nabla \cdot \mathbf{J}^i}{r} \, dv \ . \tag{8}$$

With use of the vector identity, $\nabla \cdot a\mathbf{A} = a\nabla \cdot \mathbf{A} + \mathbf{A} \cdot \nabla a$, and the divergence theorem, Eq. 8 may be written

$$\phi = \frac{1}{4\pi\sigma} \int \mathbf{J}^i \cdot \nabla\left(\frac{1}{r}\right) d\nu \ , \tag{9}$$

where the observation point is outside the source region.

In the case of cardiac muscle, $\mathbf{J}^i$ during depolarization in non-zero only in a thin sheet of thickness of the order of 1 mm. Therefore, if $\mu d\mathbf{S} = \mathbf{J}^i d\nu$, Eq. 5 becomes to a very good approximation

$$\phi = \frac{1}{4\pi\sigma} \int \mu \nabla\left(\frac{1}{r}\right) \cdot d\mathbf{S} = \frac{1}{4\pi\sigma} \int \mu \, d\Omega \ , \tag{10}$$

where $d\Omega$ is the solid angle. If the double layer, μ, is uniform and closed, then it is evident from Eq. 10 that $\phi = 0$ outside the region containing sources. Hence, a uniform double layer implies that no potentials will be observed until activity reaches the boundary of the source region.

A comparison of Eqs. 4 and 7 indicates that the current source distribution, $\mathbf{J}^i$, is given by

$$\mathbf{J}^i = -\sigma_i \nabla \phi_m = -\nabla \phi_m / \rho_i \tag{11}$$

and hence is proportional to the negative of the gradient of the transmembrane potential. If ϕ_m is continuous, which would be true as long as excitation has not reached a boundary of the myocardium, then the solution of Eq. 4 is

$$\phi_e = -\frac{\sigma_i}{\sigma_i + \sigma_e} \phi_m \ . \tag{12}$$

Outside the source region, $\phi_m = 0$ and $\phi_e = 0$. Therefore the bisyncytial model leads to the conclusion that ϕ_e is zero until the sources reach the boundary, or in other words, until epicardial or endocardial breakthrough has occurred. This conclusion is independent of whether the sources may be considered double layers, or whether the double layer is uniform. Equation 9 then indicates that $\mathbf{J}$, is everywhere zero, with current in intracellular space equal and opposite to current in extracellular space.

This result can be cast in a somewhat more formal form as follows.
From Eqs. 8, 9, and 11,

$$\phi_e = \frac{-1}{4\pi(\sigma_i + \sigma_e)} \int \sigma_i \nabla \phi_m \cdot \nabla\left(\frac{1}{r}\right) d\nu = \frac{1}{4\pi(\sigma_i + \sigma_e)} \int \frac{\nabla \cdot \sigma_i \nabla \phi_m}{r} \, d\nu \tag{13}$$

$$\int \nabla \cdot \phi_m \nabla\left(\frac{1}{r}\right) d\nu = \oint \phi_m \nabla\left(\frac{1}{r}\right) \cdot d\mathbf{S}_H = \int \phi_m \nabla^2\left(\frac{1}{r}\right) d\nu + \int \nabla \phi_m \cdot \nabla\left(\frac{1}{r}\right) d\nu \ , \tag{14}$$

where S_H is the boundary of the source region, namely the surface of the heart (epicardial and endocardial). ϕ_m is discontinuous on this surface.

$$\nabla^2\left(\frac{1}{r}\right) = -4\pi\delta(0) \ , \tag{15}$$

where δ is the Dirac delta function in three dimensions.
Therefore, from Eq. 13,

$$\begin{aligned}\phi_e &= \frac{-1}{4\pi(\sigma_i+\sigma_e)} \int \sigma_i\phi_m\nabla\left(\frac{1}{r}\right)\cdot d\mathbf{S}_H, \text{ outside heart} \\ &= \frac{-1}{4\pi(\sigma_i+\sigma_e)} \int \sigma_i\phi_m\nabla\left(\frac{1}{r}\right)\cdot d\mathbf{S}_H - \frac{\sigma_i}{\sigma_i+\sigma_e}\phi_m \ , \text{ inside heart}\end{aligned} \tag{16}$$

Equations 13 and 16 are valid in an unbounded bidomain volume conductor. If the volume conductor is bounded, then an additional term must be added. This term involves the potential, V, on the bounding surface S_o, which is found by solving the appropriate boundary value problem. From Eq. 13 the source distribution is given alternatively as a vector current dipole moment per unit volume, $-\sigma_i\nabla\phi_m$ (see Eq. 11), or as a scalar current per unit volume, $\nabla\cdot\sigma_i\nabla\phi_m$.

As long as σ_i and σ_e do not depend on $\mathbf{J}$, the problem is linear and superposition holds. The potential, ϕ, in the volume conductor, and its value, $\mathbf{V}$, on the surface, can be expressed as a weighted sum or integral of the sources throughout the myocardium. As noted, the sources are related to the gradient of the transmembrane action potential and may be expressed in either scalar or vector form. This point will be taken up again below when we discuss simulation of the electrocardiogram and anisotropy.

MAGNETOCARDIOGRAM

The magnetic field is given by

$$\mathbf{H} = \frac{1}{4\pi}\int\frac{\nabla\times\mathbf{J}}{r}\,dv = \frac{1}{4\pi}\int\mathbf{J}\times\nabla\left(\frac{1}{r}\right)dv. \tag{17}$$

From Eqs. 6 and 11, $\mathbf{J}$ is everywhere proportional to the gradient of a scalar. Hence $\nabla\times\mathbf{J}$ vanishes everywhere except where it is discontinuous on the surface of the heart, S_H, or on the surface of the volume conductor, S_o. Following the derivation given by Geselowitz (6) for a bounded volume conductor, we then obtain

$$\mathbf{H} = \frac{1}{4\pi}\int \mathbf{J}^i \times \nabla\left(\frac{1}{r}\right)dv + \frac{1}{4\pi}\int \sigma V \nabla\left(\frac{1}{r}\right) \times d\mathbf{S}_o$$
$$= \frac{1}{4\pi}\int \sigma_i \phi_m \nabla\left(\frac{1}{r}\right) \times d\mathbf{S}_H + \frac{1}{4\pi}\int \sigma V \nabla\left(\frac{1}{r}\right) \times d\mathbf{S}_o \ , \tag{18}$$

where V is the potential (electrocardiogram) on the surface of the volume conductor. Hence, there is no magnetic field until epicardial or endocardial breakthrough occurs. This result is also evident from the observation that **J** is zero until breakthrough. Note that Eq. 18 involves the solution of the boundary value problem for the electric potential (see also ref. 3).

SIMULATIONS

Miller and Geselowitz (13) have applied the bidomain model to the human electrocardiogram, and Geselowitz (7) has extended it to the human magnetocardiogram. The computer model employed a realistic human torso of homogeneous resistivity delineated by 1,426 planes triangular elements (1). The heart was represented by a three-dimensional array of approximately 4,000 points. An action potential, ϕ_m, was assigned to each point on the basis of available electrophysiological evidence.

The source term, $-\sigma_i \nabla \phi_m$, was approximated using discrete differences. To simplify the calculations of surface potentials, the source distribution was coalesced to a discrete set of 23 lumped dipoles representing 23 regions of the heart. If $\mathbf{P}_m$ is the moment of the m^{th} dipole, and V_n is the potential at the centroid of the surface element n, then

$$V_n = \sum_{m=1}^{23} (\mathbf{Z}_T)_{nm} \cdot \mathbf{P}_m \ , \tag{19}$$

where $\mathbf{Z}_T$ is a transfer coefficient matrix, each element of which is a vector. $\mathbf{Z}_T$ represents, in essence, the solution to the boundary value problem for a 23 dipole source.

A summary of the procedure used to calculate the electrocardiogram and magnetocardiogram at each instant of time is as follows:

1. The simulated cellular action potential at each of the approximately 4,000 points in the heart model is calculated using the assigned activation times and action potential data.
2. The value of the gradient of the cellular action potential distribution is approximated at each point by discrete differences of the potentials at its six nearest neighbors (see Eq. 11). The result is a current dipole at each point in the model.
3. The moments of the 23 dipoles are obtained by summing the moments of the dipoles at all of the points within the corresponding regions of the heart model.

4. Potentials on the surface of the torso are calculated using the set of 23 dipoles to yield the electrocardiogram (see Eq. 19).

5. The magnetic field intensity is calculated from Eq. 18. The torso conductivity was taken to be 2×10^{-3} ohm/cm; σ_i/σ was taken to 0.37. To simulate ischemia and infarction, abnormal action potentials are assigned to the injured region. The ischemic action potentials exhibit a shortening of duration, a decrease in the magnitude of the resulting potential, a decrease in the maximum depolarization potential, and an increase in depolarization rise time. Prolonged action potentials are also incorporated in the model.

Note that calculation of the electrocardiogram requires a value for σ_i/σ whereas calculation of the magnetocardiogram requires knowledge of σ_i and σ separately (see Eqs. 16 and 18). In their original development Miller and Geselowitz (13) used Eq. 1 and hence related volume conductor potentials to ϕ_i with a scale factor σ_i/σ_e. In practice their simulations used ϕ_m rather than ϕ_i, which differs from ϕ_m because of significant values of ϕ_e in the myocardium. In essence, therefore, they were using the formulation presented here in which the sources are proportional to $\sigma_i \nabla \phi_m$ and the appropriate scale factor is σ_i/σ. Surface electrocardiograms of the correct amplitude were obtained when this ratio was assigned a value of 0.37.

Schmitt (19) has reported an average torso resistivity of $\sigma = 2 \times 10^{-3}$ ohm/cm. This value was used in the simulation of the magnetocardiogram and gave magnetocardiographic amplitudes in close agreement with those observed experimentally. From these values of σ_i/σ and σ, one can calculate σ_i and σ_e. The results are $\sigma_i = 0.74 \times 10^{-3}$ mho/cm, $\sigma_e = 1.26 \times 10^{-3}$ mho/cm, corresponding to resistivities of $\rho_i = 1350$ ohm-cm and $\rho_e = 794$ ohm-cm.

ANISOTROPY

Both the intracellular domain and the extracellular domain exhibit anisotropy. The principal axes are determined by the fiber orientation and may be expected to be the same for both domains. A general solution to Eq. 4, for the anisotropic case is not available. If, however, we assume extracellular space to be uniform and isotropic, then this equation is Poisson's equation for which solutions can be written. See Eq. 13, which shows two alternative expressions for the potential in isotropic extracellular space outside the source region.

If intracellular space is anisotropic, then σ_i or ρ_i must be treated as a tensor. A practical difficulty arises in that we do not have good data concerning these tensors. Cable theory enables us to replace resistivity by conduction velocity, θ, a more readily measured characteristic of the tissue.

From cable theory,

$$(\rho_{it} + \rho_{et})\theta_t^2 = (\rho_{il} + \rho_{el})\,\phi_l^2 = K \ , \tag{20}$$

where the subscripts l and t designate the longitudinal and transverse directions, respectively, and K is a constant if membrane properties are independent of the direction of propagation. Tasaki and Hagiwara (24) showed that K could be related to the time constant, τ_f, of the foot of the action potential as follows:

$$1/\tau_f = 2KvC_m/a \ , \tag{21}$$

where C_m is the membrane capacitance per unit area, a is the fiber radius, and v is the volume fraction of fibers (9).

Let

$$\alpha = (1+\rho_e/\rho_i) \tag{22}$$

Then the two expressions for the extracellular potentials, taking extracellular space to be isotropic and homogeneous, but considering intracellular space to be anisotropic, are

$$\phi_e = \frac{1}{4\pi\sigma K}\int\left[\theta_t^2\alpha_t\left(\frac{\partial^2\phi_m}{\partial x^2} + \frac{\partial^2\phi_m}{\partial y^2}\right) + \theta_l^2\alpha_l \frac{\partial^2\phi_m}{\partial z^2}\right]\frac{1}{r}\,\mathrm{d}v \tag{23}$$

$$\phi_e = \frac{1}{4\pi\sigma K}\int\left\{\theta_t^2\alpha_t\left[\frac{\partial\phi_m}{\partial x}\frac{\partial}{\partial x}\left(\frac{1}{r}\right) + \frac{\partial\phi_m}{\partial y}\frac{\partial}{\partial y}\left(\frac{1}{r}\right)\right] + \theta_l^2\alpha_l \frac{\partial\phi_m}{\partial z}\frac{\partial}{\partial z}\left(\frac{1}{r}\right)\right\}\mathrm{d}v \tag{24}$$

where the z axis is taken to coincide with the longitudinal axes of the fibers.

The parameter α still poses a problem since its value depends on the resistivities. If $\rho_i >> \rho_e$ then α will approach unity. Alternatively, if $\alpha_t = \alpha_l$ then α can be taken outside the equation, where it will effectively modify the constant K. A two-dimensional version of Eq. 23 with $\alpha_t = \alpha_l = 1$ was used by Spach *et al.* (22) in studies of a tissue bath preparation.

Note that for $\rho_i >> \rho_e$,

$$\rho_{it}\theta_t^2 \simeq \rho_{il}\theta_l^2 \tag{25}$$

The data of Clerc (4) provide some experimental justification for the validity of this approximation.

In the situation where extracellular space is anisotropic but $\alpha_t = \alpha_l$, then Eq. 12 is still valid and **J** will be zero until breakthrough occurs (14). Conversely, if this condition does not hold, **J** will not be zero prior to breakthrough, and electric and magnetic fields may be expected to exist outside the source region.

Equations 23 and 24 are derived for an unbounded uniform volume conductor. If the conductor is bounded, and if there are internal inhomogeneities, then the appropriate boundary value problem must be solved to obtain the potential. Because of linearity, the potential at any point is the superposition of the contributions of the individual source elements. Let the weighting function for the scalar source be Z. Then

$$\phi_e = \frac{1}{K} \int Z \left[\alpha_t \theta_t^2 \left(\frac{\partial^2 \phi_m}{\partial x^2} + \frac{\partial^2 \phi_m}{\partial y^2} \right) + \alpha_l \theta_l^2 \frac{\partial^2 \phi_m}{\partial z^2} \right] dv \tag{26}$$

$$\phi_e = -\frac{1}{K} \int \left[\alpha_t \theta_t^2 \left(\frac{\partial \phi_m}{\partial x} \frac{\partial Z}{\partial x} + \frac{\partial \phi_m}{\partial y} \frac{\partial Z}{\partial y} \right) + \alpha_l \theta_l^2 \frac{\partial \phi_m}{\partial z} \frac{\partial Z}{\partial z} \right] dv \tag{27}$$

where $-\nabla Z$ is the transfer impedance. Note that Z and ∇Z are functions of both the source location and the observation point. In Eq. 19 $\mathbf{Z}_T$ has been used to indicate the transfer impedance for observation points on the surface of the bounded volume conductor.

INVERSE PROBLEM

Equation 16 gives the expression for the potential outside the heart. This expression is of the form of a double layer on the surface of the heart. When considering ventricular activity, it would appear reasonable to represent the ventricles such that the endocardial surface is continuous with the epicardial surface, forming a closed surface that encloses the ventricular myocardium.

If we can treat $\mathbf{S}_H$ as a closed surface, then the double layer, and hence ϕ_m, is uniquely determined on this surface to within a constant (see Appendix B). Note that the sources inside the myocardium are not determined uniquely. Furthermore, it does not follow that a solution for ϕ_m can be found which is well behaved in the presence of noise. One might expect from the geometry, i.e., the arrangement of the endocardial surface relative to the epicardial surface, that there might be severe practical difficulties. Nonetheless, the solution appears to be unique for a given surface, $\mathbf{S}_H$.

The magnetic field also depends on ϕ_m on $\mathbf{S}_H$ (see Eq. 18). Hence, it appears that, ideally, the magnetic field can be determined from the electrocardiogram, provided the shape of the heart is known (17). In the case of injury to heart muscle, however, $\mathbf{S}_H$ is no longer the only surface where $\nabla \cdot \sigma_i \nabla \phi_m$ is discontinuous. For example, in a necrotic region the cells are electrically inactive. Therefore, the boundary of this region is an internal surface that must be considered in calculating the integrals of Eqs. 16 and 18 and "breakthrough" occurs when activation reaches this boundary. The inverse solution on $\mathbf{S}_H$ is no longer unique.

Injured cells generally have a resting potential different from normal cells. Therefore, it appears reasonable to model $\nabla \phi_m$ as discontinuous across the boundary separating normal cells from injured cells during parts of the cardiac cycle (13). If such a discontinuity is present, then additional terms would appear in the equation for V or H involving $\delta \phi_m$ on all surfaces where ϕ_m changed abruptly by $\delta \phi_m$.

Either necrosis or injury gives rise to sources in addition to the double layer on $\mathbf{S}_H$. Hence this double layer is no longer unique, and the above argument relating the magnetocardiogram to the surface electrocardiogram collapses.

DISCUSSION

Schmitt (20) introduced the concept of "interpenetrating domains" based on a consideration of the electrical properties of a region containing many cells. He proposed that each point in the muscle be represented by an intracellular resistivity "representing cytoplasmic impedance of a neighborhood of like cells on a volume normalized basis," and by a similar extracellular resistivity. The two would be connected at each point by a distributed nonlinear admittivity simulating active cell membrane.

If the current voltage relations of the membrane are incorporated in the model, then the model would, in principle, predict intracellular and extracellular currents and intracellular, extracellular, and transmembrane potentials. Apparently this approach has yet to be implemented in three dimensions. Instead, we have chosen to incorporate into the model a best estimate of the spatial and temporal distribution of transmembrane potential, i.e., cellular action potentials. The resulting model is, of course, a much simpler one.

The equations of the bidomain model are a three-dimensional version of the cable equations. Spach and co-workers approached the heart model from the standpoint of cable theory. The two approaches lead to mathematically equivalent expressions relating extracellular potentials to the transmembrane potential. The source term can be represented alternatively as being proportional to $\nabla\phi_m$ (a vector) or to $\nabla \cdot \nabla\phi_m$ (a scalar). Numerical considerations may indicate which approach is more feasible to implement.

Currents, potentials, and conductivities appearing in the model may be considered averages over a region containing several cells. Clearly, potentials of interest vary over distances greater than the dimensions of a single cell during ventricular repolarization when gradients of potentials are distributed throughout the heart. Intracellular potentials vary over much shorter distances during activation, however, and spatial extent of these distributions should be considered in more detail. The width of the activation region can be estimated assuming a conduction velocity of 48 cm/sec along the fiber axis and 16 cm/sec normal to the axis, and an upstroke rise time of approximately 2 msec (4). This results in estimated wave widths of 960 μm and 320 μm, respectively, which are greater than the corresponding dimensions of a typical myocardial cell (on the order of 100 μm in length and 15 μm in diameter).

In principle, the model could incorporate time-varying conductivities. Data currently available indicate that although some variation does occur during a cardiac cycle, to a reasonable approximation the assumption of constant values for σ_i and σ_e may be valid (2,4,11). In addition to possible conductivity changes during each cardiac cycle, it is also necessary to consider changes in σ_i and σ_e that may occur over longer periods of time. Changes in the extracellular potentials measured during pathologic cardiac states can occur both through changes in the spatial distribution of intracellular potentials (i.e., changes in activation

sequence or cellular action potential shapes) and through changes in the bulk intracellular conductivity, resulting, for example, from changes in cell shape or changes in resistive cell-to-cell connections. In accordance with this view, Lepeschkin (11) has suggested that an increase in bulk intracellular conductivity corresponding to cell swelling is a major factor leading to the large extracellular potentials often observed during myocardial hypertrophy. Through such increases in bulk intracellular conductivity, extracellular potentials could increase significantly, independent of increases in the total muscle volume or the instantaneous area of the activation wave front. Similarly, the experimental studies of Holland and Arnsdorf (10) indicate the influence of decreases in bulk intracellular conductivity, related to cell dissociation, on the evolution of the ST segment deviations in chronic myocardial ischemia. Changes in bulk intracellular conductivity during certain pathologic cardiac states may thus play an important role in the generation of extracellular potentials, and further studies in this area should contribute to the understanding of the "abnormal" electrocardiogram.

The basic structure of the bidomain model readily incorporates both intracellular and extracellular anisotropy. When anisotropy is included, however, solutions of the equations become a much more formidable task. In their simulation of the electrocardiogram and magnetocardiogram, Geselowitz and Miller assumed that the torso was a homogeneous isotropic bounded volume conductor. In their simulation of a tissue bath preparation, Spach and co-workers assumed that intracellular space was anisotropic, but that extracellular space was homogeneous, isotropic, and unbounded; good agreement could not be obtained with isotropic intracellular conductivities. In all these cases simulated potentials agreed well with those measured experimentally.

Appendix A provides a clue as to why ignoring extracellular anisotropy might be reasonable for the body surface electrocardiogram (16). Equation 24 provides an indication of why intracellular anisotropy may not be an important consideration either. The anisotropy in the source term appears as an anisotropy in α and in conduction velocity. The velocity of propagation in the ventricles is, to a good approximation, uniform. Hence $\theta_t \simeq \theta_l$ which is equivalent to considering intracellular space to be isotropic provided the effect of α is not important. The condition of uniform conduction velocity is probably not valid in the case of ectopic beats or hypertropby. Hence, in these cases intracellular anisotropy may be an important factor in explaining the observed electrocardiogram.

In a tissue bath preparation, intracellular anisotropy cannot be neglected. Spach *et al.* (22) compared experimental potentials with those calculated from Eq. 23, which assumes extracellular conductivity is isotropic. In a computer model study Geselowitz and co-workers (8) incorporated extracellular anisotropy. They showed that Eq. 23 was a reasonable approximation because of the low conductivity of the perfusate. Incorporation of extracellular anisotropy explained some of the discrepancies observed in the earlier study.

SUMMARY

The myocardium can be viewed as a three-dimensional array of electrically interconnected cells intermeshed with an interstitial conducting medium. Pathways for currents exist in the intracellular network through contacts between adjacent cells, in the extracellular network around cells, and through the cell membranes from one network to the other. The mathematical description of these currents forms the basis of the bidomain model in which each domain is viewed as a syncytium.

The model predicts that the source of the extracellular potential is a volume distribution of current dipole moment equal to $-\sigma_i \nabla \phi_m$. Intracellular anisotropy cannot be ignored for potentials in or near the heart; the tensor nature of σ must then be considered. From the observed cable-like properties of cardiac muscle, one can replace the tensor σ_i by a tensor $\alpha\theta^2$, where α depends on the ratio of extracellular to intracellular resistivity. If α is close to unity, then the anisotropy enters in terms of the conduction velocity, θ. Spach and co-workers have shown good agreement between calculated and measured potentials in a tissue bath preparation with consideration of the variation of θ with direction.

Calculated electrocardiograms and magnetocardiograms for the normal heart as well as for simulated ischemia and infarction, assuming both extracellular and intracellular space to be isotropic, agree well with recordings obtained on human subjects. Arguments are presented to show why it is plausible to ignore anisotropy in this case.

The fact that the sources are proportional to the gradient of a scalar has certain mathematical consequences. For example, the volume distribution of current source moment can be replaced by a source distribution on the heart surface. In the case of injury, however, boundaries of necrotic regions, or where there is a discontinuity in resting potential, must also be considered, thus substantially reducing any possible simplifications arising from considering the heart surfaces rather than the volume of the myocardium.

APPENDIX A

Consider an anisotropic-conducting sphere of radius, R, immersed in a conducting medium of conductivity, σ_0. Let the conductivity of the sphere be σ_x, σ_y, σ_z parallel to the x, y, and z axes, respectively. We are interested in determining the potential, V, at a point outside the sphere arising from a current dipole of moment $\mathbf{P}$ within the sphere.

Let the center of the anisotropic sphere be the origin of the coordinate system and (r, θ, ϕ) be the spherical coordinates of the observation point. From considerations of linearity,

$$V = \mathbf{P} \cdot \mathbf{Z}_T \ , \tag{A-1}$$

where $\mathbf{Z}_T$ is the transfer coefficient relating the potential to the source dipole moment and where the potential at very large distances from the sphere has been taken to be zero. From reciprocity or lead field theory (12,16), $\mathbf{Z}_T$ is equal to the electric field at the point in the sphere where the dipole is located that results from a unit current injected at the observation point (r, θ, ϕ).

For simplicity we will consider the case where $r >> R$. Consider, for a moment, that all space is filled with a conductor of conductivity, σ_0, and that unit current is injected at (r, θ, ϕ). Then the electric field, $\mathbf{E}_0$, in the region $r \leq R$ is approximately uniform, and given by

$$\mathbf{E}_0 = -\frac{1}{4\pi\sigma_0 r^2}\frac{\mathbf{r}}{r} = -E_0\frac{\mathbf{r}}{r} \tag{A-2}$$

where $\mathbf{r}$ is the radius vector from the origin to the observation point.

We seek the electric field, $\mathbf{E}$, inside the anisotropic sphere. The problem is the classical one of a sphere immersed in a uniform field, except that the sphere is anisotropic. The result is

$$\mathbf{E} = \frac{3}{4\pi r^2}\left[\mathbf{i}\frac{\sin\theta\cos\phi}{\sigma_x+2\sigma_o} + \mathbf{j}\frac{\sin\theta\sin\phi}{\sigma_y+2\sigma_o} + \mathbf{k}\frac{\cos\theta}{\sigma_Z+2\sigma_o)}\right]. \tag{A-3}$$

From reciprocity, $\mathbf{E}$ is equal to $\mathbf{Z}_T$. Therefore, from Eq. A-1,

$$V = \frac{3}{4\pi r^2}\left[\frac{P_x\sin\theta\cos\phi}{\sigma_x+2\sigma_0} + \frac{P_y\sin\theta\sin\phi}{\sigma_y+2\sigma_0} + \frac{P_z\cos\theta}{\sigma_y+2\sigma_0}\right]. \tag{A-4}$$

Equation A-4 is just the form of the potential of a current dipole except that each component of the dipole has a different weighting. Note that the lead field is uniform inside the sphere. Therefore, Eq. A-4 is valid for any source dipole location within the sphere.

Let us consider that the sphere represents a region of myocardium where the z axis corresponds to the fiber axis. Then $\sigma_x = \sigma_y = \sigma_t$ represents the conductivity perpendicular to the fiber axis (transverse direction), while $\sigma_z = \sigma_l$ represents the conductivity along the fiber axis (longitudinal direction). We can define an effective dipole moment, $\hat{\mathbf{P}}$, such that

$$V = \frac{1}{4\pi\sigma_0 r^2}(\hat{\mathbf{P}}_x\sin\theta\cos\phi + \hat{\mathbf{P}}_y\sin\theta\sin\phi + \hat{\mathbf{P}}_z\cos\theta) \tag{A-5}$$

It then follows that

$$\frac{\hat{\mathbf{P}}_z}{\hat{\mathbf{P}}_x} = \frac{\hat{\mathbf{P}}_z}{\hat{\mathbf{P}}_y} = \frac{\sigma_t+2\sigma_0}{\sigma_l+2\sigma_0}\frac{\hat{\mathbf{P}}_z}{\hat{\mathbf{P}}_x} \tag{A-6}$$

Since $\sigma_l > \sigma_t$ the anisotropy will tend to enhance dipoles oriented in the transverse direction with respect to dipoles oriented in the longitudinal direction. Alternatively we can consider that the dipole is immersed in a homogeneous conductor with an effective conductivity σ_0. Then

$$\hat{\sigma}_t = \frac{\sigma_t + 2\sigma_0}{3} \tag{A-7}$$

$$\hat{\sigma}_l = \frac{\sigma_l + 2\sigma_0}{3} \tag{A-8}$$

for transverse and longitudinal dipoles, respectively.

Data for tissue conductivity in the literature are not consistent. If we take the resistivity values reported by Rush et al. (18), then $\rho_t = 563$ ohm cm, $\rho_l = 252$ ohm cm, $\rho_o = 463$ ohm cm. Using these data we obtain $\hat{\mathbf{P}}_l/\hat{\mathbf{P}}_t = 0.74\,\mathbf{P}_l/\mathbf{P}_t$ from Eq. A-6.

The above analysis does not attempt to consider the geometry of the heart or the pattern of fiber orientation, which varies from region to region. Nonetheless it should provide insight into the effect of anisotropy of the cardiac muscle on external fields such as would exist at the skin. It would be much less useful for analyzing the effect on potentials at epicardial or myocardial plunge electrodes.

If we accept the value 0.74 as a reasonable result, then it is possible to conclude that ignoring the anisotropy may not seriously distort calculations of skin potentials, given the other uncertainties in attempts to model the electrocardiogram. For example, the result can be interpreted to indicate that the effective moments of transverse and longitudinal dipoles differ by only 15% from a mean effective value. Furthermore, the variation of fiber direction in the heart may be expected to bring the effective values closer together.

APPENDIX B

Consider that on a closed surface, $\mathbf{S}_H$, there are two nonuniform double layer distributions, μ_1 and μ_2, each of which produces an identical potential distribution outside the double layer. Consider a double layer $\mu_1 - \mu_2$ on $\mathbf{S}_H$. The potential everywhere outside the double layer $\mu_1 - \mu_2$ is zero, and there are no sources inside the double layer. The double layer introduces a discontinuity in the normal derivative of the potential. Since the potential is everywhere zero outside the double layer, its normal derivative vanishes just outside the double layer. The double layer $\mu_1 - \mu_2$ introduces no discontinuity in the normal derivative. Hence, it must be zero just inside the double layer. From the uniqueness theorem, the potential everywhere inside the closed surface is therefore a

constant. Hence, at every point on the closed surface there is a constant discontinuity in potential. This discontinuity of constant amplitude must be associated with a uniform double layer. Hence μ_1 and μ_2 differ by a constant, and hence ϕ_m on S_H is unique to within a constant.

NOMENCLATURE

a	=	radius of cardiac fibers
C_m	=	membrane capacitance per unit area
$\mathbf{E}$	=	electric field
$\mathbf{H}$	=	magnetic field
$\mathbf{J}$	=	current density
$\mathbf{J}^i$	=	impressed current density
K	=	constant from cable theory. See Eqs. (20) and (21)
$\mathbf{P}$	=	current dipole moment
S_H, S_o	=	surface of heart and body, respectively
v	=	volume fraction of cardiac fibers
V	=	electric potential on body surface, or in volume conductor (Appendix A)
Z	=	transfer coefficient relating potential to scalar current source
$\mathbf{Z}_T$	=	transfer coefficient relating potential to source current dipole moment.
α	=	parameter defined in Eq. (22)
δ	=	Dirac delta (impulse) function
θ_l, θ_t	=	velocity of propagation of action potential in longitudinal, transverse directions
μ	=	moment of double layer
ρ_i, ρ_e, ρ	=	resistivity of intracellular, interstitial space, bulk resistivity. Additional subscripts l,t denote parallel or transverse to fiber axis.
σ_i, σ_e, σ	=	conductivity of intracellular, interstitial space, bulk conductivity. Additional subscripts l,t denote parallel or transverse to fiber axis.
τ_f	=	time constant of foot of action potential
ϕ_i, ϕ_e, ϕ	=	electric potential in intracellular, extracellular space, volume conductor
ϕ_m	=	transmembrane potential

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