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Accuracy of Quadratic Versus Linear Interpolation in Noninvasive Electrocardiographic Imaging (ECGI)

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Abstract

Electrocardiographic Imaging (ECGI) is a cardiac functional imaging modality, noninvasively reconstructing epicardial potentials, electrograms and isochrones (activation maps) from multi-channel body surface potential recordings. The procedure involves solving Laplace's equation in the source-free volume conductor between torso and epicardial surfaces, using Boundary Element Method (BEM). Previously, linear interpolation (LI) on three-noded triangular surface elements was used in the BEM formulation. Here, we use quadratic interpolation (QI) for potentials over six-noded linear triangles. The performance of LI and QI in ECGI is evaluated through direct comparison with measured data from an isolated canine heart suspended in a human-torso-shaped electrolyte tank. QI enhances the accuracy and resolution of ECGI reconstructions for two different inverse methods, Tikhonov regularization and Generalized Minimal Residual (GMRes) method, with the QI-GMRes combination providing the highest accuracy and resolution. QI reduces the average relative error (RE) between reconstructed and measured epicardial potentials by 25%. It preserves the amplitude (average RE reduced by 48%) and morphology of electrograms better (average correlation coefficient for QI ~ 0.97, LI ~ 0.92). We also applied QI to ECGI reconstructions in human subjects during cardiac pacing, where QI locates ventricular pacing sites with higher accuracy (≤ 10 mm) than LI (≤ 18 mm).

Keywords

Electrocardiography; Cardiac bioelectricity; Boundary Element Method; Laplace's equation; Inverse problem

INTRODUCTION

The electrical activity of the heart is reflected in the electric potential field it generates. Traditional ECG measures the electric potentials far away from the heart at a limited number of body-surface sites. Consequently, ECG suffers from low resolution and inadequate sensitivity and specificity. In contrast, potentials and isochrones (activation sequences) from the epicardial surface of the heart provide detailed information about cardiac electrical activity. Electrocardiographic Imaging (ECGI)^{21,25} is a novel noninvasive imaging modality, developed in our laboratory, that reconstructs potentials, electrograms and isochrones on the epicardial surface of the heart. ECGI was validated extensively in canine-heart experiments during normal sinus rhythm (SR),¹⁷ ventricular pacing^{18,19} and reentrant ventricular tachycardia (VT) in infarcted hearts.^{4–6} It was also shown to image cardiac repolarization and its spatial dispersion.¹⁶ Recently, ECGI was also applied in human subjects, demonstrating its ability to image normal activation and repolarization, locate initiation sites during right and

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left ventricular pacing, image the conduction abnormality associated with right bundle branch block (RBBB) and image the right-atrial reentry circuit during typical atrial flutter.²¹

The procedure of ECGI involves solving Laplace's equation in the source-free volume conductor between the torso and epicardial surfaces.²⁵ We used an integral formulation of this problem (Green's Second Theorem) and the boundary element method (BEM)³ to compute a transfer matrix $\mathbf{A}$ that relates the torso potentials $\mathbf{V}_T$ to the epicardial potentials $\mathbf{V}_E$; $\mathbf{A}\mathbf{V}_E = \mathbf{V}_T$. The transfer matrix $\mathbf{A}$ is ill-posed²⁸ and cannot be inverted directly to compute $\mathbf{V}_E$ from measured $\mathbf{V}_T$ (the objective of ECGI). In our ECGI method we obtained stable solutions to this inverse problem by imposing constraints through Tikhonov regularization²⁸ or by applying an iterative approach, the Generalized Minimal Residual (GMRes) method.^{8,20}

Implementation of BEM to compute the transfer matrix $\mathbf{A}$ requires discretization of the torso and epicardial surfaces. The surfaces are discretized into continuous, nonoverlapping triangular elements by introducing nodal points on the surface (a procedure also called meshing). The potential function over each element is assumed to be constant (average of the nodal values) or vary as a linear or higher-order function of the intrinsic element coordinates with matching values at the nodal points. In all previous ECGI applications, we used linear interpolation (LI) functions. Higher order interpolation functions can potentially yield better accuracy and convergence but at the same time increase computational complexity and cost. In this paper we implement quadratic interpolation (QI) in the ECGI algorithm and compare its performance to that of LI. Accuracy of results is evaluated by direct comparison to measured data in a human-shaped torso tank containing a canine heart and in human subjects during right and left ventricular pacing.

METHODS

Formulating the Boundary Integral Equation for ECGI

The electric potential field ϕ in a three-dimensional domain Ω comprising the source-free volume conductor between the torso and the epicardial surfaces is governed by Laplace's equation:

$$\nabla^2 \phi = 0 \quad (1)$$

with the following boundary conditions:

1. Essential condition: $\phi = \mathbf{V}_E$ on the epicardial surface Γ_E .
2. Natural condition: $\mathbf{q} = \partial\phi/\partial\mathbf{n} = \mathbf{0}$ on the torso surface Γ_T .

Figure 1 illustrates the torso and the epicardial surfaces and the boundary conditions applied to each surface for our ECGI problem.

The discretized form of boundary integral equation for Laplace's equation³ is

$$c^i \phi^i + \sum_{j=1}^N \int_{\Gamma_j} \phi q^* d\Gamma = \sum_{j=1}^N \int_{\Gamma_j} \phi^* q d\Gamma \quad (2)$$

where $\phi^* = 1/4\pi r$ is the fundamental solution of potential generated by a concentrated unit charge located at a point i on the boundary. r is the distance from the source point to the field point under consideration, ϕ^i is the potential at the point i , q^* and q are the normal derivatives $q^* = \partial\phi^*/\partial n$, $q = \partial\phi/\partial n$ and $\Gamma (= \Gamma_E + \Gamma_T)$ is the boundary of Ω and N is the total number of two dimensional triangular surface elements used to discretize the torso and epicardial surfaces.

The value of the coefficient c^i is

$$c^i = \theta^i / 2\pi$$

where θ^i is the internal solid angle subtended by the boundary at point i (in radians).

The value of ϕ at any point within a three-noded triangular element with LI is given in terms of the nodal values (ϕ^k) by

$$\phi = \phi^1 a_1 + \phi^2 a_2 + \phi^3 a_3 \quad (3)$$

or, for the case of six-noded triangular elements with QI,

$$\phi = \phi^1 \beta_1 + \phi^2 \beta_2 + \phi^3 \beta_3 + \phi^4 \beta_4 + \phi^5 \beta_5 + \phi^6 \beta_6 \quad (4)$$

where ϕ^k is the potential at node k in the element where the nodes are numbered in the counterclockwise sense, and α_k and β_k represent linear and QI functions which are expressed in terms of intrinsic element coordinates (η_1, η_2, η_3) as

$$\begin{aligned} \alpha_1 &= \eta_1, & \alpha_2 &= \eta_2 \text{ and } & \alpha_3 &= \eta_3 \\ \beta_1 &= \eta_1(2\eta_1 - 1), & \beta_2 &= \eta_2(2\eta_2 - 1), & \beta_3 &= \eta_3(2\eta_3 - 1) \\ \beta_4 &= 4\eta_1\eta_2, & \beta_5 &= 4\eta_2\eta_3, & \beta_6 &= 4\eta_3\eta_1 \end{aligned}$$

For the six-noded linear triangular element shown in Fig. 2(A), the intrinsic coordinates are

$$\eta_1 = \text{area } P23 / \text{area } 123 \quad (5a)$$

$$\eta_2 = \text{area } P31 / \text{area } 123 \quad (5b)$$

$$\eta_3 = 1 - \eta_1 - \eta_2 \quad (5c)$$

where area XYZ is the area of the triangle with vertices X, Y and Z. Using the same interpolation functions for the derivative $q = \partial\phi/\partial n$, we can write Eq. (2) in the form

$$\mathbf{H} \Phi = \mathbf{G} \mathbf{Q} \quad (6)$$

where $\mathbf{G}$ and $\mathbf{H}$ are the BEM coefficient matrices. The elements of matrix $\mathbf{G}$ are

$$G_{ij} = \sum_j \int_{\Gamma_j} \beta_k \phi^* d\Gamma_j$$

where the integral is evaluated over an element Γ_j containing the node j , the Green's function ϕ^* is evaluated with the node i as the source point, and k is the number of the node j in the element Γ_j with the nodes numbered from 1 to 6 in the anticlockwise sense. The integral is summed over all elements containing node j . The elements of matrix $\mathbf{H}$ can be written as

$$\begin{aligned} H_{ij} &= \hat{H}_{ij} \text{ for } i \neq j \\ H_{ij} &= \hat{H}_{ij} + c^i \text{ for } i = j. \end{aligned}$$

The terms $\hat{H}_{ij}$ are formed similarly to G_{ij} except that ϕ^* is replaced by its spatial gradient. The vector Φ contains potentials at epicardial and torso nodes and vector $\mathbf{Q}$ contains their normal derivatives. Note that the diagonal terms of $\mathbf{H}$ can be computed by using the fact that for uniform potential on torso and epicardial surfaces, the values of the normal derivative are 0, so that Eq. (6) reduces to

$$\mathbf{H} \mathbf{I} = \mathbf{0}$$

where $\mathbf{I}$ is the identity matrix. Using this approach we need not compute the solid angle separately for computing the coefficient c^i and the diagonal terms H_{ii} can be computed from other elements of $\mathbf{H}$ matrix.

Computation of Nonsingular and Singular Integrals

Integrals of the form $\int \varphi^* \beta_k d\Gamma$ (single layer) contain the Green's function $\varphi^* = 1/4\pi r$. For nonsingular terms ($r \neq 0$; source and field points are different), a transformation from global (x, y, z) to intrinsic element coordinates (η_1, η_2) is performed.³ The differential surface area is

$$d\Gamma = |\mathbf{J}| d\eta_1 d\eta_2$$

where the normal vector $\mathbf{J}$ is

$$\mathbf{J} = \frac{\partial \mathbf{r}}{\partial \eta_1} \times \frac{\partial \mathbf{r}}{\partial \eta_2} = (j_1, j_2, j_3)$$

and

$$\begin{aligned} j_1 &= \frac{\partial y}{\partial \eta_1} \frac{\partial z}{\partial \eta_2} - \frac{\partial y}{\partial \eta_2} \frac{\partial z}{\partial \eta_1} \\ j_2 &= \frac{\partial z}{\partial \eta_1} \frac{\partial x}{\partial \eta_2} - \frac{\partial z}{\partial \eta_2} \frac{\partial x}{\partial \eta_1} \\ j_3 &= \frac{\partial x}{\partial \eta_1} \frac{\partial y}{\partial \eta_2} - \frac{\partial x}{\partial \eta_2} \frac{\partial y}{\partial \eta_1} \end{aligned}$$

The integrals after transformation to intrinsic coordinates, are evaluated by 4×4 Gauss-Legendre quadrature

$$\int_{\Gamma} \beta_k \varphi^* d\Gamma = \sum_{j=1}^4 \sum_{i=1}^4 w_j w_i \varphi^*(\eta_{1i}, \eta_{2j}) |\mathbf{J}(\eta_{1j}, \eta_{2j})|$$

In above equation, w_j and w_i represent the weights and (η_{1i}, η_{2j}) represent the abscissae for 4×4 Gauss-Legendre quadrature for surface integration. It is to be noted that for a linear six-noded triangular element, the magnitude of the normal vector $\mathbf{J}$ is independent of the abscissae (η_{1i}, η_{2j}) and hence can be taken out of the summation.

When the source point coincides with one of the vertices or mid-side nodes of the element over which the integration is performed, the single layer integral has a singularity of order $O(1/r)$. We compute the singular integrals by introducing polar coordinates to eliminate the singularity.^{9,11} Considering the triangular element (Fig. 2(B)), assume that the singularity is at node 3 of the element. If the singularity is at node 1 or 2, the order of the nodes can be interchanged keeping the same direction (counterclockwise numbering of nodes) without loss of generality. Suppose that the origin O of the polar coordinate system coincides with node 3 (singular node) and the reference axis is along OR , parallel to the edge 1–2 of the triangular element. A point P within the triangle can be represented by (r, Θ) where $P-3 = r$ and $\angle P3R = \Theta$. From Eq. (5), we can express the interpolation function η_1 in terms of the polar coordinates (r, Θ) as

$$\begin{aligned} n_1 &= \frac{[(P-S) \cdot r_{23}]/(b_1 \cdot r_{12})}{[r_{23} \cdot r \sin(\theta_1 + \theta_3 - \Theta)]/(b_1 \cdot r_{12})} \end{aligned} \quad (7)$$

where θ_1 = angle at vertex 1, θ_3 = angle at vertex 3, r_{23} and r_{12} represent the edges 2–3 and 1–2 respectively. (Note that $P-S = r \sin(\angle P3S)$ and $\angle P3S = \angle R32 - \angle P3R = \theta_1 + \theta_3 - \Theta$).

Using trigonometric expansion for $\sin(A-B)$, we can write (6) as

$$\eta_1 = \frac{[r \cdot r_{23} \sin(\theta_1 + \theta_3) \cos \Theta - r \cdot r_{23} \cos(\theta_1 + \theta_3) \sin \Theta]}{[b_1 \cdot r_{12}]} \quad (8)$$

Considering triangle 2M3 in Fig. 2(B), we have

$$\begin{aligned} b_1 &= r_{23} \cdot \sin(\angle M32) = r_{23} \cdot \sin(\pi - \theta_1 - \theta_3) \\ &= r_{23} \cdot \sin(\theta_1 + \theta_3) \end{aligned} \quad (9a)$$

$$\begin{aligned} a_1 &= r_{23} \cdot \cos(\angle M32) = r_{23} \cdot \cos(\pi - \theta_1 - \theta_3) \\ &= -r_{23} \cdot \cos(\theta_1 + \theta_3) \end{aligned} \quad (9b)$$

Substituting (9a) and (9b) in (8), we obtain

$$\eta_1 = \left[r \cdot b_1 \cos \theta + r \cdot a_1 \sin \theta \right] / (b_1 \cdot r_{12}) \quad (10)$$

and a similar expression can be obtained for η_2 . We now compute the integrals with singularity of order $O(1/r)$ analytically in the (r, θ) coordinate system.

$$\int \beta_k(\eta_1, \eta_2) O(1/r) d\Gamma = \int_{\theta_1}^{\theta_1+\theta_3} \int_0^{r(\theta)} \beta_k(\eta_1(r, \theta), \eta_2(r, \theta)) O(1/r) r dr d\theta$$

where $r(\theta) = b_1/\sin\theta$

For mid-side node singularity (nodes 4, 5 and 6), the same approach can be used by dividing the triangle into two parts along the median corresponding to the singular node and transforming to polar coordinates with origin at the singular node. The reference axis is taken parallel to the opposite side of the triangle under consideration. The total integral is computed by adding the integrals over the two parts.

Forward and Inverse Problems

The forward problem, defined as computing torso potentials from epicardial potentials, can be formulated from Eq. (6) by extracting rows and columns of the matrices $\mathbf{G}$ and $\mathbf{H}$ (LU factorization of $\mathbf{H}$ matrix is done using the routine f0adf7 in NAG Foundation Toolbox for Matlab 6) to relate the vector of torso potentials $\mathbf{V}_T$ to the vector of epicardial potentials $\mathbf{V}_E$ in the form of a matrix equation.

$$\mathbf{V}_T = \mathbf{A} \mathbf{V}_E$$

The objective of ECGI is to invert this equation and solve the inverse problem to compute $\mathbf{V}_E$ from $\mathbf{V}_T$. However, the matrix $\mathbf{A}$ is ill-posed and its direct inversion will result in amplification of measurement noise and an unstable solution. A commonly used method for obtaining solutions of ill-posed problems is Tikhonov regularization.²⁸ We also recently implemented an alternative method, the GMRes method for ECGI computation.²⁰

Torso Boundary Nodes and Electrode Positions

An important consideration for practical ECGI application is correspondence of the torso boundary nodes with actual measurement points (electrode positions). We choose linear triangular elements to cover the torso and epicardial surfaces because a triangular mesh can be generated easily and quickly from the input set of electrode positions on the body surface. The electrodes are visible and can be located in 3D space from Computed Tomographic (CT) scans in the clinical application of ECGI; their locations define the vertices of the triangular elements. The triangular element also allows for QI by generating additional nodes at the middle point of the sides of each element. However, these middle points are not measurement points and require assignment of potential values. Burnes and Rudy⁷ introduced a field compatible method for interpolation of body-surface potentials at missing data points. The basis of this method is application of Laplace's equation in the source-free torso volume conductor to compute potentials on an interior surface between the torso and epicardial surfaces. The interior surface was created by radially deflating the torso by 5%, ensuring that it does not cross the epicardial surface; it was digitized using the same number of nodes as the torso surface. Potentials were inversely computed on this interior surface from measured body-surface potentials and the computed interior surface potentials were then used to compute potentials at 'missing' data points on the torso using the forward problem. This inverse-forward (IF) interpolation, as a consequence of its physical basis, was able to recreate all key potential features (e.g., minima and maxima) that were not reconstructed by other conventional interpolation techniques.⁷ In this paper, we use the IF interpolation method to generate the

potentials at the mid-side nodes of each torso element. These values are then used in the BEM quadratic interpolation along with the measured torso potentials at the vertices, to obtain the inverse solution on the epicardial surface. Because IF generated values are not limited to measurement points, this approach can be used to assign potential values to torso-nodes which do not coincide with electrode sites.

Experimental Methods and Protocols

We evaluated and compared the performance of linear and quadratic BEM interpolation on the inverse solution using data from an isolated canine heart suspended in the correct anatomic position in a human-shaped electrolytic torso-tank. The directly measured epicardial data provided a ‘gold standard’ for evaluation. We also applied these methods to clinical data from patients undergoing resynchronization therapy, with an implanted bi-ventricular pacing device. For the human data the basis for evaluation was the location of the pacing sites as determined from CT and the known patterns of activation and repolarization generated by point stimulation. Descriptions of protocols are provided below.

Isolated Canine Hearts Suspended in a Human-Torso-Shaped Tank—This set-up (Experiments conducted in Dr Bruno Taccardi’s Laboratory at the University of Utah, Salt Lake City) consisted of an isolated canine heart suspended¹⁹ in a homogenous electrolytic medium in the correct anatomical position inside a tank molded in the shape of a 10-year old boy. The tank had 384 surface electrodes recording torso potentials and 242 rods with electrodes at their tips that formed an epicardial recording envelope around the heart. The torso-surface potentials and epicardial potentials were recorded simultaneously. The torso-surface potentials provided the input data for ECGI reconstruction of epicardial potentials, electrograms and isochrones which were then evaluated by comparison with those measured directly by the rod-tip electrodes. Data were obtained for single-site pacing from an anterior epicardial location and for dual-site pacing from epicardial electrodes placed 2.5 cm apart. Different datasets using similar protocols with LI only were published previously.^{19,20} In particular, previous inverse reconstruction of dual pacing from sites 2.5 cm apart was performed in a homogeneous torso from forward-computed body surface potentials in an inhomogeneous torso (the goal was to evaluate the homogeneous approximation for inverse reconstruction²²). Here, all ECGI reconstructions were performed from measured torso potentials using LI and QI and compared to directly measured epicardial potentials.

Pacing in Human Subjects—We used the linear and QI methods with ECGI in four patients²¹ during pacing from an implanted pacing device. Subject 1 was paced from the right ventricular (RV) apex. Subjects 2, 3 and 4 were each paced from an RV site and (not simultaneously) from a left ventricular (LV) site. Body surface potentials were recorded with a 224-channel mapping system using an electrode-vest as previously described. Epicardial geometry and location of the torso electrodes were obtained from CT images of the thorax. The locations of the cardiac pacing leads were also determined from the CT images and served as a measure of ECGI accuracy.

Data Processing and Evaluation Protocols

For all data sets presented in this paper, epicardial potentials were reconstructed using Tikhonov regularization and/or GMRes and forming the transfer matrix **A** using linear or QI functions. Epicardial potential maps reflect the spatial variation of potentials on the epicardial surface at a given instant of time. Maps were computed at intervals of 1 ms during ventricular depolarization and repolarization. Epicardial electrogram provides the time variation of the epicardial potential during the cardiac cycle at a given point on the epicardium. Electrograms were generated by assembling reconstructed epicardial potentials from all time frames at each epicardial node. Isochrone maps which depict the activation sequence during ventricular

depolarization, were constructed by assigning local activation time as the time-point when the negative time derivative of the electrogram reached a maximum ($-dV/dt_{\max}$). For the tank-torso protocols, quantitative measures of ECGI accuracy were obtained by computing relative errors (RE) and correlation coefficients (CC) between the reconstructed and measured epicardial data.

$$\text{RE} = \sqrt{\frac{\sum_{i=1}^N (V_i^C - V_i^M)^2}{\sum_{i=1}^N (V_i^M)^2}}$$

$$\text{CC} = \frac{\sum_{i=1}^N (V_i^M - V_m^M)(V_i^C - V_m^C)}{\sqrt{\sum_{i=1}^N (V_i^M - V_m^M)^2 \sum_{i=1}^N (V_i^C - V_m^C)^2}}$$

where N is the number of epicardial nodes for epicardial potential or isochrone comparisons, or number of time-points for comparing electrograms. V_i^C is the noninvasively reconstructed (computed) potential at the i th node or time-point, V_i^M is the corresponding measured potential, V_m^C and V_m^M are their respective mean values. It is to be noted that for computing RE and CC, the original three nodes per triangular element on the epicardial surface were used for both LI and QI schemes, because measured potentials were obtained only at these nodes. The interpolation was performed over three-noded elements (LI) or over six-noded elements (QI). In addition to these measures, accuracy and resolution of ECGI determination of pacing sites were used in the evaluation of both torso-tank and human reconstructions. Pacing sites from reconstructed epicardial potential maps were estimated as the center of an ellipse that best fits the quasi-elliptical negative potential region that develops around the pacing site at the earliest time frame. Pacing sites were also determined from isochrone maps as the sites of earliest activation. Qualitative evaluation of ECGI reconstructions was also conducted by visual comparison to measured data (torso-tank experiments) and to well established potentials, electrograms and isochrone patterns associated with pacing (human subjects).

RESULTS

Torso-Tank Data

Single Site Pacing—Figure 3(A) shows epicardial potential maps for epicardial pacing from a single anterior RV site, at a time frame of 25 ms after pacing. On the left are the directly measured epicardial potentials with the corresponding reconstructed epicardial potentials using linear (LI) or quadratic (QI) BEM interpolation functions in the middle and right panels, respectively. Zero order Tikhonov regularization was employed in these reconstructions. The white asterisk marks the pacing site location (left panel) and its estimation from reconstructed potential maps (middle and right panels). The measured potentials display a central quasi-elliptical negative region (blue) flanked by two positive regions (red) as expected in the anisotropic myocardium.^{27,19} This pattern is captured by both LI and QI. However, localization of the negative region is more precise with QI which locates the pacing site with an error of 2 mm as compared to 4 mm for LI. Both CC (a measure of pattern similarity) and RE (indicative of amplitude accuracy) are improved by QI with major improvement in RE.

Figure 3(B) shows the same data for the same time frame with the inverse solution computed using GMRes. As for Tikhonov regularization, localization errors of pacing site for LI and QI are 4 mm and 2 mm, respectively. However, CC and RE are improved with the highest accuracy obtained using GMRes with QI.

Figure 4 shows measured (green) and computed (GMRes) electrograms using LI (blue) and QI (red). Three typical electrogram morphologies are shown (locations are depicted in Panel A; the pacing site is shown by the asterisk): B, Q wave morphology which is typical of electrograms near a pacing site, C, Biphasic morphology typical of electrograms some distance

away from the pacing site and D, R-wave morphology of electrograms measured remote to the pacing site. QI improved both CC (a measure of morphology similarity) and RE (indicative of amplitude accuracy) compared to LI for all electrogram morphologies. (CC and RE are provided in Fig. 3). Note dramatic improvement of amplitude accuracy with QI and closeness to the measured amplitudes and morphologies. For all GMRes (Tikhonov) reconstructed epicardial electrograms over the entire epicardium, the average CC was 0.91 (0.91) and RE 0.74 (0.76) for LI; CC was 0.97 (0.96) and RE 0.38 (0.39) for QI.

Dual Site Pacing—Figure 5(A) shows epicardial potentials for simultaneous pacing from two closely spaced anterior epicardial sites, 2.5 cm apart. Epicardial potential map during activation, 25 ms after pacing stimulus, is shown. Right panel shows measured potentials; middle and left panels show LI and QI reconstructed epicardial potentials, respectively, using Tikhonov regularization. Accuracy of reconstruction is improved by QI as indicated by higher CC and lower RE values. Importantly, with QI, two discrete potential minima (blue) are reconstructed around the pacing sites, providing their locations with errors of 3 mm and 2 mm. In contrast, LI reconstructs only one elongated minimum, failing to capture and distinguish the two pacing sites.

Figure 5(B) is of similar protocol and format to Fig. 5(A), except that the epicardial potential maps are at 93 ms after pacing during early ventricular repolarization. For paced beats, conduction is slow (no or minimal conduction system involvement) and the repolarization sequence follows the activation sequence (intrinsic repolarization duration differences are small compared to activation time differences when conduction is slow). Because repolarization is reversed in polarity relative to depolarization, epicardial potential maps during early repolarization are expected to be of a similar pattern but reversed polarity compared to those during early activation (Fig. 5(A)). Indeed, two maxima around the pacing sites, replacing the early-activation minima, are reconstructed using QI (Fig. 5(B), right). These maxima merge into a single maximum when LI is used (Fig. 5(B), middle).

Figures 5(C) and 5(D) is of similar protocol (dual-site pacing) and format to Figs. 5(A) and 5(B), except that GMRes, rather than Tikhonov regularization, is used in the inverse computation. Due to its better spatial resolution (less smoothing), GMRes can capture and distinguish the two pacing sites even when LI is used, with localization errors of 2 mm and 1 mm for both LI and QI.

Electrograms (reconstructed with GMRes) for the dual pacing data (Fig. 6) show typical Q-wave and R-wave morphologies from locations near and far from the pacing sites, respectively. As in the case of single-site pacing, QI enhances the accuracy of the reconstructed electrograms significantly with major improvement of amplitude accuracy (CC and RE values in figure). Average correlation between GMRes (Tikhonov) reconstructed and measured electrograms over the entire epicardium is 0.93 (0.91) for LI and 0.97 (0.96) for QI; mean RE is 0.71 (0.75) for LI and 0.47 (0.51) for QI.

Figure 7 shows measured (left) and GMRes reconstructed isochrone (activation-sequence) maps using LI (middle) or QI (right). ECGI using QI captures two distinct sites of earliest activation, corresponding to the two pacing sites, with errors of 3 mm and 2 mm. LI reconstructs only one area of earliest activation, missing the dual-pacing pattern. Note that both QI and LI image correctly the radial spread of activation wave from the region of early activation.

Figures 8(A) and 8(B) show RE and CC (LI-light, QI-dark) between GMRes solutions and measured epicardial potentials with time over one cardiac cycle for single site pacing, Figs. 8(C) and 8(D) show the same for dual site pacing. Table 1 shows the average RE and the average CC between measured and reconstructed epicardial potentials over four cardiac cycle for two

different inverse methods, Tikhonov and GMRes, for both single and dual site pacing. Note that for both methods, QI substantially lowers the average RE, indicating an overall improvement in accuracy of the reconstructed potentials.

Pacing in Human Subjects

Subject 1 Figures 9(A) and 9(B) show GMRes reconstructed epicardial potential maps for RV pacing (asterisk) in subject 1 using LI (left) and QI (right). Panel A shows the potential pattern for an early activation (26 ms) frame; Panel B for early repolarization (246 ms). The pacing site is located from the reconstructed epicardial potential maps (center of negative elliptical region, Panel A) to within 18 mm (LI) and 10 mm (QI) of the pacing lead location as determined from CT (asterisk). LI generates additional, more superior minima that do not appear with QI. As expected, during early repolarization, the pacing minimum is replaced by a maximum (Panel B, red).

Figures 9(C) and 9(D) show the GMRes reconstructed epicardial isochrones for the same subject. The pacing site is determined as the site of earliest activation. The errors in localization are 21 mm (LI) and 12 mm (QI). Note that localization of the pacing site based on the potential map is more accurate than localization based on the isochrone map. Also note that both interpolation schemes capture the general spread of activation from the pacing site.

Subject 2 Reconstructed (GMRes) epicardial potential maps for apical RV pacing in subject 2 are shown in Fig. 10, using LI (left) or QI (right). Panel A shows reconstructed epicardial potential maps during activation, 42 ms after pacing stimulus. Panel B shows the potential maps during early repolarization, 210 ms after pacing stimulus. The errors in locating the RV pacing site from the activation potential map are 7 mm (LI) and 2 mm (QI). Panels C and D show GMRes reconstructed epicardial potentials during activation (42 ms after pacing, Panel C) and early repolarization, (205 ms after pacing, Panel D) during LV pacing in the same subject. The errors in localization of the LV pacing site are 15 mm (LI) and 7 mm (QI) relative to the CT determined pacing-lead placement. Again, the activation potential minimum around the pacing site is replaced by a maximum during early repolarization.

Subjects 3 and 4 Reconstructed (GMRes) epicardial potential maps for pacing in subject 3 are shown in Figs. 11(A) and 11(B), using LI (left) or QI (right). Panel A shows reconstructed epicardial potential maps during activation, 32 ms after pacing stimulus. The errors in locating the RV pacing site from the activation potential map are 8 mm (LI) and 4 mm (QI). Panel B shows epicardial potential maps during LV pacing, 32 ms after pacing stimulus. Errors of localization in the LV are 9 mm (LI) and 4 mm (QI). Figures 11(C) and 11(D) show GMRes reconstructed epicardial potentials in subject 4 during activation (36 ms after pacing) for RV and LV pacing, respectively. The errors in localization of the RV pacing site are 6 mm (LI) and 2 mm (QI). The LV pacing site is located to within an accuracy of 10 mm (LI) and 3 mm (QI).

DISCUSSION

In this paper we formulate a QI scheme for noninvasive ECGI. This scheme uses a superparametric formulation with linear element geometry (six-noded triangle) and QI for potential. We compare the performance of this higher order method to isoparametric formulation with three-noded triangles for geometry and LI for potential that we have used previously. The number of elements used for LI is four times that used for QI (Table 2). The evaluations and comparisons are conducted using data from an isolated canine heart in a human-shaped torso tank, where directly measured epicardial data provide a “gold standard”. Values of RE and correlation coefficient are shown for the time frames exhibited in Fig. 3 and Fig. 5,

as well as averaged over four different cardiac cycles (Table 1). ECGI reconstructions are performed on a beat-by-beat basis and the signal and noise properties of different beats in the same pacing protocol are not exactly identical. Therefore, there are small variations in the average values of RE from one cycle to another within the same pacing protocol. Cycle to cycle variations in CC are even smaller, so that the spatial pattern of reconstructed epicardial potentials remains unchanged from beat to beat within the same pacing protocol. The ability to obtain accurate reconstructions during a single beat is of clinical significance, because it permits mapping, on a beat-by-beat basis, polymorphic or nonsustained arrhythmias that cannot be mapped by collecting data from many beats.

We also apply ECGI using the two interpolation schemes to four human subjects during cardiac pacing. The evaluation includes epicardial potential maps, epicardial electrograms, and isochrone maps. Pacing from single and dual sites provides a measure of accuracy and resolution in imaging localized electrophysiological events in the heart. Importantly, pacing simulates the initiation site of a focal cardiac arrhythmia or the exit site from a reentry pathway of a reentrant cardiac arrhythmia. These sites are important targets for ablation in the clinical treatment of cardiac rhythm disorders. In the human studies, the placement of the pacing-lead tip, as determined by CT, provides a “gold standard” for evaluation. For canine experiments, the minimum negative voltage at which the pacing site was determined (corresponding to the center of the negative potential region in blue, Fig. 3 and Fig. 5) was -4.8mV (single pacing) and -5.4mV (dual pacing). For human subjects, the voltage level of the negative minimum at the pacing site ranged from -2mV to -6mV . Localization accuracy of initiation sites to within 2 mm (the best accuracy obtained with QI) in humans can guide ablation very precisely. The worst case accuracy (within 10 mm) with QI could be sufficient for ablation in many cases. However, if greater accuracy/resolution is needed, local catheter mapping can be performed in the area indicated by ECGI. Regarding arrhythmia mapping, spontaneous arrhythmias that are sustained or occur sufficiently frequently (e.g. sustained VT; premature ventricular contractions, PVC; atrial fibrillation and atrial flutter²¹) can be mapped using ECGI without additional manipulation. For nonsustained arrhythmias that occur infrequently, the arrhythmia could be induced during ECGI using a catheter, so that it can be mapped during a single beat. In this case, the completely noninvasive application of ECGI will be combined with the invasive use of a catheter. However, unlike the roving-probe method of catheter mapping that requires data collection from many identical beats, the ECGI/catheter approach can perform the mapping during a single beat, thus shortening significantly catheterization time and allowing for mapping of nonsustained and polymorphic arrhythmias. More than 30% of clinical ventricular tachycardias have epicardial or subepicardial components which cannot be ablated with endocardial catheters. This led to the development of a transthoracic technique²⁶ for epicardial ablation. ECGI is an ideal tool for guiding such interventions. It could also be used to assess the outcome of an intervention (e.g. ablation or drug therapy) noninvasively in follow-up studies. In other applications, ECGI could be used for risk stratification by detecting, noninvasively, arrhythmogenic substrates such as myocardial infarction with fractionated electrograms^{4,5} or regions of high dispersion of repolarization.¹⁶ Noninvasive screening and identification of patients at high risk will enable intervention (e.g. implanting a pacemaker or a defibrillator) before fatal arrhythmia has occurred.

Higher order elements and interpolation schemes for bioelectric volume conduction problems have been implemented previously by many different groups.^{2,13–15,29} However, their application was mostly limited to analytical problems involving simple geometries such as sphere and cylinder¹⁴ and dealt mainly with improvement of accuracy in modeling the forward problem.^{15,27} Bradley *et al.*² describes methods, advantages and disadvantages associated with fitting human torso geometry with higher order surface elements, without evaluating the comparative accuracies of linear and higher order interpolation schemes in the electrocardiographic inverse problem. The study by Fischer *et al.*¹³ describes application of

higher order elements to the electrocardiographic inverse problem but lacks evaluation of accuracy relative to linear elements. Importantly, none of the previous studies examined the electrocardiographic inverse problem in human subjects in the actual clinical setting, adapting to individual patient's heart and torso geometry. In this study, we conduct an objective comparative evaluation of linear and higher order interpolations in ECGI. This is achieved using datasets from torso-tank experiments where epicardial potentials are directly measured, simultaneously with torso potentials, providing a "gold standard" for evaluation. In addition, we compare, for the first time, the performance of linear and higher order interpolation in humans in the clinical setting of ECGI. An important conclusion of the study is that QI provides higher accuracy and resolution which allow to distinguish between electrical events occurring in close spatial proximity on the heart surface. It also locates single pacing sites in both LV and RV with higher accuracy than LI. This capability has important clinical significance in that it provides high resolution epicardial maps that can accurately localize initiation sites and distinguish between single and closely-spaced multifocal origins of arrhythmogenic activity and other details that affect diagnosis and intervention. These properties were not conclusively shown in previous applications of higher order interpolation in the context of electrocardiography.

Van Uitert *et al.*²⁹ compared linear versus QI in finite element EEG and MEG simulations with realistic head model. They observed that in the forward problem, "the quadratic element method more precisely defines the area of electric potential." We investigated the effect of higher order BEM interpolation on localization capability, accuracy and resolution of cardiac ECGI images. In all cases we observed a marked improvement with QI compared to LI. QI enhanced the spatial resolution of the reconstructed potentials. For dual-pacing data in the torso-tank experiment, QI resolved the two pacing sites located 2.5 cm apart on the anterior epicardium with excellent accuracy using Tikhonov regularization or GMRes. In contrast, LI could not resolve the two discrete pacing sites using Tikhonov regularization. The resolution of reconstructed epicardial potentials is very important clinically, especially for identifying and distinguishing multiple electrophysiological events occurring in close spatial proximity (for example, two accessory pathways in Wolff Parkinson White Syndrome). Another major improvement of QI is the accuracy of amplitude and morphology of reconstructed electrograms. Reconstruction of accurate electrogram morphologies is clinically important, as electrogram morphologies help identify electrophysiologically abnormal substrates⁵ (for example, fractionated electrograms from infarcted myocardium), provide the basis for determining local activation and recovery times, and reflect electrophysiological events like wavefront collisions (producing R-wave morphology). This study shows, through comparison with measured epicardial data in the torso tank experiment, that the QI scheme can reconstruct electrograms containing small deflections and rapid slope changes better than LI, with CC near 1. This high correlation shows that the QI scheme can preserve the morphology of the reconstructed electrograms with a very high degree of accuracy. This capability and previous successful application of LI to fractionated electrograms from infarcted myocardium⁵ indicate that QI has a strong capability to reconstruct electrogram fractionation, an important clinical indicator of arrhythmogenic substrates. Thus, the improvements brought about by use of QI are significant not only from the view point of numerical accuracy but also from the standpoint of electrophysiology and clinical application.

Frijns *et al.*¹⁴ evaluated the accuracy of different BEM formulations in a four concentric spheres problem (simulating the EEG volume conductor problem with the four spheres representing the brain tissue, cerebrospinal fluid, skull and scalp) and found that the highest accuracy was obtained using linear triangles and QI or curved triangles and QI. They further computed potentials in a homogenous cylinder and found that the accuracy of linear triangles and QI was substantially lower than that of curved triangles and QI. In this paper, we use six-noded linear triangles for geometry because a linear triangular mesh can be generated with

minimum time and effort. Moreover it also allows for QI of potentials over each element. Curved triangles may give a better approximation of the epicardial and torso geometries but they entail a much greater preprocessing time and effort. Moreover, while working with curved elements, one needs to specify accurate estimates of torso potential values at boundary nodes on the torso which do not coincide with electrodes. Otherwise the benefit of having a better geometry representation may be offset by errors in values of the torso potential at the boundary nodes. The inverse-forward (IF) interpolation method developed previously⁷ cannot be used in this case, because it first requires generation of a torso-mesh which contains only the electrode sites (i.e. nodes with known torso-potentials) without additional torso-nodes where the potential values are unspecified. This is easily done with linear triangular elements but not with curved elements. The potential value at the mid-point of each side of the triangular torso-element is then computed using the IF interpolation method. This method is based on field theory, and being consistent with the physics of the problem, provides accurate estimate of potentials at the mid points of sides of each torso-element. Using the IF-generated values, a linear mesh can be used with QI for the potential. The QI represents more accurately the variation of potential over each boundary element than LI. It is to be noted that the QI scheme is applied to both epicardial and torso surfaces. Our results show that such an approach generates ECGI images of high resolution and accuracy that are significantly improved compared to linear geometry and linear potential interpolation.

One issue with higher order interpolation is computation time. Table 2 shows the number of nodes and elements used to construct the boundary and the corresponding computation time for each interpolation method. QI requires about twice the computing time of LI for the same number of boundary nodes. However, as shown in this study, it improves significantly the accuracy and resolution of ECGI reconstructions for both Tikhonov regularization and GMRes. The combination of QI in BEM and GMRes in computing the inverse solution provides the highest accuracy and resolution overall.

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FIGURE 1.

Schematic showing the torso surface and the epicardial surface forming the boundary of the source-free torso-volume-conductor, where Laplace's equation applies to the potential ϕ . Boundary conditions are also shown.

FIGURE 2.

(A) Six noded linear superparametric triangle used for quadratic interpolation of potentials in the BEM formulation. (B) Geometry for computing an integral over a triangular element 123 with singularity at vertex node 3. (r, Θ) are polar coordinates with origin at the singular node and reference axis M-R parallel to the side opposite to the singular node.

FIGURE 3.

(A) Epicardial potential map, 25 ms after pacing, comparing measured data (*left*) and reconstructed potentials using linear interpolation (LI; *middle*) and quadratic interpolation (QI; *right*). Inverse solutions are computed using Tikhonov regularization. The higher order interpolation gives a better accuracy as indicated by a lower relative error (RE). Correlation coefficient (CC) and RE are computed relative to directly measured data. (B) Epicardial potential maps 25 ms after pacing, reconstructed using GMRes. Same format as in (A). Asterisk marks the pacing site. Lead V_2 of the ECG is provided for timing purposes.

FIGURE 4.

(A) Epicardial envelope mesh; letters depict the sites from which computed and measured electrograms are shown. (B) Electrogram with Q-wave morphology from site B, near a pacing site (marked by asterisk). (C) Biphasic electrogram from site C at some distance away from the pacing site. (D) Electrogram with R-wave morphology from site D, remote to the pacing site. Measured electrograms are in green, LI in blue and QI in red. CC and RE values are relative to measured electrograms.

FIGURE 5.

(A) Epicardial potential maps during activation, 25 ms after simultaneous dual pacing (pacing sites marked by asterisks). (B) Epicardial potential maps during early repolarization, 93 ms after pacing. *Left* column shows measured potential maps; *middle* and *right* columns show reconstructed potential maps using LI and QI, respectively. Inverse is computed using Tikhonov regularization. (C) Same format as (A), except that GMRes is used for computing the inverse. (D) Same format as (B), except that GMRes is used for inverse computation. Inset shows lead V2 of the ECG for timing purposes.

FIGURE 6.

(A) Q-wave electrogram from a site (site B in Fig. 4(A)) near a pacing site. (B) R-wave electrogram from a site (site D in Fig. 4(A)) far away from the anterior pacing site. Measured electrogram in green, computed LI in blue and QI in red.

FIGURE 7.

Isochrone maps from dual site pacing data: measured (*left*), LI (*middle*) and QI (*right*). QI reconstructs two distinct sites of earliest activation on the anterior epicardium, which correspond to the two pacing sites (asterisks). LI is able to reconstruct only one site of earliest activation.

FIGURE 8.

Relative error (RE) and correlation coefficient (CC) between reconstructed (GMRes) and measured epicardial potentials over one cardiac cycle; (A) and (B). Single Site Pacing. (C) and (D). Dual Site Pacing. Note a lower RE and a better CC for QI (*dark*) compared to LI (*light*) during most of the cardiac cycle.

FIGURE 9.

(A) Reconstructed epicardial potential map in Subject 1, 26 ms after RV apical pacing from asterisk, using LI (*left*) and QI (*right*). The left anterior descending coronary artery (LAD) is shown for orientation. (B) Reconstructed epicardial potential map during early repolarization, 246 ms after pacing stimulus, showing the RV apical potential minimum (blue) in Panel A replaced by a potential maximum (red). Inset shows lead V_2 of ECG, the red and green lines correspond to the times at which the epicardial potential maps are displayed in Panels A and B, respectively. (C) Isochrone map for RV apical pacing in subject 1, showing the anterior RV pacing site (asterisk) using LI. (D) Same as (C), except that QI is used. The epicardial nodes of earliest activation determined from the reconstructed isochrone maps in (C) and (D) are marked by open circles.

FIGURE 10.

(A) Anterior view of reconstructed epicardial potential maps showing potential minimum (dark blue) in the apical RV region during RV apical pacing in subject 2. LAD is shown for anatomic orientation. Maps are reconstructed using LI (left) and QI (right). Anterior view is tilted by 10° to show the RV pacing site (asterisk) as determined from CT images. (B) Reconstructed epicardial potential pattern during early repolarization (same view as in A). Lead V_2 of ECG shown in the inset with the red and green lines corresponding to the times displayed in A and B, respectively. (C) Posterior view of reconstructed epicardial potential maps showing potential minimum (dark blue) around the LV pacing site during LV pacing in subject 2. Maps are reconstructed using LI (left) and QI (right). (D) Reconstructed epicardial potential maps during early repolarization for LV pacing (same view as in (C)). Inset shows lead V_2 of the ECG, the red and green lines indicating the times displayed in Panels C and D, respectively. The asterisk in each panel indicates the location of the corresponding pacing site determined from CT images.

FIGURE 11.

(A) Anterior view of reconstructed epicardial potential maps showing potential minimum (dark blue) 32 ms after pacing stimulus for RV apical pacing in subject 3. Left anterior descending coronary artery (LAD) is shown for anatomic orientation. Maps are reconstructed using LI (left) and QI (right). (B) Posterior view of reconstructed epicardial potential maps in subject 3, 32 ms after stimulus, for LV pacing. (C) Same as A for subject 4, 36 ms after RV pacing. (D) Same as (B) for subject 4, 36 ms after LV pacing.

TABLE 1

Average relative error (RE) and average correlation coefficient (CC) between measured and computed epicardial potentials, over four cardiac cycles.

Protocol	Cycle 1				Cycle 2				Cycle 3				Cycle 4			
	Tikhonov		GMRes		Tikhonov		GMRes		Tikhonov		GMRes		Tikhonov		GMRes	
	LI	QI	LI	QI	LI	QI	LI	QI	LI	QI	LI	QI	LI	QI	LI	QI
Single site pacing																
RE	0.88	0.68	0.84	0.66	0.85	0.63	0.82	0.65	0.86	0.67	0.84	0.68	0.85	0.62	0.83	0.60
CC	0.742	0.811	0.753	0.794	0.744	0.814	0.755	0.795	0.745	0.813	0.754	0.795	0.742	0.811	0.754	0.793
Dual site pacing																
RE	0.87	0.62	0.82	0.59	0.85	0.59	0.79	0.55	0.90	0.63	0.84	0.60	0.90	0.63	0.85	0.60
CC	0.764	0.782	0.784	0.814	0.766	0.782	0.781	0.814	0.759	0.780	0.781	0.813	0.762	0.782	0.781	0.811

TABLE 2
Computation times for the transfer matrix A for linear and quadratic interpolation.

Data	Linear				Quadratic					
	N_T	E_T	N_E	E_E	Computing time	N_T	E_T	N_E	E_E	Computing time
Single/dual site	1538	3072	954	1904	6 min 48 s	1538	768	954	476	14 min 12 s
pacing in										
canine heart										
Subject 1	582	1160	1470	2936	4 min 30 s	582	290	1470	734	10 min 21 s
Subject 2	906	1808	1742	3480	7 min 34 s	906	452	1742	870	17 min 14 s
Subject 3	610	1216	1670	3336	5 min 57 s	610	304	1670	834	13 min 26 s
Subject 4	638	1272	1494	2984	5 min 2 s	638	318	1494	746	12 min 29 s

Note. N_T and E_T denote the number of nodes and number of elements on the torso surface and N_E and E_E on epicardial surface. All computing times were measured with respect to a single 3.2 GHz processor with 2 GB memory. The codes were written in Matlab 6.5.