Cardiac tissue has long been considered to be an electrically anisotropic syncytium, with equal density of myocyte coupling in all directions transverse to the myofiber. Electrical conductivity is thought to be greatest along the myocyte axis allowing most rapid propagation of electrical activation in this direction, and that conductivity is isotropic transverse to the myocyte axis supporting a slower uniform spread of activation in this plane. In this context, knowledge of conductivity in two directions, parallel and transverse to the myofiber axis, is sufficient to characterize the electrical action of the heart. Here we present new experimental data that challenge this view. We have used a novel combination of intramural electrical mapping, and experiment-specific computer modeling, to demonstrate that left ventricular myocardium has unique bulk conductivities associated with three microstructurally-defined axes. We show that voltage fields induced by intramural current injection are influenced by not only myofiber direction, but also the transmural arrangement of muscle layers or myolaminae. Computer models of these experiments, in which measured 3D tissue structure was reconstructed in-silico, best matched recorded voltages with conductivities in the myofiber direction, and parallel and normal to myolaminae, set in the ratio 4:2:1, respectively. These findings redefine cardiac tissue as an electrically orthotropic substrate and enhance our understanding of how external shocks may act to successfully reset the fibrillating heart into a uniform electrical state. More generally, the mechanisms governing the destabilization of coordinated electrical propagation into ventricular arrhythmia need to be evaluated in the light of this discovery. (Circ Res. 2007;101:e103-e112.)

Key Words: conductivity \( \text{■} \) electrical mapping \( \text{■} \) ventricular microstructure \( \text{■} \) computer modeling

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travel in that direction. A subsequent computer modeling study incorporated detailed measurements of ventricular microstructure and investigated the likely role that laminar discontinuities in myocyte coupling have in facilitating the synchronous resetting of myocardium during application of defibrillating shock. This study predicted three unique (orthotropic) electrical conductivities defined, at any point in the myocardium, by local myofiber and myolamina orientations. However, in the absence of supportive experimental evidence, the postulated role of myolaminae in modulation of electrical conductivity has remained controversial. In this study, we used a novel combination of intramural electrical mapping, and experiment-specific computer modeling, to test this prediction. Specifically, we hypothesized that ventricular myocardium has unique bulk conductivities associated with three microstructurally-defined axes, oriented at any location (1) along myofibers, (2) transverse to myofibers but in the plane of myolaminae, and (3) normal to myolaminae. Conductivity was expected to be of greatest, intermediate, and lowest magnitude in these three directions, respectively.

Materials and Methods

Voltage Recording

To address the hypothesis, tissue conductivities were estimated in three-dimensions (3D) by mapping the voltage field generated by focal intramural current injection. Six pigs (54.6±7 kg; Animal Resource Unit, Auckland University, New Zealand) underwent midline sternotomy and lateral thoracotomy under halothane anesthesia to allow placement of a quasi-3D array of plunge electrodes (described in detail previously) into the anterior left ventricular (LV) freewall, in the region of watershed between the circumflex and left anterior descending artery supply territories (Figure 1A). All animal procedures were approved by the Auckland Animal Ethics Committee. Arterial pressure, heart rate, and reflex monitoring was used to assess depth of anesthesia. Expiratory CO2 content and blood gases were analyzed to maintain the animal within normal physiological limits. A water-heated pad preserved normal body temperature. A pericardial sling was created to stabilize the heart, and the electrode array platform sutured flush to the epicardium with eight 6.0 silk sutures. Regular application of saline across the epicardium kept the heart surface moist.

The electrode array was used to sample at 137 sites the extracellular voltage field generated during focal current application. Steady-state voltages were recorded on intersecting longitudinal-transmural (y-z) and circumferential-transmural (x-z) planes (Figure 1A) 1 ms after onset of a square current pulse of 2-ms duration.
(Figure 1B), supplied from a cathodal electrode located at various transmural depths along the intersection of the 2 recording planes. A typical map of the induced potential field is shown in Figure 1C. For each experiment, recordings were made with current applied at ~10 different transmural sites, giving a total of 61 voltage fields across 6 hearts. Voltages recorded at electrodes within the array were referred to an indifferent electrode placed within the chest cavity, and were sampled at 5 kHz with a bandwidth of 0.01 to 2000 Hz. Current pulses were of magnitude 0.01 to 0.05 mA, being ~1.5× the threshold for capture of the ventricles, and were applied between the cathode and an anode located >30 cm distant, on the chest wall. Use of supra-threshold stimuli ensured that induced potentials were not obscured by sinus rhythm ventricular activity. Recordings were averaged over 10 to 20 consecutive pulses and maps of the induced voltage field constructed from the discretely sampled data using Kriging interpolation of distance multiplied voltages. The exact locations within the chest cavity of the recording indifferent electrode and the anode involved in current application did not affect the induced voltage field.

**Tissue Processing**

After completion of recordings, hearts were arrested with potassium citrate, excited, and the coronary arteries flushed with saline and 2-3-BDM (50 mmol/L) to delay onset of contracture. Plunge electrodes were replaced with 0.5-mm diameter styrene rods, and hearts were imaged with 4.5T MRI to quantify LV surface geometry and rod locations in 3D. Reconstructed rod locations were used in one experiment to correct voltage maps for imperfect parallel placement of the electrodes, but this was not necessary otherwise. After MRI, hearts were perfusion fixed with 3% formalin in phosphate buffer. A segment of tissue encompassing the recording array region was then excised, and frozen rapidly in a cryostat cooled to ~30°C. The architecture of myofibers and myolaminae throughout this tissue block was then reconstructed by cutting frozen sections on orthogonal planes (Figure 1D) as described in detail previously. In brief, automated detection of the intersection angles of myofibers and myolaminae with these planes was used to reconstruct the spatial fields of these microstructural components, throughout the tissue segment (Figure 1D). This method of reconstruction allowed for spatial variation of myofiber angle in the transmural direction, whereas lamina orientations could vary in both longitudinal and transmural directions. An intensity-gradient algorithm was used for angle detection. Left ventricular wall thickness within the region of the electrode array was 17.5±1.9 mm. Time elapsed from excision of the heart from the animal to fixation was in all cases <2 hours. A further 30 minutes was allowed between perfusion of fixative and tissue freezing to ensure complete fixation.

**Computer Modeling**

To relate the voltage maps recorded experimentally to the underlying tissue microstructure, each voltage field was simulated by solving a Poisson equation on the reconstructed tissue architectures, where \( \phi \) is the voltage field, \( I_{app} \) the applied stimulus current, and \( G \) is a conductivity tensor of the form:

\[
G = [a_f, a_i, a_n] \begin{bmatrix}
g_f & 0 & 0 \\
0 & g_i & 0 \\
0 & 0 & g_n
\end{bmatrix} \begin{bmatrix}
a'_f \\
a'_i \\
a'_n
\end{bmatrix}
\]

where the column vectors \( a_f, a_i, \) and \( a_n \) are 3 orthogonal unit vectors such that \( a_i \) is everywhere aligned parallel to local myofiber direction, \( a_f \) is transverse to myofibers but in the plane of myocyte laminae, and \( a_n \) is normal to these laminae. Equation 1 models current flux in the absence of any active cellular membrane response. The active response, at 1 ms following onset of the stimulus pulse, is expected to be confined to tissue immediately adjacent to the cathode and should not significantly perturb the extracellular voltage field at recording electrodes.

Current matching that used in the experiment (\( I_{app} \)) was extracted at the location of the cathode and current of equal total magnitude, but opposite sign, was distributed equitably between all the model boundaries except for the epicardium, on which no-flux condition was set, to replicate the experimental situation. To allow for the cubic geometry of the model boundaries, the current magnitude supplied along each boundary varied according to \( (1) \) the distance from the cathode and \( (2) \) the angle between the boundary normal and a local vector connecting the cathode point to the boundary location. In this way, current was constrained to enter the model volume in a radially uniform fashion. This approach is justified by the large distance between cathode and anode during experimentation compared with the dimensions of the model. The model domain extended the full transmural thickness of the tissue, and beyond the boundary of the electrode array in the circumferential (\( x \)) and longitudinal (\( y \)) directions by ~10 mm. This volume was discretised to a resolution of 0.25 mm, giving ~5 million degrees of freedom for each of the 61 simulations. Domain sizes and resolutions were selected after extensive model convergence testing. Fitting of the model to the experimentally recorded voltages used sequential 1-dimensional line (bisection method) minimizations, along the axes (\( g_i,0,0 \), (0,\( g_i,0 \), and (0,0,\( g_n \)), of the relative RMS difference function (objective function; \( e \)):

\[
e = \sqrt{\sum_{i=1}^{137} (\theta_{i_{exp}} - \theta_{i_{mod}})^2} \sum_{i=1}^{137} (\theta_{i_{exp}})^2
\]

where \( i \) indexes the set of 137 electrodes, \( \theta_{i_{exp}} \) is the \( i \)th experimentally recorded voltage, and \( \theta_{i_{mod}} \) the model voltage at the same location. The simulations were parallelized over 18 threads of an IBM Regatta (1.9 GHz processors). On average 130 solves of the model and a total of 196 minutes of CPU wall time were required to reach each objective function minimum. Given the 61 sites of stimulation, the minimum computational overhead of the study was therefore ~9 days.

Testing for statistical significance was performed with Bonferonni protected 2-tailed, paired Student \( t \) tests. All data are reported as mean±SD.
Results

Model Construction

Tissue sections used in construction of the computer model for 1 heart are shown in Figure 2. The single section taken in the longitudinal-transmural (y-z) plane is shown at upper-left. To the right are 3 (from a total of 30) representative circumferential-transmural (x-z) plane slices, registered to the y-z section at 3 y locations. Beneath are 5 (from a total of 28) epicardial (x-y) plane sections showing fiber angle orientations at different transmural depths in the tissue. Microstructural angles were measured from sections in each of these 3 planes. Angles measured in the epicardial plane slices indicated a smooth rotation of myofiber orientation through the ventricular wall. Angles measured on the y-z slice are termed $\alpha$, those measured on the x-z plane slices $\beta'$, and those on the y-z plane slices $\beta''$.

The measured angles $\alpha$, $\beta'$ and $\beta''$ were combined mathematically\cite{18} to form the basis of the structural model. Figure 3 shows complete sets of $\beta'$ and $\beta''$ angles for the same tissue block as in Figure 2. Myolamina orientation was usually difficult to discern from longitudinal-transmural and circumferential-transmural sections immediately adjacent to the epicardium and endocardium, where coupling of adjacent laminae is known to be tightest\cite{26}. In these areas, and where blood vessels obscured the laminar structure, the automatically computed microstructural angle was computed for all epicardial plane sections. Following notation used previously\cite{16,18} the microstructural angles measured on epicardial plane sections are termed $\alpha$, those measured on the y-z slice are termed $\beta'$, and those on the x-z plane slices $\beta''$.

The set (30×30 elements) of $\beta'$ angles shown in the left panel of Figure 3A are derived directly from the y-z plane image shown in Figure 2 (upper-left panel). The corresponding set of $\beta''$ angles (Figure 3A; right panel) consists of 30 rows each of which is derived from a single x-z plane tissue section, along its edge
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abuting the y-z plane section. Each of the 900 model elements therefore had unique $\beta'$ and $\beta''$ angles which were combined with the local myofiber angle to determine the 3-dimensional lamina angle $\beta$, as previously defined. In this heart myofibers rotated in near-linear fashion throughout the extent of the electrode array, from approximately $-50^\circ$ at the epicardium, to $+90^\circ$ at the endocardium (Figure 3B). Lamina angles ($\beta$) were predominantly negative, however reversed in orientation toward the endocardium (Figure 3B).

In some areas of the ventricular wall, there were 2 distinct populations of laminae. Typically, this took the form of a dominant lamina population with interspersed small “pockets” of laminae approximately perpendicular to the principal alignment. Examples of such pockets of nondominant lamina angle can be seen in the tissue sections of Figure 2 (see region around the lower edge of the red y-z plane inset, and also the upper-right region of the upper-most x-z plane section). The level of structural discretization in the model (ie, 900 discrete myolamina angles) was chosen to capture the abrupt transitions between dominant and nondominant lamina populations. Observation of the inset (lower-right panel) of Figure 2 demonstrates that this was achieved effectively.

Reference to the tissue geometry at time of MRI revealed that the tissue blocks shrank on average 7±6% along the y axis, during processing. Correction for this shrinkage was applied in isotropic fashion throughout the tissue volume during model construction.

Model-Based Analysis of Voltage Recordings

Voltage fields recorded in all experiments confirm that bulk conductivity is greatest along the local myocyte axis, as voltage gradients were consistently least in this direction. However, the fields were not consistent with the notion that conductivity is uniform or isotropic transverse to the myofiber direction, in that voltage maps in either of the y-z or x-z planes were not symmetric across the z axis (Figure 1A), which is oriented normal to myofibers at all points.

Representative voltage maps for a midwall site of current application in the same heart as that used in Figures 2 and 3, are presented in Figure 4. The voltage field experimentally recorded on y-z and x-z planes is shown (column A), along with the simulated voltage field (column B) that used the $g_\alpha$, $g_\beta$, and $g_\gamma$ condition of electrical orthotropy. Figure 4C demonstrates that this was achieved effectively.

Figure 3. Model description of tissue block. A, Left panel: Lamina angles ($\beta'$) computed for the longitudinal-transmural (y-z) section shown in Figure 2 upper-left, on a 30×30 grid. Right panel: Lamina angles ($\beta''$) computed from serial circumferential-transmural (x-z) plane sections, mapped to the same y-z plane as in the left panel. Each row of angles is derived from a single x-z plane tissue section, along its edge that abuts the y-z plane section. Missing angles in the grids of both $\beta'$ and $\beta''$ panels represent areas of indeterminate lamina angle. B, Graph of the full model description including the transmural dependence of myofibre angle ($\alpha$; line), from epicardium (epi) to endocardium (endo), and transmural distribution of lamina angles ($\beta$; dots) as derived from mathematical combination of the $\beta'$, $\beta''$, and $\alpha$ fields. This description of microstructure forms the framework on which the model of current flux is solved. The extent of the electrode array is shown by the red boxes.
to best match the model to experiment for this current application site. The objective function is plotted along 3 axes, each with origin at the function minimum, and with orientations of \((g_f,0,0)\), \((0,g_l,0)\), and \((0,0,g_n)\). The minimum relative RMS difference between model and experiment was 0.124. Data from all 10 sites of current application used in this heart are shown in Figure 5. For each site, the experimentally recorded voltage field, the corresponding fitted simulated field, a plot of the objective function, and the optimal set of conductivities \(g_f\), \(g_l\), and \(g_n\) are given. Anisotropy of the experimental fields was in all cases well matched by the optimized models, and in this heart orthotropic conductivities were fitted for all sites of current application.

Optimized conductivity sets were similarly obtained for the 61 sites of current application, across 6 hearts. Statistically distinct mean values for \(g_f\), \(g_l\), and \(g_n\) (S/m) were obtained (Figure 6) in the approximate ratio 4:2:1 \((g_f=0.70, g_l=0.35, g_n=0.16)\), demonstrating that as a whole, the hearts could be considered as electrically orthotropic. In all cases the objective function had a well defined single minimum similar to those shown in Figures 4C and Figure 5. Analysis of individual sites of current application (Figure 6B,C) revealed...
that the 2 component conditions for orthotropy, namely $g_l > g_i$ and $g_n > g_e$, were satisfied for 61 and 56 of the 61 application sites, respectively. The minimum relative RMS difference between model and experimental potential fields averaged across all sites of current application was 0.146±0.035.

**Discussion**

This study provides the first experimental evidence that the laminar arrangement of ventricular myocytes influences the electrical behavior of the heart. We have demonstrated that ventricular myocardium has at any location 3 unique bulk conductivities, of relative magnitude \( \approx 4:2:1 \), oriented (1) along myofibers, (2) transverse to myofibers but in the plane of myolaminae, and (3) normal to myolaminae. This is a fundamental discovery which has broad impact across many areas of cardiac study, including the fields of defibrillation and arrhythmia research.

**Analysis of Bulk Conductivity Estimates**

It is interesting to compare our estimates of bulk conductivity to classical studies which estimated electrical conductance in both the intracellular and extracellular spaces of myocardium, in the directions parallel and perpendicular to myofiber orientation.\(^1\) Bulk conductivities, as measured in this study, closely approximate the parallel combination (sum) of intracellular and extracellular conductivities.\(^2\) Our overall estimate of $g_f$ (0.70 S/m) is in excellent agreement with the value of 0.79 S/m, derived from the sum of intra- and extracellular conductances obtained from bovine hearts in the landmark study of Clerc.\(^1\) Previous estimates of conductivity “transverse” to myofibers ($g_e$)\(^1\) were taken without knowledge of the laminar structure of myocardium, and therefore the relationship of the transverse axes used in these studies, to the laminae of myolaminae, and the possible contributions of intracellular and extracellular conductivities to this. Intracellular conductivities transverse to the myofibers have been estimated using a bidomain model simulation of the spread of electrical activation through a 3D segment of rat LV myocardium, in which the laminar arrangement of myocytes had been reconstructed with high spatial resolution.\(^2\) It was found that intracellular current flowing normal to myolaminae was redirected at cleavage planes because of the absence of side-to-side connections between myocytes at the interface between muscle layers. These planes, which define the laminar cellular organization,\(^1\) lengthen the path traversed by the lamina-normal component of intracellular current, and consequently reduce conductivity in this direction. The predicted intracellular conductivity ratio in the lamina versus lamina-normal directions was around 3:1 (0.0263 versus \( \approx 0.008 \) S/m).\(^2\)

Although this detailed model exhibits structure-based electrical orthotropy, the magnitudes of the intracellular conductivities above are too small to fully explain the difference in transverse bulk conductivities reported here. Under the assumption of an extracellular space with uniform conductivity (0.109 S/m)\(^2\) in all directions transverse to the myofiber (so called “transverse isotropy”), the model predicts the ratio of bulk conductivities $g_f: g_e$ to be 1.16:1, which under-estimates the mean ratio observed in this study (\( \approx 2:1 \)). The rat model result is sensitive to the average conductivity parameters used, and either an increase in average intracellular conductivity transverse to the myofiber or a reduction in extracellular conductivity in these directions would increase the predicted bulk conductivity ratio $g_f: g_e$. Experimental estimates of intracellular conductivity transverse to the myofiber range from 0.019 to 0.060 S/m,\(^1\) whereas corresponding estimates of transverse extracellular conductivity range from 0.080 to 0.240 S/m.\(^1\) We estimate that the bulk conductivity ratio $g_f: g_e$ predicted by the model would rise to around 1.55:1 if the parameters were matched to the experimental results above for which transverse intracellular conductivity is greatest and
transverse extracellular conductivity is least. A further increase to the predicted bulk conductivity ratio could only be achieved by introduction of transverse anisotropy to the extracellular space. On the basis of the information available, therefore, it seems probable that conductivity transverse to the myofiber direction is anisotropic in both intracellular and extracellular domains.

The notion that extracellular current can travel in the space between myocyte layers relatively unhindered in directions parallel to laminae, but not perpendicular to them, provides a plausible explanation for transverse anisotropy in the extracellular space. This is also consistent with numerous recent cardiac DTMRI findings that demonstrate preferential water diffusion transverse to the myofiber axis in a direction parallel to myolaminae. Structure-based models that simulate current flux at a cellular level by incorporating data from the literature on cytoplasmic and gap junction resistance have been used to estimate intra- and extracellular conductivities in fiber and “transverse” directions. However, these models did not include any form of laminar myocyte architecture. For more complete theoretical analyses of conductivity in LV myocardium, it is necessary to account for the 3D organization of both intracellular and extracellular spaces, with the connectedness of each domain quantified at appropriate resolution. This requires robust descriptions of (1) the spatial arrangement of myolaminae and the connections between them, and (2) the separation distances between adjacent myolaminae in vivo. Although some of this information is available for the rat heart, the structural data acquired in the present study do not have sufficient resolution to support such analysis. Alternatively, combination of the present bulk conductivity data with experimental measurements of conduction velocity may provide sufficient additional information to extract both intra- and extracellular conductivities, and work in this area is ongoing in our laboratory.

Several recent theoretical works have investigated epicardial electrode plaque designs which would allow streamlined measurement of intra- and extracellular cardiac tissue conductances in 2D, for use in clinical settings such as the monitoring of cellular hypoxia during cardiac bypass surgery, or in experimental settings such as whole heart optical mapping of VF. Importantly, although these latest works focus on elegant resolution of the intra- and extracellular conductivities, they seek to determine conductivity on myofiber and “transverse” axes alone, neglecting the effects of the laminar architecture of myocardium. On the cardiac surfaces transverse coupling of myocytes is uniform, however the effects of intramural laminar discontinuities in coupling need to be evaluated with respect to these electrode designs. It is likely that conductivities measured by the proposed arrays will be perturbed by the underlying laminar arrangement of myocytes, and this effect may contribute varying degrees of artifact to the recordings made.

Three-Dimensional Arrangement of Ventricular Myolaminae

It has been recognized that in some areas of the ventricular wall, 2 distinct lamina populations can be identified, and in general these 2 populations are oriented orthogonally to each other. These populations appear when lamina orientations from the same ventricular wall location of several hearts are pooled together. In addition, orthogonally oriented populations of laminae can exist in neighboring regions within the same tissue section. A strength of the structure-based modeling used in this study is that it incorporates the observed intramural variation of laminar orientation. The level of structural discretization in the model is sufficient to capture both the dominant and nondominant sheet populations, and the abrupt transitions between them. As a result, this structural heterogeneity is accounted for in the estimates of bulk conductivity presented here.

Similar to a previous study, measured lamina projections β’ and β’’ from any given location, when combined with local myofiber angle, were generally, but not always, self-consistent with a single lamina angle (β) at that site. Discrepancies arise partly because the tissue is not a simple (synthetic) laminate, but rather adjacent myocyte layers branch and interconnect. Structural inhomogeneity can exist within any region of measurement, to which a single microstructural angle is assigned (for example see the third-from-right angle of the bottom row of inset in Figure 2). Inconsistencies also occur because of measurement errors arising from (1) small imperfections (<0.5 mm) in spatial registration of the tissue slices, (2) minor tissue distortions introduced during tissue transfer from cryostat blade to glass slide, (3) departures (typically <5°) from orthogonality of the section orientations, and (4) occasional nonlamina features (such as blood vessels) influencing the angle detection algorithm. However, such errors are at a scale comparable to uncertainty in the 3D location of extracellular potential measurements and would not affect the findings of this study.

Implications for Defibrillation and Arrhythmogenesis

Computer simulation predicts the laminar structure of myocardium not only to provide a substrate for electrical orthotropy, but additionally to have importance in the tissue response to defibrillation strength shocks. Insofar as the present study contributes evidence for the former phenomenon, we conjecture that the case for the latter is also strengthened. Remarkably, despite massive recent growth in the clinical use of implantable defibrillation therapies, and considerable research focus on defibrillation, the mechanisms by which an electric shock uniformly resets electrical activity throughout the ventricular walls of the heart remain poorly understood. Specifically, it has been unclear whether the bulk of myocardium located deep to the cardiac surfaces escapes influence from the shock, and if so, how fibrillatory activity is abolished in this tissue. Current flowing into the heart at its boundaries is directed across the cellular membrane and alters membrane potential along the cardiac surfaces. However, it has long been unknown how shock-induced current could have influence on the majority of myocytes lying deep in the ventricular walls. It has been proposed that nonuniform electrical coupling of myocytes may provide the key to this dilemma.
cellular coupling are postulated to redirect shock-induced current across the cellular membrane, giving rise to multiple interspersed intramural islands of shock-induced polarization which assist synchronous electrical resetting throughout the bulk of the tissue.26,37–43 Such a theory is widely consistent with observations that the laminar arrangement of myocytes provides extensive planar discontinuities in myocyte coupling, throughout the ventricular wall. In this regard, the laminar architecture of ventricular myocardium offers a unifying and attractive explanation for the general success of electrical defibrillation.26,39,40 However, in the absence of experimental demonstration that the laminar structure influences the electrical function of the heart, the laminar view of myocardium and its postulated role in defibrillation has remained controversial.27 By observing that bulk conductivity remains controversial.27 By observing that bulk conductivity is diminished in the direction normal to myolaminae, we strengthen the model-based contention that current flows are modulated, or directed by the discontinuities in myocyte coupling inherent in the laminar organization of myocytes.26 In turn, this study lends weight to the hypothesis that laminar nonuniformities play an important role in facilitating defibrillation by similarly redirecting shock-induced current flows across the cellular membrane.26,39

The study of ventricular arrhythmia has recently been advanced by the development of organ-level computer models of cardiac behavior.42–44 Such models have an increasing role in aiding interpretation of the mechanisms governing arrhythmogenesis. Whether coordinated electrical propagation undergoes fragmentation into ventricular fibrillation (VF) is determined by a delicate balance of cellular-kinetic and geometrical factors.9–11,45 For example, it has been shown that action potential duration restitution is a major determinant of breakup of the reentrant “scroll waves” thought to underlie most ventricular tachycardia.10 However, it has also been shown that transmural fiber rotation induces curvature in a scroll wave which further facilitates wave break and induction of VF.9,10 The present study indicates that the nonuniform laminar architecture of myocardium, and ensuing electrical orthotropy, should be included in future computer models of cardiac arrhythmia, in addition to myofiber rotation. Whether the laminar arrangement of myocytes shifts the balance in favor of reentrant wavefront stability or instability remains to be seen. Moreover, the spatiotemporal dynamics of reentrant wavefront disintegration, amalgamation, and annihilation during VF9–11,42,45 are all expected to depend on the electrical orthotropy of ventricular tissue.

Limitations
Performing 3D electrical measurements and relating these to underlying microstructural architecture required a complex study design. Simplifications needed in the modeling methodology likely contributed to the intraexperiment scatter of estimated conductivities (Figure 6B and 6C) using different intramural sites of current application. Firstly, although the extent of coupling between adjacent myocyte layers varies through the ventricular wall, with denser coupling in the subepi- and subendocardial regions, and sparser coupling in the midwall,19,26 the models treated layers in binary fashion as either present (in regions where lamina angles could be clearly identified in tissue sections) or absent. Secondly, the techniques for reconstructing tissue micro-architecture constrained model myolamina orientation to be constant in the circumferential direction.18 Thirdly, no attempt was made to incorporate the effects of different cell types within the model. Ventricular midwall “M-cells”46 and Purkinje cells which penetrate the wall in porcine hearts47 may contribute to a regional variation in bulk conductivity which could not be elucidated in this study. Nonetheless, there was in all cases sufficiently good match between model and experiment to give confidence in the use of these simplifications. None of the limitations outlined are expected to alter the conclusions of the study.

Conclusion
In summary, this study reveals that 3 principal directions of conductivity can be defined at any point within the cardiac ventricles. This finding defines ventricular myocardium as electrically orthotropic, and dramatically changes the landscape on which cardiac electrophysiological phenomena are interpreted.

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Laminar Arrangement of Ventricular Myocytes Influences Electrical Behavior of the Heart

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