Forward Problem of Electrocardiography
Is It Solved?

Laura R. Bear, PhD; Leo K. Cheng, PhD; Ian J. LeGrice, MBChB, PhD; Gregory B. Sands, PhD; Nigel A. Lever, MD; David J. Paterson, DSc; Bruce H. Smaill, PhD

Background—The relationship between epicardial and body surface potentials defines the forward problem of electrocardiography. A robust formulation of the forward problem is instrumental to solving the inverse problem, in which epicardial potentials are computed from known body surface potentials. Here, the accuracy of different forward models has been evaluated experimentally.

Methods and Results—Body surface and epicardial potentials were recorded simultaneously in anesthetized closed-chest pigs (n=5) during sinus rhythm, and epicardial and endocardial ventricular pacing (65 records in total). Body surface potentials were simulated from epicardial recordings using experiment-specific volume conductor models constructed from magnetic resonance imaging. Results for homogeneous (isotropic electric properties) and inhomogeneous (incorporating lungs, anisotropic skeletal muscle, and subcutaneous fat) forward models were compared with measured body surface potentials. Correlation coefficients were 0.85±0.08 across all animals and activation sequences with no significant difference between homogeneous and inhomogeneous solutions (P=0.85). Despite this, there was considerable variance between simulated and measured body surface potential distributions. Differences between the body surface potential extrema predicted with homogeneous forward models were 55% to 78% greater than observed (<0.05) and attenuation of potentials adjacent to extrema were 10% to 171% greater (<0.03). The length and orientation of the vector between potential extrema were also significantly different. Inclusion of inhomogeneous electric properties in the forward model reduced, but did not eliminate these differences.

Conclusions—These results demonstrate that homogeneous volume conductor models introduce substantial spatial inaccuracies in forward problem solutions. This probably affects the precision of inverse reconstructions of cardiac potentials, in which this assumption is made. (Circ Arrhythm Electrophysiol. 2015;8:677-684. DOI: 10.1161/CIRCEP.114.001573.)

Key Words: body surface potential mapping  electrocardiography  epicardial mapping

Intracardiac mapping of endocardial potentials is widely used in clinical cardiac electrophysiology to identify sites of conduction block and potential pathways for reentrant electric activation, so that structural substrates for reentry can be ablated. However, this approach provides limited information about possible intramural activation pathways. Noninvasive imaging of cardiac electric activity from body surface measurements (the inverse problem) may aid in resolving this problem by providing further information about intramural breakthrough and epicardial exit sites. The inverse problem is inherently ill-posed, meaning small levels of noise in the model or measured potentials can result in large errors in the solution, which may bear little resemblance to the true cardiac source. Various inverse algorithms have been developed to overcome this problem.4,5 Accurate identification of the transfer matrix, which describes the body surface potentials resulting from a known cardiac source (the forward problem) is fundamental to the inverse solution.6 This raises the question: how much detail is required to produce a sufficiently accurate forward model? Previous studies have shown that it is necessary to include realistic heart and torso geometries,7–10 but the extent to which the inhomogeneous electric properties of internal structures needs to be accounted for is less clear. There is a reasonable consensus that body surface potential distributions are not significantly affected by the liver, stomach,11 blood vessels,11,12 intestines, spleen, kidney, spine, sternum, and other bones.11–13 Furthermore, although it is agreed that lungs, anisotropic skeletal muscle, and subcutaneous fat have the greatest impact on body surface potentials, the magnitude of their contributions is widely debated.11–14

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The sensitivity of forward solutions to sources of error has been investigated in several studies, but only one has allowed direct experimental validation. Ramsey et al. recorded corresponding cardiac source potentials and body surface potentials in dogs. Correlation coefficients (CCs) between measured body surface potential maps (BSPMs) and those simulated with a homogeneous forward solution were high. Despite this, they reported substantial differences between observed and predicted potential distributions in regions around maximum and minimum potentials on the body surface. Using the same data, Stanley et al. demonstrated the inclusion of inhomogeneities (lungs, sternum, spine, and anisotropic skeletal muscle) markedly reduced differences between predicted and measured BSPMs, although there was no significant difference in CCs. These findings seem to have received relatively limited attention, perhaps because the spatial and temporal resolution of the experimental data were low by modern standards. However, they indicate that (1) homogeneous forward models produce qualitatively inaccurate body surface potential simulations, and (2) CCs are a relatively insensitive measure of the correspondence between observed and measured BSPMs.

This study addresses these issues by obtaining a complete experimental data set with simultaneously recorded body surface and epicardial potentials, as well as corresponding information on torso anatomy and 3-dimensional (3D) electrode locations. Using the experimental data, we developed and analyzed a forward model by comparing simulated and recorded body surface potentials. We also developed methods to quantify the differences seen in the BSPM patterns, and finally determined the effects that anisotropic skeletal muscle, subcutaneous fat, and the lungs have on simulated potential distributions.

**Methods**

All surgical procedures were approved by the Animal Ethics Committee of the University of Auckland and conform to the Guide for the Care and Use of Laboratory Animals (National Institutes of Health publication No. 85-23). Detailed Methods are available in the Data Supplement.

A midline sternotomy was performed on 5 anesthetized pigs (30–40 kg). The heart was exposed, and supported in a pericardial cradle. A custom-made elastic sock containing 239 unipolar silver-wire electrodes (5- to 10-mm spacing) was drawn over the ventricles (Figure 1A), after which the thorax was closed and air expelled. Flexible strips (BioSemi, Amsterdam, The Netherlands) containing 184 electrodes (30- to 45-mm spacing) were attached to the body surface (Figure 1B). Epicardial and body surface potentials were bandlimited (0.05–1000 Hz) and recorded simultaneously at 2 kHz.
using separate acquisition systems (UnEmap, Auckland Uniservices Ltd, Auckland, New Zealand and ActiveTwo, BioSemi, respectively). Signals were temporally aligned by identifying the onset of a short burst of square 2-ms pulses recorded simultaneously on a single channel in both the systems. For each pig, recordings were made during (1) sinus rhythm (n=1–4), (2) pacing from left and right ventricular sites endocardially (n=4–12), and epicardially (n=4–9). Overall, 65 records were obtained. The heart was arrested and magnetic resonance imaging (MRI) of heart and thorax acquired. The heart was excised, perfusion-fixed, and epicardial electrode locations were captured with a multiaxis digitizing arm (FARO Technologies, Lake Mary, FL). MRI contrast markers placed on the sock and body surface strips were localized in the MRI and used to register electrode locations.

Instantaneous, measured epicardial potentials (\(\partial_H\)) were linearly related to body surface potentials (\(\partial_j\)) through the transfer matrix\(^1\)(A)

\[
\partial_j = A \partial_H
\]

For each study, A was constructed using a coupled finite/boundary element\(^1\) torso model customized to the MRI (Figure S1). This model incorporated descriptions of the ventricular epicardial and lung surfaces, and skeletal muscle and subcutaneous fat volumes. Computational and conductivity parameters for the volume conductor models are presented in Tables I and II in the Data Supplement.

Simulated and measured BSPMs were compared at each time instant using root-mean-squared (RMS) potential, relative RMS error (rRMSE), and CC.

\[
\text{RMS potential}_j = \frac{\sum_{i=1}^{N} (\partial'_i)^2}{N}, \quad j = M \text{ or } S
\]

\[
r\text{RMSE} = \frac{\sum_{i=1}^{N} (\partial'_i - \partial_i)^2}{\sum_{i=1}^{N} (\partial'_i)^2}
\]

\[
\text{CC} = \frac{\sum_{i=1}^{N} (\partial'_i - \mu_M)(\partial_i - \mu_S)}{\sqrt{\sum_{i=1}^{N} (\partial'_i - \mu_M)^2 \sum_{i=1}^{N} (\partial_i - \mu_S)^2}}
\]

where \(N\) is the number of body surface electrodes; \(\phi_i\), the potential at electrode \(i\); \(\mu_i\), the mean potential; and \(M\) and \(S\) are measured and simulated data.

Key BSPM features during ventricular activation (Figure 2) were quantified as follows. Maximum and minimum body surface potentials (\(\phi_{\text{max}}\) and \(\phi_{\text{min}}\), respectively) were identified and the potential difference (\(\Delta\phi\)) between them determined. The length (\(L\)) and orientation with respect to the X–Z plane (\(\theta\)) of the vector between the extrema were evaluated. Finally, average potential attenuations (\(A_{\text{max/min}}\)) adjacent to \(\phi_{\text{max}}\) and \(\phi_{\text{min}}\) were estimated from normalized body surface potentials, by computing the average potential gradients at \(N\) points within 35 mm of the extrema

\[
A_{\text{max/min}} = \frac{\sum_{i=1}^{N} \partial_i - \partial_{\text{max/min}}}{d(P, P_{\text{max/min}})}
\]

where \(\partial_i\) is the normalized potential and \(d(P, P_{\text{max/min}})\), the Euclidean distance between point \(P\) and the extrema (\(P_{\text{max/min}}\)). Simulated and measured body surface potentials were normalized as follows:

\[
\overline{\partial}_i = \frac{\partial_i - \partial_{\text{max}}}{\partial_{\text{max}} - \partial_{\text{min}}}
\]

Data analysis was conducted with SPSS 21.0 (SPSS Inc, Chicago, IL). For each metric evaluated normality was tested with a Shapiro–Wilk test (\(P<0.05\)) and visual inspection of their histograms, normal QQ-plots and box plots. A 3-way ANOVA with a Bonferroni correction was used to investigate differences between the within-subject repeated variable; body surface potential type (measured, homogeneous forward model, and inhomogeneous forward model). This accounted for the effects and interactions of between-subject variables; activation sequence type (sinus rhythm, endocardial pacing, and epicardial pacing) and animal. Statistical significance was accepted for \(P<0.05\). All data are expressed as mean±SD.

**Results**

**Body Surface Potentials**

In Figure 3, we present simulated and measured body surface potential distributions for 2 representative case studies, such as (1) pig 3 in sinus rhythm and (2) pig 2 during epicardial pacing from the left ventricle. BSPM snapshots are presented with measured epicardial potential maps during ventricular depolarization and repolarization. The measured epicardial potentials provide inputs to forward simulations, in which either (1) the conductivity within the torso is assumed to be homogeneous, or (2) more realistic inhomogeneous electric properties were incorporated (including lungs, anisotropic skeletal muscle, and subcutaneous fat).

In case study A, epicardial depolarization was initially most evident near the left ventricular apex and spread toward the base of the left ventricle. This gave rise to measured BSPMs with adjacent regions of positive and negative potential on the upper and lower anterior torso, respectively. This bipolar distribution rotated and shifted toward the upper left quadrant in the later stages of depolarization. A bipolar potential distribution was observed during repolarization, with polarity reversed. Similar patterns were observed with case study B. Here, epicardial depolarization occurred first on the anterior left ventricle, spreading over the ventricles toward the base of the RV. The measured BSPMs were again bipolar, with near vertical alignment of positive and negative potential regions.

Although there is correspondence between measured and simulated BSPMs, clear differences are evident in both
the cases. First, the potential magnitudes were substantially greater in simulated than in measured BSPMs. Second, the maximum and minimum potentials were inaccurately localized by the forward model. Specifically, the vector between extrema was substantially longer in the simulated BSPMs and at a different angle with respect to the $X-Z$ plane. Finally, the attenuation of potential adjacent to extrema was steeper in the simulations. Although inclusion of inhomogeneity in the model reduced the differences between simulated and measured BSPMs, they remained substantial nonetheless.

In Figure 4, RMS potential, $r$RMSE, and CCs were calculated during ventricular activation for both the case studies. RMS potentials predicted by homogeneous (red) and inhomogeneous (blue) simulations were nearly twice as great as

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**Figure 3.** Typical potential distributions on epicardial and body surfaces during ventricular activation and repolarization for case studies (A) in sinus rhythm and (B) during left ventricle apical pacing. The left most column shows anterior and posterior views of recorded epicardial potentials. Representative electrograms are presented with a bar indicating times corresponding to the potential maps. The central columns show anterior views of simulated body surface potential maps (BSPMs) generated from epicardial potentials, using homogeneous and inhomogeneous models. Corresponding measured BSPMs are presented in the right most column. Magnitudes of black contours indicated on associated color bars.

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**Figure 4.** A and B. Quantitative comparison of body surface potential maps during the QRS complex for case studies. In the left column, root-mean-square (RMS) potentials are compared throughout a 100-ms window over the QRS for experimental measurements (black), and simulated results using homogeneous (blue) and inhomogeneous (red) models, respectively. In the middle and rightmost columns, root-mean-squared error (RMSE) and correlation coefficient (CC) between measured and simulated potentials are given for the same time interval.
those observed experimentally (black). This was reflected in rRMSE plots where differences between simulated and experimental BSPMs were 50% to 100%. CCs between simulated and measured BSPMs were high (≈0.9) for most of the activation sequence. There were no obvious differences in the CCs and rRMSE values computed for homogeneous and inhomogeneous simulations.

These observations were replicated across the complete data set. For each activation sequence recorded from the 5 pigs, RMS potential, rRMSE, and CC values were averaged over a 50-ms window centered on the peak of the measured RMS potential. There was no significant interaction between sequence difference or interanimal difference for any metric. There was also no significant interactions between either activation sequence type or animal, and the body surface potential type for any index (Results in the Data Supplement). In contrast, measured RMS potentials were 0.21 to 0.31 mV less than those predicted with homogeneous simulations, and 0.20 to 0.29 mV less than those predicted with inhomogeneous simulations (P<0.001). There was no significant difference between homogeneous and inhomogeneous simulations for RMS potential, CC or rRMSE (P values were 0.17, 0.85, and 0.36, respectively). Grand averages for these indices are presented in Table 1. The variance of these pooled data matches interanimal variance closely (Figure II in the Data Supplement).

**BSPM Characteristics**

Differences between measured and simulated BSPMs were assessed by quantifying key features of the potential distributions observed during ventricular activation, namely the difference between maximum and minimum potentials, the length and orientation of the vector joining these extrema, and the potential attenuation adjacent (definitions are given in Methods section of this article). These indices captured distinct differences between the measured and simulated BSPMs that were replicated across the complete data set.

Figure 5 presents these indices for measured and simulated BSPMs in case study B during a 50-ms window centered on the measured RMS potential peak. The potential difference between extrema (Figure 5A) was ≈2× less in measured (black) than in simulated BSPMs throughout this window, although was less for inhomogeneous (blue) than homogeneous (red) forward simulations. The distance between extrema (Figure 5B) was ≈2× greater in measured than simulated BSPMs, although inclusion of inhomogeneous electric properties increased it by ≈15 mm. The orientation of the vector (Figure 5C) remained ≈80° in measured BSPMs, but varied from 40° to 70° in simulations with little to no difference between homogeneous and inhomogeneous models. Attenuation in potential (Figure 5D) was much greater for BSPMs simulated with a homogeneous forward model (red) than those observed experimentally (black), but inclusion of inhomogeneities (blue) reduced this difference. Finally, attenuation was greater adjacent to the minimum (dotted lines) than the maximum body surface potentials (solid lines).

In Figure 6, body surface potentials adjacent to the minimum potential are shown at the instant when measured RMS potential was greatest for case study B. These are presented as a function of distance along the line between extrema and are normalized to correct for the different magnitudes of measured and simulated BSPMs. Attenuation was steepest for the homogeneous simulations (red). Inclusion of inhomogeneities in the simulation reduced this gradient (blue), but did not replicate the much more gradual attenuation seen experimentally (black).

BSPM indices were averaged during a 50-ms window centered on the measured RMS potential peak for each activation sequence in all 5 pigs. Statistical analyses revealed no significant interaction sequence or interanimal difference for any of these measures. There was also no significant interaction between either activation sequence type or animal, and the body surface potential type for any index (Figures III and

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**Table 1. Comparison of Simulated and Measured Body Surface Potential Maps for All Animals Over a 50 ms Window Centered on the Measured RMS Potential Peak**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Measured</th>
<th>Homogeneous</th>
<th>Inhomogeneous</th>
</tr>
</thead>
<tbody>
<tr>
<td>RMS potential, mV†</td>
<td>0.74±0.20</td>
<td>1.00±0.22</td>
<td>0.98±0.22</td>
</tr>
<tr>
<td>rRMSE</td>
<td>...</td>
<td>0.37±0.19</td>
<td>0.35±0.20</td>
</tr>
<tr>
<td>CC</td>
<td>...</td>
<td>0.85±0.08</td>
<td>0.85±0.07</td>
</tr>
</tbody>
</table>

Results presented as mean±SD of pooled data for each index. CC indicates correlation coefficient; RMS, root-mean-square; and rRMSE, relative RMS error.

†Significant difference between measured values and those simulated with a homogeneous forward model.
### Table 2. Body Surface Potential Map Characteristics for all Animals Averaged Over a 50 ms Window Centered on the Measured Root-Mean-Squared Potential Peak

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Measured</th>
<th>Homogeneous</th>
<th>Inhomogeneous</th>
</tr>
</thead>
<tbody>
<tr>
<td>(\Delta \phi), mV*†‡</td>
<td>2.19±0.56</td>
<td>3.66±0.88</td>
<td>2.90±0.68</td>
</tr>
<tr>
<td>(L), mm*†‡</td>
<td>185±52</td>
<td>126±34</td>
<td>144±36</td>
</tr>
<tr>
<td>(\theta), degrees*†</td>
<td>47±24</td>
<td>28±19</td>
<td>35±21</td>
</tr>
<tr>
<td>(A_{\text{max}} \times 10^{-3}) mV mm(^{-1})*</td>
<td>-2.1±1.1</td>
<td>-2.9±1.4</td>
<td>-2.6±1.3</td>
</tr>
<tr>
<td>(A_{\text{min}} \times 10^{-3}) mV mm(^{-1})*†</td>
<td>1.0±0.7</td>
<td>2.0±1.3</td>
<td>1.7±1.2</td>
</tr>
</tbody>
</table>

Parameter descriptions are given in Methods section of this article. Results presented as mean±SD of pooled data.

*Significant difference between measured values and those simulated with a homogeneous forward model.
†Significant difference between measured values and inhomogeneous simulations.
‡Significant difference between homogeneous and inhomogeneous simulations.
differences in potential are most evident, are a relatively small subset of those over which the CC is calculated. Similar qualifications apply to the other correspondence measures, such as rRMSE. Second, CC is normalized with respect to SD to identify similarity of patterns in data. Therefore, it does not register systematic differences in the magnitudes of predicted and measured potentials.

In this work, we used alternate measures that capture characteristic features of the potential distribution on the body surface adjacent to the heart during ventricular activation. These include the difference between maximum and minimum potentials, the length and orientation of the vector joining these extrema, and the average potential attenuation adjacent. For each index, differences between measured potential distributions and those predicted with a homogeneous model were substantial and statistically significant (Table 1), illustrating the difference is not only simply in magnitude but also in pattern. The difference between measured and predicted potential distributions was reduced but not removed when an inhomogeneous model was used.

Although we have questioned the interpretation of previous structure-based forward model simulations, they nonetheless demonstrate that regions close to the torso surface have greater influence on predicted BPSMs than deeper structures. In a study that aligns more closely with our work, Stanley et al used the data acquired by Ramsey et al. Body surface potentials were simulated using measured epicardial potentials and structure-specific forward models that incorporated torso electric inhomogeneities. Predicted and observed potential distributions were then compared. The lungs and spine had little influence on potential distributions, but measured potentials were reproduced when an outer layer of anisotropic skeletal muscle was included.

**Why Does the Forward Problem of Electrocardiography Matter?**

On the basis of the findings presented and reviewed in this study, we contend that the forward problem of electrocardiography is not solved and that models which treat the torso as a uniform, isotropic volume conductor do not provide accurate predictions of active body surface potential distributions. An important question is whether, and to what extent, this affects the inverse mapping techniques that are increasingly being used in a clinical setting.

Extensive studies of inverse solution accuracy have been performed in a well-controlled ex vivo experimental model. A metabolically supported dog heart was suspended in a tank-shaped like the torso of a 10-year-old boy and filled with saline and sucrose. Epicardial and body surface potentials were recorded, and epicardial potentials predicted using an inverse model were compared with measured potentials. This work has demonstrated the efficacy of inverse mapping in a physical context where electric properties are homogeneous: pacing sites were located to within 10 mm and most measured epicardial electrograms were reconstructed faithfully. However, inverse solutions that use homogeneous models seem to be less accurate in vivo. The need to incorporate inhomogeneities in inverse mapping techniques, which could be used in a clinical setting has been widely debated. On the one hand, it has been shown that inhomogeneous inverse solutions correspond more closely with epicardial potential maps in the absence of noise. On the other hand, it is argued that this correspondence is degraded by geometric error and noise because transfer matrices for the inverse problem are ill-conditioned and are less robust for inhomogeneous than for homogeneous torso models. These analyses are based on numeric experiments, in which forward models are used to construct the BSPMs that provide the input for the inverse solution tests. However, the results presented in this article indicate that the forward models used do not reproduce the body surface potentials recorded in vivo. A systematic experimental study of the effects of inhomogeneities on the inverse problem is, therefore, needed to resolve these issues.

**Limitations**

This study has some potential limitations. First, our reconstructions of torso anatomy, and 3D electrode locations were based on postmortem rather than in vivo imaging. MRI was performed immediately after cardiac arrest and care was taken to ensure that lung inflation was maintained at physiological levels throughout. Furthermore, MRIs acquired in 1 pig before and after arrest demonstrated no significant difference between end-diastolic and postmortem epicardial geometries. Therefore, we think that 3D torso anatomy is represented with appropriate fidelity during the QRS complex because ventricular geometry is relatively invariant immediately before and during isovolumetric ventricular contraction.

The epicardial sock used in this study could alter conductivity adjacent to the heart and affect the resultant potential field. However, in a preliminary study, BSPMs were acquired before sternotomy during 2 pacing sequences and compared with corresponding maps recorded after chest closure with the sock in place. The results suggest that neither the sock, nor the surgery required to position it, has any material effect on body surface potential distributions (Results and Table III in the Data Supplement).

In this study, we have confirmed that the introduction of skeletal muscle anisotropy in forward models produces body surface potential distributions, which better match experimental observations than isotropic simulations. Here, we assumed that conductivity in the skeletal muscle layer is least in the direction normal to the body surface. However, we have not captured the complex arrangement of skeletal muscle anatomy in the torso. We think this is an important source of residual difference between observed and predicted BSPMs, but experiment-specific data on skeletal muscle anatomy necessary to test this hypothesis were not acquired in this study. More empirical approaches could also be used to investigate the electric properties of the torso. Because our data set provides simultaneous measures of forward problem inputs and solutions, conductivity within the torso could be optimized to these data. Optimization of the transfer matrix might, therefore, provide insight into the spatial location and characteristics of torso electric properties that influence the forward matrix, provided that consistent results are obtained between activation sequences and animals. Further work on these issues is being conducted in our laboratory.
Conclusions
We have assembled a comprehensive data set that includes torso and epicardial potentials recorded simultaneously in vivo in the pig, as well as corresponding information on torso anatomy and 3D electrode locations. This has provided a platform for systematic validation of forward models that use specific torso anatomy and its component properties to map cardiac potentials onto the body surface. Considerable disparity was demonstrated between observed body surface potentials and those predicted with forward models, in which torso conductivities were assumed to be uniform and isotropic. Inclusion of inhomogeneous electric properties in the forward model reduced, but did not remove these differences. This may affect the spatial precision of inverse mapping procedures, which recover cardiac potentials from BSPMs and assume that the torso is a uniformly isotropic volume conductor.

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We thank Associate Professors Denis Loiselle and Cameron Walker for their advice on statistical analysis and Linley Nisbett for her expert technical assistance.

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Disclosures
None.

References

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SUPPLEMENTAL MATERIAL
Supplemental Methods

Surgical Preparation: The experimental protocol used in this study was similar to that employed by Nash et al\(^1\). All surgical procedures were approved by the Animal Ethics Committee of the University of Auckland and conform to the Guide for the Care and Use of Laboratory Animals (NIH publication No. 85-23).

Five pigs (30-40 kg) were anesthetized and maintained with isoflurane (2-5%) in oxygen using positive pressure ventilation. The torso of the animal was shaved, cleaned and swabbed with ethanol. The heart was exposed via a midline sternotomy. The pericardium was opened and sutures attached to the cut edges were used to form a sling that supported the heart in its normal position. A custom-made elastic "sock", with 239 silver wires attached, was drawn over the ventricles ([http://www.abi.auckland.ac.nz/en/about/commercial-activities/unemap.html](http://www.abi.auckland.ac.nz/en/about/commercial-activities/unemap.html)). The end of each wire was spot-heated to remove the insulation and form a ball ~ 0.8 mm in diameter. These were fixed to the inner surface of the "sock" producing an array of unipolar electrodes spaced 5-10 mm apart. The chest was sutured closed and sealed tightly around the "sock" electrode wires. Air was expelled from the thoracic cavity via chest drains. Body surface potentials were recorded using 19 flexible rubber strips (Biosemi, The Netherlands) containing a total of 184 integrated carbon electrodes (inter-electrode spacing 30-45 mm on each strip). These were attached in a regular pattern around the torso using adhesive tape. Electrode gel was applied to all body surface electrodes to maximize signal-to-noise ratio (SNR). Fixed to both the "sock" and the body surface strips were small markers containing vitamin E, which has a high MRI contrast.
Experimental Protocol: The torso strips were connected to a multi-channel recording system (BioSemi, The Netherlands) and the "sock" electrodes to a separate 448 channel acquisition system (UnEmap, Uniservices, Auckland, New Zealand). Epicardial and body surface potentials were band-limited (0.05 - 1000 Hz), recorded simultaneously at a sampling rate of 2 kHz, and post-processed with a 50 Hz notch filter. For each data set, signals acquired with UnEmap and BioSemi systems were temporally aligned by identifying a fiducial marker consisting of a short burst of square 2 ms pulses generated with an external stimulator and simultaneously recorded on both systems.

Channels in which signals were absent as a result of lead fracture or poor electrode contact were immediately evident on visual inspection and were discarded. Across all experiments, data were recorded in 118±9 torso and 229±4 "sock" electrodes. Signal-to-noise ratio (SNR) was typically >30 dB for functional electrodes and signal averaging was not used. For each animal, records of at least 30 s duration were acquired for the following activation sequences: (i) sinus rhythm (n=1-4) (ii) endocardial pacing from left and right ventricular sites (n=4-12) and (iii) pacing from epicardial electrodes (n=4-9). A total of 65 activation sequences were recorded across the 5 pigs studied.

On completion of recording, the heart was arrested with potassium citrate injected via a left ventricular (LV) catheter. For each study, two sets of MRIs were obtained post-mortem: (i) a T1- weighted scan of the whole body with 2D planes (1 mm resolution) spaced 5 mm apart, and (ii) a T2-weighted scan of the heart with 2D planes (0.5 mm resolution) spaced 0.8 mm apart.
**Electrode Localization:** At the end of each study, the chest was reopened, and the heart was excised and perfusion-fixed with the "sock" in place. The heart was mounted on a stage and a multi-axis mechanical digitizing arm (FARO Technologies, Lake Mary, FL) was used to capture a 3D cloud of data points representing the epicardial surface of the ventricles. The 3D "sock" electrode locations and 5 attached markers were manually digitized from these FARO scans. As all other anatomic data were recorded in the MRI frame, the "sock" electrode locations also had to be transformed to this frame. A rigid body transformation of the 3D electrode locations was defined by minimizing the root mean square (RMS) distance between the 3D locations of the 5 markers measured with the FARO arm and identified from the MR images. The electrode locations were then orthogonally projected onto the epicardial surface mesh using a least squares method (RMS error = 4±2 mm). MRI compatible markers were used to identify the body surface electrode locations (2 electrodes per strip). The remaining electrode locations were interpolated using the known distance between them.

**Model Construction:** Customized volume conductor models were created from the serial transverse MR images acquired at the end of each study. These images were manually segmented and digitized, creating 3D data point clouds for the body surface, subcutaneous fat, skeletal muscle, lungs, and the epicardial surface of the heart, as illustrated for one study in Figure S1A and S1B. Finite element surface meshes from an anatomically realistic generic pig model were customized to the 3D data clouds using a linear fitting procedure. Sobolev constraints were imposed to maintain mesh smoothness. The appropriate level of refinement for the computational model was determined by systematically refining each surface until solutions were numerically converged. To solve the forward problem and simulate body
surface potentials, Kriging interpolation was used to interpolate the potentials onto the epicardial surface nodes from the "sock" electrodes.

The surface meshes were coupled together to form complete experiment-specific volume conductor models. As has been previously described\textsuperscript{2,4}, each region of the volume conductor was discretized on different scales depending on their electrical properties. Bicubic-Hermite-linear-Lagrange finite element volume elements were used model the anisotropy of the skeletal muscle. The proximity of the homogeneous fat region meant it was convenient to extend the finite element region to include it. These finite element volumes meshes were coupled to the bicubic-Hermite boundary element epicardial, lung and cavity (the volume bounded by the inner skeletal muscle surface, lung surfaces and epicardial surface) surfaces to create the volume conductor models. The final anatomic model for one study is presented in Figure S1C. The parameters of the volume conductor models are presented in Table S1 where characteristic element size was defined as the square root of the mean element area and the cube root of the mean element volume. For each torso model, bounding surfaces were fitted within an RMS error ≤3 mm.

The transversely isotropic electrical properties of skeletal muscle were incorporated through a finite element description of the myofiber orientation. Skeletal muscle groups are arranged in layers, lying over one another throughout the skeletal muscle thickness. Skeletal muscle anisotropy was incorporated into the model for a preliminary investigation of its influence on torso potentials. For this reason, a simplified representation of muscle fiber orientation was used. To approximate regional conductivity in the skeletal muscle layer, the muscle fiber
orientation was assumed to be circumferential for all elements and to rotate in a linear fashion through 360° between the inner to the outer surfaces of the skeletal muscle volume. Therefore, fibers at the outer muscle surface are oriented in the same direction as those on the inner surface. Skeletal muscle fiber orientations on the outer muscle surface are shown in Figure S1D. The conductivities used in the inhomogeneous model are given in Table S2 and are consistent with values reported in the literature\textsuperscript{5,6,7}. For homogeneous models, all inhomogeneities (lungs, fat and skeletal muscle) were included and given the same conductivity as the cavity (an average torso conductivity value of 0.22 mS mm\textsuperscript{-1}).
Supplemental Results

Effects of sternotomy and epicardial sock placement on BSPMs: In a preliminary study, body surface potentials were acquired immediately before sternotomy during pacing from fixed endocardial leads (RV base, 12 cycles and LV apex, 20 cycles). BSPM characteristics were then compared with those obtained during equivalent activation sequences after chest closure with the “sock” in place (Table S3).

The distributions of body surface potentials for both activation sequences were very similar before sternotomy and after chest closure, but potential magnitudes were uniformly somewhat higher, initially. Reflecting this, the difference between maximum and minimum body surface potentials was greater, but there was no difference in the length or orientation of the vector joining the extrema. The reduction in body surface potential was most likely due to chest expansion as a result of incomplete removal of air from the thoracic cavity following closure. Such changes in geometry were accounted for in this study because torso anatomy was imaged post-mortem.

Pre-sternotomy recordings was not carried out in all animals studied, because it required body surface electrodes to be positioned prior to opening the chest. This was achieved more easily and with greater reliability after chest closure.

Body Surface Potentials: RMS potentials, rRMSE and CC values were calculated during ventricular activation for each activation sequence recorded from the five pigs. These values were then averaged over a 50 ms window centered on the peak of the measured RMS potential.
This minimized contamination of these mean values with noise and improved statistical discrimination (the CCs between measured and simulated BSPMs, in particular, were relatively stable throughout this time window, see Figure 4).

A visual inspection of histograms, normal Q-Q plots and box plots demonstrated the measured and simulated RMS voltages, CCs and rRMSEs values were approximately normally distributed for each and all animals (boxplots are presented in Figure S2). Where sample size was small (n<10), up to one data point could be removed if it was a clear outlier. Using the Shapiro-Wilk’s test, we were unable to prove the null hypothesis in any case (p-values>0.05); that is, the distributions of data for all measures were not statistically different from normal within or across animals.

For each of these measures, variability between activation sequences and between animals were modelled using a factorial repeated measures ANOVA with a Bonferroni correction. For each metric, there was no significant inter-animal difference (p-values were >0.30) nor a significant difference between sinus rhythm, epicardial pacing or endocardial pacing sequences (p-values were >0.20). Similarly, there was no significant interaction for any metric between body surface potential type and either activation sequence type (p-values were >0.20) or animal (p-values were >0.60). Box plots of RMS voltage, rRMSE and CC are presented in Figure S2 for each animal, and for all animals. These provide an indication of the overall within-pig variance for each measure.

There was a significant difference between the experimentally measured and simulated RMS potentials (p-value <0.001), with measured RMS potentials 0.21-0.31 mV less than
homogeneous and 0.20-0.29 mV less than inhomogeneous mean RMS potentials. However, there was no difference between homogeneous and inhomogeneous values (p-value=0.17). Across all studies, CC showed strong correspondence between measured and simulated BSPMs (CC= 0.85±0.08 with a homogeneous model), but there was no difference between the CC or rRMSE values with homogeneous and inhomogeneous models (p-values were 0.85 and 0.36 respectively).

**BSPM Characteristics:** Similar analyses were also carried out for characteristic measures of body surface potential distribution. For each activation sequence, the difference between maximum and minimum body surface potentials, the length and orientation in the X-Z plane of the vector joining these extrema, and potential attenuation adjacent to them were calculated and averaged over the 50 ms window centered on the peak of the measured RMS voltage, as outlined above. Inspection of measured and simulated metrics revealed the distributions were again approximately normal for each and all animals (box plots presented for each metric in Figures S3 and S4).

There was no significant difference between activation sequence type for any of these measures (p-values were >0.05). Likewise, there was no significant inter-animal difference (p-values were >0.05). There was also no significant interaction between either activation sequence type, or animal, and body surface potential type for any of these measures (p-values were >0.05). Box plots of these indices for measured and simulated BSPMs are presented for each animal and for all animals in Figures S3 and S4.

Statistical analysis also confirmed differences evident in case study B between observed
BSPMs and those simulated with a homogeneous forward model. That is, the difference between maximum and minimum body surface potentials was 1.2 to 1.7 mV smaller, the length of the vector between extrema was 31 to 53 mm longer and its orientation was also significantly different (p-values <0.05). In addition, the attenuation of potential adjacent to maxima and minima was 98-171% and 10-59% greater, respectively (p-value <0.03).

The introduction of inhomogeneous electrical properties in the forward model reduced the variance between observed and simulated results and in many cases this was statistically significant. The difference between maximum and minimum body surface potentials was 0.6 to 1.0 mV smaller than with the homogeneous model, the length of the vector between extrema was 12 to 23 mm longer and attenuation from the maximum was 10-37% greater (p-values <0.05).
Supplemental Tables

Table S1: Computational parameters for volume conductor models

<table>
<thead>
<tr>
<th>Surface Mesh</th>
<th># Nodes</th>
<th># Elements</th>
<th>Characteristic Element Size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epicardium</td>
<td>622</td>
<td>640</td>
<td>5.3</td>
</tr>
<tr>
<td>Left Lung</td>
<td>306</td>
<td>120</td>
<td>9.8</td>
</tr>
<tr>
<td>Right Lung</td>
<td>306</td>
<td>120</td>
<td>10.7</td>
</tr>
<tr>
<td>Skeletal Muscle</td>
<td>2068</td>
<td>1056</td>
<td>18.5</td>
</tr>
<tr>
<td>Subcutaneous Fat</td>
<td>2068</td>
<td>1056</td>
<td>15.0</td>
</tr>
</tbody>
</table>

Characteristic Element Size defined as the square root of mean element area or cube root of mean element volume (mm).

Table S2: Material conductivities used for volume conductor models

<table>
<thead>
<tr>
<th>Tissue</th>
<th>Resistivity (Ohm.cm)</th>
<th>Conductivity (mS.mm$^{-1}$)</th>
<th>Ratio to Cavity $^1$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cavity</td>
<td>455</td>
<td>0.220</td>
<td>1.00</td>
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<tr>
<td>Heart</td>
<td>333</td>
<td>0.300</td>
<td>1.36</td>
</tr>
<tr>
<td>Lungs</td>
<td>2000</td>
<td>0.050</td>
<td>0.23</td>
</tr>
<tr>
<td>Subcutaneous Fat</td>
<td>2500</td>
<td>0.040</td>
<td>0.18</td>
</tr>
<tr>
<td>Skeletal Muscle (L)</td>
<td>192</td>
<td>0.520</td>
<td>2.37</td>
</tr>
<tr>
<td>Skeletal Muscle (T)</td>
<td>1390</td>
<td>0.072</td>
<td>0.33</td>
</tr>
</tbody>
</table>

$L$, Longitudinal; $T$, Transverse
Table S3: Comparison of BSPMs acquired for two pacing sequences immediately before sternotomy and after chest closure with the “sock” in place. Results presented as mean ± SD.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>LV Pacing (n=20)</th>
<th>RV Pacing (n=12)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre-Sternotomy</td>
<td>Post-Sternotomy</td>
</tr>
<tr>
<td>Δ∅ (mV)</td>
<td>2.40±0.10</td>
<td>1.95±0.07</td>
</tr>
<tr>
<td>L (mm)</td>
<td>143±15</td>
<td>147±12</td>
</tr>
<tr>
<td>θ (degrees)</td>
<td>60±2</td>
<td>61±3</td>
</tr>
</tbody>
</table>

Δ∅ (mV) | 2.02±0.03 | 1.88±0.04
L (mm)   | 130±7     | 134±12
θ (degrees) | 23±3       | 24±3
Supplemental Figures:

Figure S1: Experiment specific forward model construction: (A) Transverse images from the MRI stack for each experiment were segmented and digitized. In the lower image, subcutaneous fat is shaded yellow, skeletal muscle is red, the lungs are pink and the heart wall is gold. (B) Clouds of 3D geometric data were obtained by identifying points on external surfaces that bound the anatomic structures in a) and have corresponding color coding. The torso surface is indicated by grey points. (C) Finite element surface meshes were fitted to the data clouds and coupled to form experiment-specific volume-conductor models. (D) The red surface represents the outer layer of skeletal muscle while the unrefined surface mesh shown in black indicates the extent of the subcutaneous fat layer.
Figure S2: Comparison between animals for average (A) RMS potentials (mV), (B) rRMSE and (C) CC between measured (black) and simulated body surface potentials using either homogeneous (red) or inhomogeneous (blue) models. Metrics were averaged over a 50 ms window centered on the peak of the measured RMS body surface potential. Box plots show mean values, upper and lower quartiles, and range of these metrics across all activation sequences for each animal and for all animals. Data points indicated in red are outliers.
Figure S3: Comparison between animals for the average (A) difference between maximum and minimum body surface potentials (mV), (B) Length (mm), and (C) orientation with respect to the X-Z axis (degrees) of the vector joining the extrema. Results from measured body surface potentials (black) are compared with simulations using homogeneous (red) or inhomogeneous (blue) models. Metrics were averaged over a 50 ms window centered on the peak of the
measured RMS body surface potential. Box plots show mean values, upper and lower quartiles, and range of these metrics across all activation sequences for each animal and for all animals. Data points indicated in red are outliers.
Figure S4: Comparison between animals for the average potential attenuation ($10^{-3} \text{ mV.mm}^{-1}$) adjacent to (A) maximum and (B) minimum body surface potentials. Results from measured body surface potentials (black) are compared with simulations using homogeneous (red) or inhomogeneous (blue) models. Metrics were averaged over a 50 ms window centered on the peak of the measured RMS body surface potential. Box plots show mean values, upper and lower quartiles, and range of these metrics across all activation sequences for each animal and for all animals. Data points indicated in red are outliers.
Supplemental References:


