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Estimation of Epicardial Activation Maps From Intravascular Recordings

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Abstract: Multielectrode catheters provide a percutaneous means of recording activation near the epicardium but only for a relatively small number of sites that are restricted to the major coronary vessels. We have applied a statistical signal processing technique to estimate the value of activation time over the entire epicardium (490 sites) from leadsets consisting of 4 to 40 sites aligned with major branches of the coronary veins. We tested this method using data from high-resolution epicardial mapping from six dog hearts and 153 activation sequences. A study including data from both normal and infarcted dog hearts yielded estimates of activation time, with mean correlation coefficients ranging from 0.97 to 0.84 and achieved localization of earliest site of activation to within 3 to 15 mm, depending on training parameters and leadset. These results suggest that with 10 to 15 catheter-mounted electrodes, it may be possible to reconstruct epicardial activation maps from percutaneous recordings. **Key words:** electrocardiography, statistical estimation, cardiac mapping, activation, multielectrode vascular catheters.

Extracellular potentials measured from the outer cardiac surface (epicardial electrograms) provide a direct means of studying the electrical activity of the heart (1–6). Specific clinical examples of using epicardial potentials to characterize abnormal cardiac activity in humans include focal ventricular tachycardia (7), accessory pathways (8), reentry (9,10) or the functional role of the subepicardium in postinfarction tachycardias (11–13).

By recording from multiple sites on the heart simultaneously—a technique known as cardiac mapping—it is possible to combine spatial and temporal information to reveal at least some of the electrophysiologic behavior of the underlying tissue. Specific approaches to the analysis of cardiac maps include examining sequences of isopotential contour maps corresponding to instants in time or iso-value maps of parameters extracted from the potential signals. Perhaps the most useful parameter for capturing the path of the spread of activation is the time at which the activation wavefront passes each electrode—the "activation time." Measurement of activation times from more than a few sites on the epicardium, however, requires highly invasive open-chest surgery. Consequently, epicardial potential and activation time mapping are techniques used extensively in animal experiments but reserved clinically for special cases such as treating

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complex arrhythmias that do not respond to conservative treatment (11,14).

Of much greater clinical importance is the use of catheter electrodes to measure endocardial and epicardial potentials (15–19). This approach is considerably less invasive than open-chest cardiac mapping, but is limited by the number of simultaneous measurement sites and the locations accessible by means of vessels, especially when mapping the epicardium. A recent technical innovation that attempts to address the first limitation is the manufacture of multielectrode (4- to 16-channel) catheters that are small enough to fit within the coronary veins. Several reports in the literature describe the use of such catheters in localizing critical regions of reentrant ventricular tachycardia in subepicardial regions (13,15,19). The second limitation remains, however, as even the smallest multielectrode catheters can reach only into the major side branches of the main coronary veins, leaving most of the epicardium inaccessible to direct measurement (19).

In view of both the advantages of percutaneous measurement and the limits of constrained access, we have begun to investigate the feasibility of catheter-based epicardial mapping. The underlying premise of this research—and the hypothesis tested in this report—is that certain comprehensive spatial features of cardiac electrophysiology can be detected and characterized from measurements that are constrained to the main coronary veins and their major branches provided there is sufficient a priori knowledge, here in the form of a previously recorded database. The origins of this hypothesis lie in numerous previous studies that have demonstrated considerable redundancy in spatial features measured with body surface potential mapping (20–22). Some of this redundancy results from the smoothing effect of the thorax on the potential fields generated by the heart (23). However, redundancy also suggests the existence of patterns that can be captured statistically and used to describe subsequent distributions, often with a much smaller number of measuring electrodes than was originally required.

The field of statistical signal processing provides techniques for characterizing redundancy in spatiotemporal data and for developing estimation methods based on reduced sets of measurement sites (24). The first use of statistical techniques for lead selection in electrocardiology was by Barr et al. (20), while Lux et al. described statistical techniques for both limited lead selection (25,26) and later for data compression (22,27). Uijen et al. then described a slightly more efficient approach to data compression in body surface potential mapping (28).

The research reported here consists of two studies required to extend the techniques of limited lead mapping to the epicardial surface. The goal was to investigate the feasibility of a venous catheter-based measurement system as a means of capturing spatial details of the activation sequence of ectopic ventricular beats. The first study consisted of comparing the signals recorded from multielectrode venous catheters to electrograms from nearby epicardial sites. In the second study, we utilized a database of activation times from high-resolution, epicardial mapping experiments to examine several methods of reconstructing complete activation maps from leadsets that were limited to paths corresponding to coronary veins. Taken together, the results of these studies suggest that it is, indeed, feasible to capture complete epicardial activation patterns by means of statistical estimation techniques and sets of 20 to 40 leads that are located in the coronary vessels.

We have presented portions of this work previously at the 1998 North American Society for Pacing and Electrophysiology Annual Scientific Session (29) and in the Masters of Science thesis of the first author (30).

Methods

This report describes results using a statistical method of estimating epicardial activation maps from measurements that are constrained to the coronary veins. This method requires that a large number of measurements at all desired lead locations be available for training. For testing the resulting estimator, a separate set of such measurements must also be available. To generate such a database would require simultaneous recordings from both catheter and epicardial electrodes for at least several experiments. The catheter electrode configuration chosen for these experiments would essentially dictate the choice of lead subsets available for testing. Each new lead subset would require a completely new series of experiments.

We pursued a different strategy in which high-resolution epicardial maps would provide all the necessary signals. To test a specific leadset, we would simply select a subset from the complete electrode set to serve as surrogates for catheter electrodes and then derive the statistical estimator that would generate all remaining (previously measured) values. By this route, it is possible to test

many lead subsets from a single series of experiments. This strategy requires, however, that the epicardial electrograms are very similar to those from nearby catheter electrodes, a condition that we tested in the first study reported here. The results from this study then permitted us to pursue a second study of statistical estimation of cardiac activation time based on a database of epicardial activation maps.

In this section, we first briefly outline the experimental methods used in the comparison of catheter and epicardial signals, then we describe the database of epicardial maps and the estimation techniques applied to this database.

Catheter Experiments

To compare catheter and epicardial signals, we conducted experiments on two mongrel dogs (20 and 28 kg), which were anesthetized with 30 mg/kg IV sodium pentobarbital, intubated, and prepared for open-chest epicardial potential mapping as described by Taccardi et al. (6). Before surgically exposing the heart, multielectrode Pathfinder catheters (Cardima Inc., Fremont, CA) with 2- to 6-mm spacing in 4-, 8-, or 16-electrode configurations were inserted by means of either the external jugular or femoral vein and advanced into coronary veins via the coronary sinus. Once recording catheters were in place, the heart was exposed through either a midsternal sternotomy or lateral thoracotomy and pericardial cradle. To record nearby epicardial signals, we placed two different electrode arrays with regular, 2- and 4-mm spacing directly over the mapping catheters. When visual inspection did not reveal the location of the catheter in the vessel, fluoroscopy was used to ensure coverage by the epicardial electrode array. The arrays contained either 182 (13 × 14 points with 4-mm spacing), or 192 (16 × 12 points with 2-mm spacing) regularly spaced electrodes sewn into nylon stocking material (4).

Epicardial Map Database

The database of epicardial measurements used in this study consisted of recordings from a total of six separate experiments with open-chest dogs performed between November 1994 and February 1997 by Dr. Bruno Taccardi. Each experiment included the recording of epicardial potentials from the exposed heart of an anesthetized, 20- to 25-kg dog by means of a 490-electrode sock array that covered both ventricles (4). Consistent alignment of markings on the sock with anatomic landmarks provided approximately similar placement of the electrodes across experiments.

One of the most important goals in clinical mapping is to localize sites of early activation resulting from ectopic activity or the escape of activation from a region of slow conduction, as occurs in the Wolff–Parkinson–White syndrome and in reentrant and focal tachycardias (8). Most challenging in this context are beats that originate from epicardial or subepicardial regions (12,13,31,32). For this study, we concentrated on reconstructing beats that followed single-point, epicardial, and subepicardial stimulation. For the database, we selected a set of 153 beats stimulated from epicardial and subepicardial sites located over both ventricles. Five days prior to one of the six experiments, the left anterior descending artery of the heart was permanently occluded just below the first diagonal branch. The resulting infarct, documented after the experiment by means of 2,3,5-triphenyl tetrazolium chloride (Sigma, St Louis, MO) staining, was subendocardial, ranging in extent from the apex to approximately 5 cm above the apex and encompassing one half of the circumference of the left ventricle. Beats from this particular experiment made up 31 of the 153 beats included in the database.

Signal Acquisition

In both studies, stimulation was performed by means of either an atrial hook, subepicardial bipolar needle electrodes inserted into the left and right ventricles, or unipolar epicardial electrodes from the 490-lead sock. Our custom-made acquisition system sampled all signals (up to 512) simultaneously at 1000 Hz with 12-bit resolution in 4- to 7-second epochs. Recorded electrograms were then gain adjusted, baseline corrected, windowed, and either signal averaged or individual beats selected to create representative beats from each epoch. We defined activation times for each lead of each representative beat in the usual manner as the time of occurrence of the negative peak in the first time derivative of the unipolar electrograms (33). Each resulting activation map was manually checked for accuracy of activation time determination.

Lead Subset Selection

Because the goal of this research was to evaluate the feasibility of map reconstruction based on venous catheter measurements, the selection of lead subsets from the epicardial mapping database was

critical. The basis of lead selection was a three-dimensional geometric model of the 490 recording sites and the associated cardiac vascular anatomy, which we created by mechanically digitizing the physical mold used to construct the epicardial sock arrays (see Fig. 1). To be eligible for selection, an electrode from the sock had to lie over a major, superficial coronary vein suitable for catheter cannulation (19). Targeted vessels included the coronary sinus (CS), great cardiac vein (GCV), left ventricular posterior vein (LVP), and middle cardiac vein (MCV). The result was a set of 42 sites with a mean spacing of 6 mm, which we could then further subsample to investigate the effect of sampling density on reconstruction accuracy. Vascular leadsets included 42, 21, 14, 10, 9, 6, and 4 leads, spaced approximately evenly along the associated veins.

Implementation of Estimation Algorithm

The statistical technique we employed to reconstruct the full epicardial activation maps from limited leadsets was a linear least squared estimator (24) based on a database of measured epicardial activation maps. The resulting linear transform—in the form of a matrix—could then be applied to any subsequent measurements from the limited leads in order to obtain the full resolution estimate. Figure 2 summarizes the steps required in the estimation technique. The following section describes our particular implementation of this method; Lux et al. provide a derivation for body surface potentials (25), but for a more general derivation of linear estimators, see, for example, Deutsch (24).

The first component of the estimation technique is the training phase, which begins by defining the training database and selecting the particular vascular leadset. The training database is composed of N activation maps each containing M values, from which we constructed a matrix $\mathbf{A}$ of N column vectors, each of size $M \times 1$. As described above, for this study we selected from the 490-electrode sock subsets of 10 to 42 sites that lay over major branches of coronary veins. The resulting M_K leads contained values that we assumed would be known during subsequent estimations. We then reordered the values in each column of $\mathbf{A}$ such that the known values filled the upper M_K rows. Each selection of a new lead subset thus required a different ordering of $\mathbf{A}$ and resulted in a different estimation matrix. In the schematic example shown in Figure 2, the high-resolution map contains 49 (7×7) electrodes with a subset of vascular leads containing only eight leads. Therefore, $M_K = 8$ and M_U (the number of unknown values) $= 41$. The matrix $\mathbf{A}$

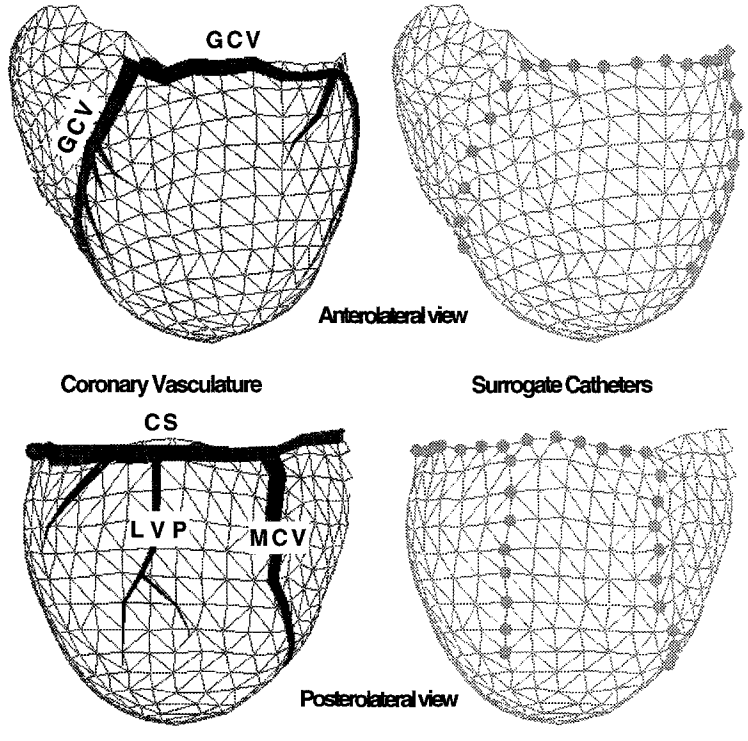

Fig. 1. The 490-lead epicardial sock model used to select surrogate catheters and evaluate the statistical estimation procedure. Nodes of the triangulated mesh correspond to the electrode locations. The two left panels show the anterolateral and posterolateral views of major elements of the coronary vasculature. The two right panels show the same views with the 42-lead vascular leadset superimposed. Large vessels include the great cardiac vein (GCV) ascending along the anterior interventricular groove, the left ventricular posterior vein (LVP), and coronary sinus (CS), and the middle cardiac vein (MCV) ascending along the posterior interventricular groove.

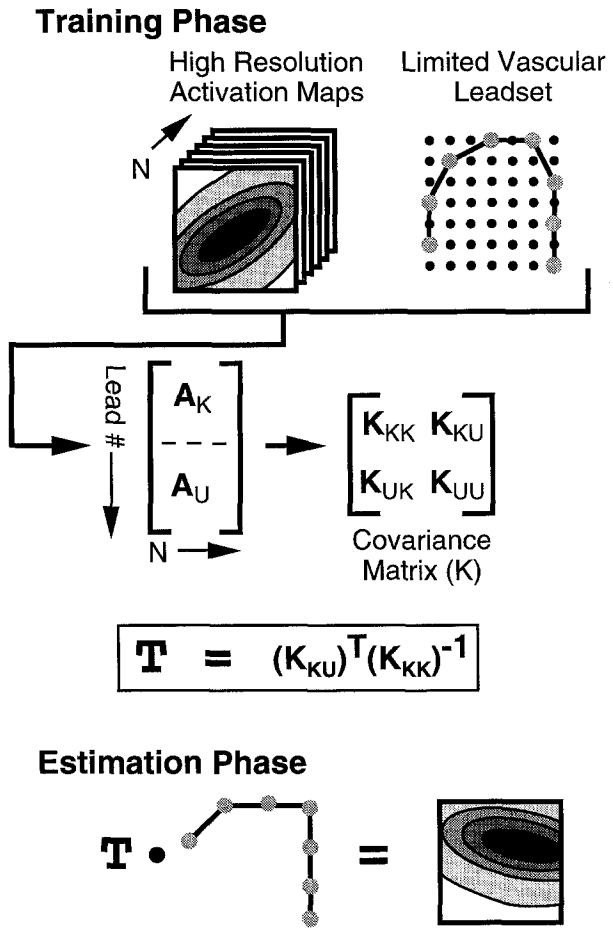

Fig. 2. Training and estimation phases of the statistical estimation method. The training phase required collecting numerous high resolution activation maps and defining a vascular leadset. A lead-specific transformation was derived from the covariance of the high resolution maps and the leadset information as described by Lux et al. (25). The *estimation phase* applied the linear transformation matrix (**T**) to expand subsequent measurements from the vascular leadset to complete epicardial activation maps. See text for details.

can then be partitioned into an $8 \times N$ upper partition $\mathbf{A}_K$ and $\mathbf{A}_U$, the $41 \times N$ lower partition.

The next step in the training phase is to calculate the covariance matrix **K** according to

$$\mathbf{K} = \frac{(\mathbf{A} - \bar{\mathbf{A}})(\mathbf{A} - \bar{\mathbf{A}})^T}{M} \quad (1)$$

where $\bar{\mathbf{A}}$ is a matrix with identical columns, each of which is the mean activation vector across all maps. We then partition **K** into blocks according to M_K and M_U

$$\begin{bmatrix} \mathbf{K}_{KK} & \mathbf{K}_{KU} \\ \mathbf{K}_{UK} & \mathbf{K}_{UU} \end{bmatrix} \quad (2)$$

where $\mathbf{K}_{KK}$ and $\mathbf{K}_{UU}$ are both square submatrices of size M_K and M_U, respectively, $\mathbf{K}_{KU}$ is of size $M_K \times M_U$ and $\mathbf{K}_{UK}$ is its transpose. Finally, the transformation, **T**, is formed by solving the simple matrix equation,

$$\mathbf{T} = (\mathbf{K}_{KU})^T(\mathbf{K}_{KK})^{-1} \quad (3)$$

The result from the training phase is a $M_U \times M_K$ matrix of basis functions, **T**, that is unique to the selected lead subset and the training database. Left multiplication by **T** of any subsequent measurement vector of the same M_K electrodes yields an estimate of the values at all M_U remaining sites and thus a complete, high-resolution map according to the equation

$$A_U^i = \mathbf{T} \times (A_K^i - \bar{A}_K) + \bar{A}_U \quad (4)$$

where A_K^i and A_U^i are the measured and estimated portions, respectively, of a single activation time vector.

Training Protocol

A key consideration in training and then testing a statistical method such as estimation is how to divide the database. The estimation matrix contains the best least squares fit to the information in the training dataset, which we assume is also applicable to the test dataset. In selecting training and test subsets from the database of epicardial activation maps, we attempted to create situations that would evaluate the estimation approach under a variety of realistic conditions. One example is the case of a number of technically poor quality signals in a single experiment, as might arise when electrode contact was poor or varied over time. A more clinically relevant example is one in which epicardial maps from one cohort of patients are used to create the **T** matrix that is applied to catheter-based recordings from a completely new patient. To capture these situations, we created a training/testing paradigm consisting of three levels, each with a progressive decrease in the amount of training. The first level of training used all activation maps in the training phase and then measured the ability the resulting transform matrix to estimate each individual member of the set. We have adopted the notation of Fukunaga (34) in referring to this protocol as "resubstitution" (RESUB). The second training level was a version of the "leave-one-out" protocol in which we left out one activation map from the training set used this for testing, and repeated this for each map to generate means errors over the entire database. This we referred to as

"leave-one-map-out" (L-MAP). The third level was similar to the second in that we used a leave-one-out protocol, but this time all the maps from one entire experiment were left out, which we referred to as "leave-one-experiment-out" (L-EXP).

Statistical Measures

The goal of the first study was to compare electrogram measured from catheter electrodes to those from nearby epicardial sites. In the second study, the comparison was between measured values of activation time and those predicted using the statistical estimation technique. We used similar statistical measures of error for both studies: correlation coefficient (CC), root mean square error (RMSE), and relative error (RE), which were computed from the same equations,

$$(5)\quad CC = \frac{\sum_{i=1}^{N}(V_i^c - \overline{V^c})(V_i^e - \overline{V^e})}{\sqrt{\sum_{i=1}^{N}(V_i^c - \overline{V^c})^2}\sqrt{\sum_{i=1}^{N}(V_i^e - \overline{V^e})^2}}$$

$$(6)\quad RMSE = \sqrt{\frac{\sum_{i=1}^{N}(V_i^e - V_i^c)^2}{N}}$$

$$(7)\quad RE = \sqrt{\frac{\sum_{i=1}^{N}(V_i^e - V_i^c)^2}{\sum_{i=1}^{N}(V_i^c)^2}}$$

but with different variables. In comparing electrograms, V_i^c represents catheter potentials and V_i^e epicardial potentials for time instant i, while N is the number of time instants. For estimated activation times, V_i^c is a measured activation time, V_i^e is the associated estimated value, and $N = N_U$ is the number of sites for which values were estimated. $\overline{V^c}$ is the mean of V_i^c, and $\overline{V^e}$ is the mean of V_i^e. CC exhibits greater sensitivity to differences in pattern than in amplitude of signals. RMSE represents the averaged squared error between signals in absolute terms and RE is RMSE normalized by the mean signal power.

For the comparison in the first study of electrograms recorded from catheters and epicardial sock electrodes, we computed difference statistics separately for the excitation (QRS wave) and repolarization (T wave) components of the signals, which we defined temporally based on visual inspection of the root mean square signal computed from all channels of data. We also computed some additional quantities to compare electrogram features including peak-to-peak amplitude during QRS, time of activation, and first time-derivative value at activation.

To obtain a better evaluation of the estimation technique, we performed a cross-validation test in which we repeated the division of the database into training and testing subsets for all possible permutations and then computed the mean error for each. For example, in the L-MAP protocol, we computed a **T** matrix for each of the 153 possible cases in which one of the activation maps was left out for testing. The values displayed for L-MAP in the results section therefore represent means (and standard deviations) computed from 153 individual validation tests. As a further measure of overall performance, we computed mean error values at each electrode location over a range of estimated beats and displayed the results as iso-error maps for different training protocols and lead subsets. The resulting figures provide a spatial description of the level of error relative to the location of the subsampled electrodes (see, for example, Fig. 9).

Finally, to measure the ability of estimated activation maps to recover a particularly useful clinical parameter, we also computed the euclidean distance (LDist), based on the three-dimensional geometric model of the heart, between the location of the measured and estimated earliest sites of activation.

Results

Catheter Versus Epicardial Electrograms

We first show results from the catheter experiments in order to provide evidence that signals acquired from within the coronary veins are, indeed, similar to those recorded from nearby true epicardial sites.

A consistent finding after performing statistical comparison of catheter and epicardial signals was that for each catheter electrode, the most similar epicardial sites were the first-order nearest neighbors. Figure 3 contains an example of simultaneously recorded electrograms from three different catheter electrodes and their four respective nearest epicardial signals over three activation sequences. Catheter signals were strongly correlated with the nearest epicardial signals, with the largest differences occurring during the QRS complex. The sources of these differences were largely in the timing, as would be expected given the 2- to 4-mm

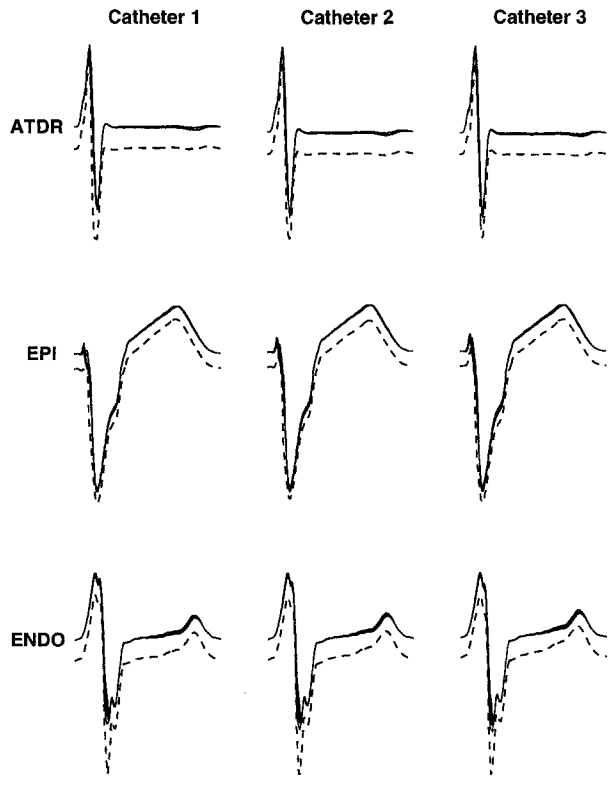

Fig. 3. Simultaneously sampled intravascular and nearby epicardial electrograms. Dashed lines indicate the electrograms from venous catheters while the solid lines are composed of the electrograms from the four nearest (within 2 mm) epicardial electrodes. Each column contains signals from the same set of electrodes for three different pacing sequences: atrial (ATDR), epicardial (EPI), and endocardial stimulation (ENDO). The rows contain signals from the same pacing sequence for three different sets of leads. Note that all catheter electrograms have been shifted down by 4 mV for visualization purposes.

spacing between electrodes, and also in slight changes in QRS morphology.

Table 1 contains a summary of statistical comparison between catheter and neighboring epicardial electrograms. Two sets of values are provided for neighbors within 2 mm and those between 2 and 4 mm from the catheter electrode. Correlations rarely dropped below 0.95, while the mean RMS error ranged from only 1.3 to 2.8 mV.

As an additional means of comparing epicardial and catheter signals, we extracted activation times from both sets of electrograms. From these data, we counted the number of times the activation time from the catheter electrode fell within the range of activation times determined by the four nearest neighbors. With epicardial electrode spacing of 4 mm, catheter activation time was within the range of its four neighbors in 86.78% of the cases, while even over the smaller neighborhood region for the 2-mm epicardial sock, the values was still 82.50%.

Limited-Lead Reconstructions

With the high degree of similarity between epicardial and catheter electrograms well established, we continued with the second study, in which we estimated activation times for the entire 490-electrode sock array from limited-lead subsets of 10 to 40 electrodes. To evaluate the accuracy and feasibility of the estimation approach, we varied parameters such as lead number and density, site of ectopic stimulus, level of training, and composition of the training and test sets. To describe the resulting reconstruction errors, we used both qualitative and quantitative measures of the difference between the original 490-lead epicardial sock measurements and the reconstruction from a lead subset. The results that follow are organized according to the parameter that was varied.

Effect of Lead Sampling. From the original subsampled set of 42 leads aligned with the coronary veins, we selected progressively sparser leadsets and reconstructed activation maps for each configuration. The main criterion for the subsampling was to preserve relatively uniform spacing and the same coverage of the veins as in the original 42 leads. Figure 4 shows the resulting isochrone maps for a single pacing site in the left ventricular apex for the original high-resolution maps and sets of 21, 14, and 10 leads, estimated using the L-MAP protocol. Values of CC between original and reconstructions varied from 0.99 to 0.95 as the number of leads diminished. Examination of the maps reveals excellent maintenance of the site of earliest activation (within 6.94 mm) and a progressive smooth-

Table 1. Signal Similarity Between Vascular and Nearest Epicardial Electrograms (Mean Values ± SD)

		Electrode Proximity	
		≤4 mm, ≥2 mm	≤2 mm
CC	Whole signal	0.955 ± 0.077	0.964 ± 0.054
	QT	0.951 ± 0.074	0.964 ± 0.054
	QRS	0.949 ± 0.070	0.960 ± 0.046
RMSE (mv)	Whole signal	1.316 ± 0.747	1.422 ± 0.431
	QT	1.481 ± 0.819	1.595 ± 0.482
	QRS	2.485 ± 1.360	2.801 ± 0.981
# of electrograms compared	(n)	484	160

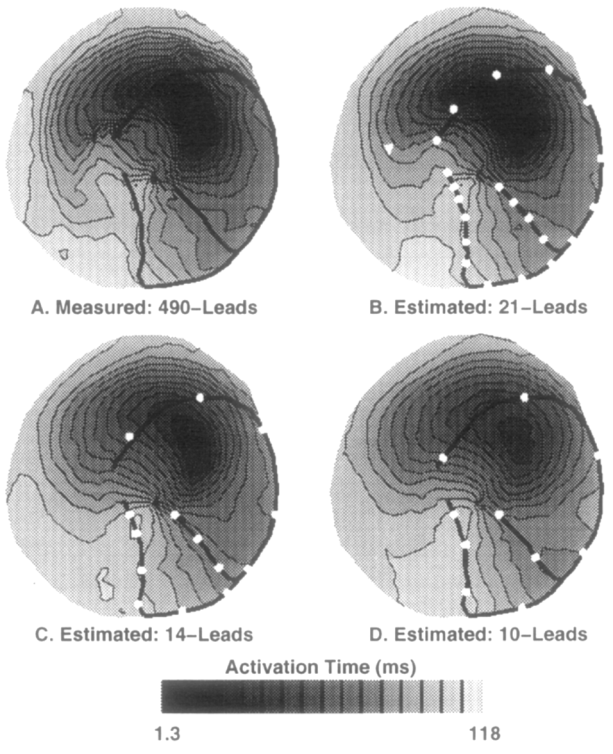

Fig. 4. Polar projections of the original and statistically estimated isochrone maps of activation for an epicardial pacing site in the left ventricle for the L-MAP case. The locations of the selected measurement leads are indicated by the white dots on the heavy black lines. Isochrones are displayed every 7.3 msec. (A) Original. (B) Estimation from 21 leads (CC = 0.99; RMSE = 4.2 msec; RE = 4.87%; LDist = 6.94). (C) Estimation from 14 leads (CC = 0.97; RMSE = 6.32 msec; RE = 7.33%; LDist = 6.94). (D) Estimation from 10 leads (CC = 0.95; RMSE = 8.35; RE = 9.68%; LDist = 5.02).

ing of the isochrone lines with reduction in lead number.

To create statistical indices of the effect of lead sampling, we repeated the calculation of reconstruction error for all ectopic pacing sites and all possible compositions of the training and test sets. Tables 2 through 4 contain the results for seven different lead subsets and all statistical indicators. Each table corresponds to a different training protocol. Figure 5 contains the same data in graphical form.

As should be expected, as the number of measured leads increased, the accuracy of reconstruction improved, at least for the L-MAP and RESUB protocols. For the L-EXP, mean relative error actually increased with number of leads, but the change was small compared to the associated standard deviations.

Effect of Training Protocol. To isolate the effect of training protocol, we compared maps reconstructed with the same lead subset but for all combinations of training. Figure 6 contains an example of isochrone maps for an apical pacing site and a 14-lead subset for each of the three training protocols. Tables 2 through 4 also contain data that illustrate the relationship between training and reconstruction accuracy. In the RESUB case, the average CC for 14 leads was 0.954. In the L-MAP case, CC values for 14 leads dropped only slightly to 0.943. The L-EXP for the same lead subset demonstrated a further reduced accuracy, with mean CC = 0.897. This reduction of accuracy going from RESUB to L-MAP to L-EXP protocols is also visible in the graphs in Figure 5 and the activation maps in Figure 6. Accuracy of the predicted site of earliest activation for the case shown in Figure 6 dropped from 5.89 to 14.97 mm, although the drop in the mean value for this parameter was slightly less precipitous (6.9 to 11.57 mm).

Effect of Pacing Site. The values for standard deviation of the error statistics give some impression of the variation caused by pacing site location. To further illustrate this effect, Figure 7 contains a comparison of measured and reconstructed maps for the L-EXP protocol with pacing from left ventricle, apex, and right ventricle. The errors in earliest activation site range from 5.27 to 12.67 mm, and the CC values likewise vary from 0.96 to 0.92. The isochrone maps support these results, indicating

Table 2. Effect of Varying Lead Density on Reconstruction Accuracy for the RESUB Protocol

# Leads	CC	RMSE (msec)	RE (%)	LDist (mm)
42	0.977 ± 0.015	4.74 ± 1.43	6.59 ± 2.09	2.62 ± 4.14
21	0.963 ± 0.038	5.91 ± 1.96	8.15 ± 2.67	5.19 ± 6.06
14	0.954 ± 0.042	6.62 ± 2.26	9.12 ± 3.00	6.90 ± 6.21
10	0.946 ± 0.045	7.15 ± 2.13	9.82 ± 2.85	8.27 ± 6.32
9	0.940 ± 0.059	7.54 ± 2.37	10.36 ± 3.25	8.91 ± 6.53
6	0.908 ± 0.076	9.97 ± 3.33	13.71 ± 4.51	12.19 ± 8.31
4	0.878 ± 0.098	11.56 ± 3.71	15.82 ± 4.77	14.84 ± 8.96

Table 3. Effect of Varying Lead Density on Reconstruction Accuracy for the L-MAP Protocol

# Leads	CC	RMSE (msec)	RE (%)	LDist (mm)
42	0.949 ± 0.048	6.86 ± 2.62	9.46 ± 3.71	6.85 ± 6.04
21	0.947 ± 0.057	7.01 ± 2.61	9.63 ± 3.46	8.02 ± 6.44
14	0.943 ± 0.051	7.37 ± 2.59	10.11 ± 3.34	8.88 ± 6.47
10	0.938 ± 0.051	7.74 ± 2.45	10.61 ± 3.18	9.97 ± 6.59
9	0.931 ± 0.070	8.09 ± 2.64	11.09 ± 3.52	10.27 ± 6.37
6	0.899 ± 0.084	10.46 ± 3.55	14.36 ± 4.72	12.92 ± 8.08
4	0.868 ± 0.107	11.97 ± 3.97	16.38 ± 5.04	15.58 ± 8.82

shifts and smearing of the distributions that are much larger in the case of right ventricular pacing than for apical or left ventricular ectopic beats.

To further capture the effect of pacing site on the estimation technique, we separated all the beats in the database into left (106 beats) and right (47 beats) ventricular paced subsets and repeated the analysis, reconstructing the left ventricular beats using an estimator derived from former subset and the right ventricular beats with the latter subset. The results are shown in Figure 8 in graphical form as errors in site of earliest activation as functions of the number of leads in the selected subset. We found improved results from left ventricular pacing compared to right ventricular, but the overall shape of the curves and the effects of training protocol were qualitatively similar to those seen in Figure 5.

Effect of Infarction. Of the 153 beats in the complete epicardial activation dataset, 31 were from an experiment in which the heart had extensive infarcted tissue resulting from a surgical occlusion of the left anterior descending artery five days before cardiac mapping. This provided an opportunity to evaluate performance of the algorithm under conditions closer to those present in a clinical case of postmyocardial infarct patients. In all lead configurations, the average errors from this subset of cases varied from the overall averages shown in Tables 2 through 4 by no more than a few percent. Most notably, the differences for the L-EXP case, in which beats from the five noninfarct experiments provided the training data for the estimator, which we then applied to the beats from the remaining infarcted heart experiment, were also negligible. CC and RE values for the infarcted case with 21 leads were 0.90 ± 0.08 and 14 ± 5%, respectively, while the equivalent values over all cases were 0.89 ± 0.08 and 15 ± 5%.

Spatial Distribution of Mean Errors. Finally, by computing the mean error at each reconstructed electrode site over all beats, and then assigning that value to the electrode site, it was possible to create iso-error maps of the epicardial surface. These distributions suggest an effective spatial range over which there is some statistical confidence of a result at a particular error level. Figure 9, for example, contains the iso-error plots for the RMS error in activation time for three different leadsets. A region colored with a particular shade of grey indicates that the mean error in this area lies within the bounds shown in the legend for the selected gray scale. Figure 10 contains similar maps, but this time organized according to training protocol, with a fixed number of leads (14). Both plots suggest that the smallest errors are in the regions surrounding the measurement leads but that the region with mean errors below 10.33 ms (the fifth gray-scale bin) cover almost the entire left ventricle and portions of the right ventricle.

Discussion

The results from this study show that performing epicardial mapping from catheter-based measure-

Table 4. Effect of Varying Lead Density on Reconstruction Accuracy for the L-EXP Protocol

# Leads	CC	RMSE (msec)	RE (%)	LDist (mm)
42	0.864 ± 0.082	11.73 ± 3.71	16.33 ± 5.42	11.78 ± 10.86
21	0.886 ± 0.084	10.86 ± 3.67	15.16 ± 5.48	11.20 ± 9.83
14	0.897 ± 0.068	10.35 ± 3.07	14.37 ± 4.50	11.57 ± 10.00
10	0.898 ± 0.067	10.16 ± 2.89	14.03 ± 3.95	11.95 ± 8.42
9	0.890 ± 0.085	10.52 ± 3.05	14.56 ± 4.32	11.86 ± 8.16
6	0.866 ± 0.087	12.75 ± 4.33	17.63 ± 5.99	15.35 ± 10.55
4	0.842 ± 0.112	13.57 ± 4.96	18.71 ± 6.62	17.58 ± 10.48

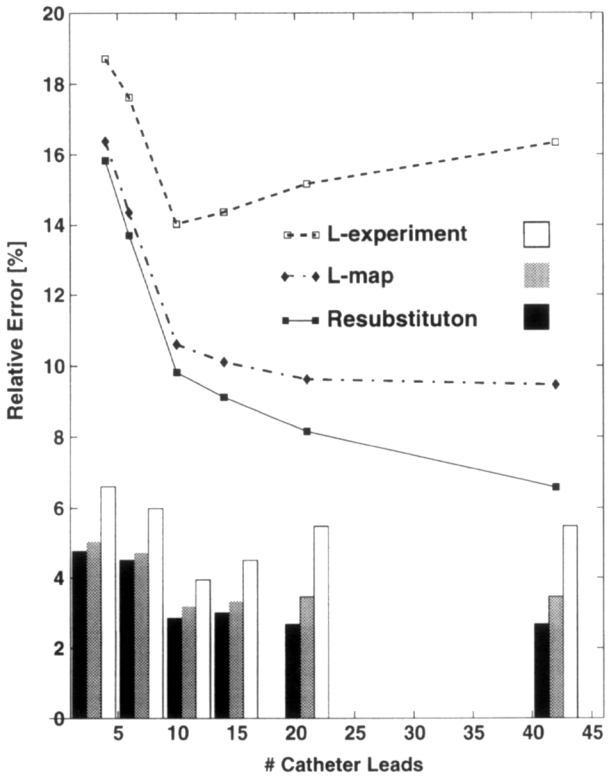

Fig. 5. Mean relative error (RE) and standard deviation as a function of lead subsampling and training protocol. Mean RE are displayed as line plots with standard deviations error bars drawn below. Standard deviation bars have been shifted down so as not to obscure the display.

ments is both electrophysiologically justified and technically feasible. A fundamental finding from the first study that is relevant to all forms of vascular catheter measurements is that the electrograms recorded from venous catheters were highly correlated with those from nearby epicardial contact electrodes. Differences in activation times between catheters and epicardial electrodes were also negligible over the 2-mm spacing of the epicardial mesh. These findings provide essential support for subsequent components of the research described here, in which we sought to use small subsets of epicardial leads to reconstruct a complete image of the spread of cardiac activation.

Although catheter-based mapping is very common on the endocardial surfaces of the heart, there have to date been very few published reports on mapping of the epicardium by means of venous catheters (13,15,19,31), even though significant numbers of tachycardias are known to exhibit early activation or critical components of reentry in the subepicardial region (12). While new, narrow-gauge catheters will expand the number of veins accessible for mapping, a fundamental limitation to the technique is the restricted number of sites directly adjacent to coronary vessels (19). The research described here represents a novel means of addressing this limitation by applying advanced mapping and statistical signal processing techniques.

A standard approach to reconstructing data values at sites between measurement electrodes is interpolation. However, the sparse placement of electrodes inherent to vascular catheter mapping limits the utility of interpolation techniques for this situation, as shown by our preliminary findings (30). Here we report instead on a statistical approach using a linear estimation model that derives its basis functions and weights out of an existing database of high-resolution activation time maps. In this way, it makes almost no assumptions (other than linearity) about the relationship between mea-

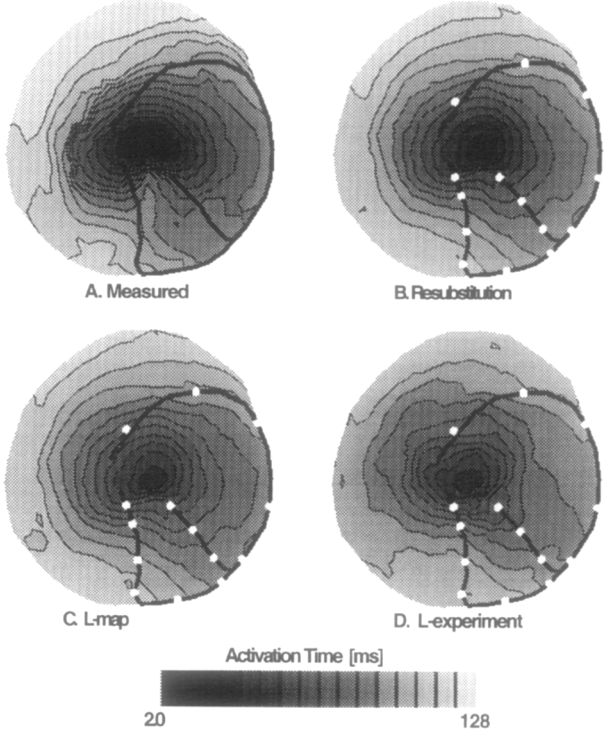

Fig. 6. Polar projections of measured and statistically estimated activation maps for an epicardial pacing site in the apex under various training protocol. The 14 leads in the subset are represented in white. Isochrones are displayed every 7.88 msec. (A) Original. (B) Estimation derived from RESUB protocol (CC = 0.97; RMSE = 9.17 msec; RE = 10.42%; LDist = 5.89 mm). (B) Statistical estimation from L-MAP protocol (CC = 0.96; RMSE = 10.00 msec; RE = 11.36%; LDist = 6.30 mm). (D) Statistical estimation for L-EXP protocol (CC = 0.88; RMSE = 16.30 msec; RE = 18.52%, LDist = 14.97 mm).

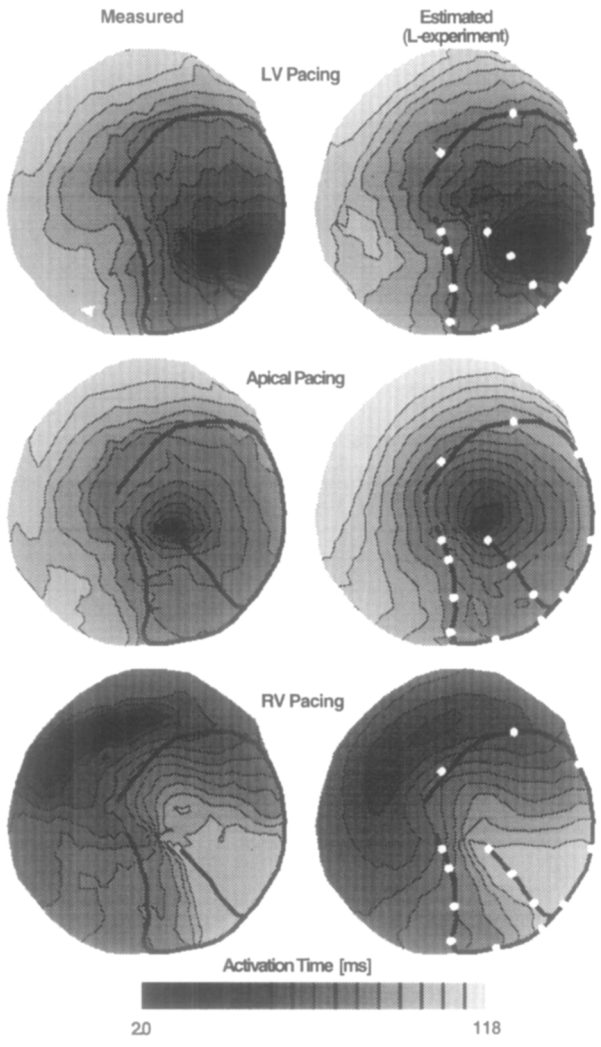

Fig. 7. Polar projections of measured and L-EXP maps of activation from 14 leads for several different epicardial pacing locations. In each row of the figure is displayed a measured activation map on the right next to the associated estimated map on the left. Isochrones are spaced every 7.25 msec. (Top) Left ventricular pacing (CC = 0.96; RMSE = 5.85 msec; RE = 7.30%; LDist = 5.27 mm). (Middle) Apical pacing (CC = 0.95; RMSE = 8.31 msec; RE = 10.67%; LDist = 12.67 mm). (Bottom) Right ventricular pacing (CC = 0.92; RMSE = 8.40 msec; RE = 12.09%; LDist = 9.65 mm).

sured activation times and those at other, unmeasured sites. As a result, this technique carries no guarantee of a given degree of accuracy, only that in a least squares sense it will do the best job possible given a prescribed subset of known signals and a database containing values for all possible locations. The important prerequisite is therefore the presence of a suitable database, while the relevant design considerations include composition of the database and selection of the limited leads.

Selection of Lead Subsets

The dictated goal of selecting lead subsets was to match locations that would realistically be accessible to catheters in the coronary veins. Starting from a three-dimensional model of the canine heart, and the 490-electrode sock array that covered it, we located a set of 42 electrodes

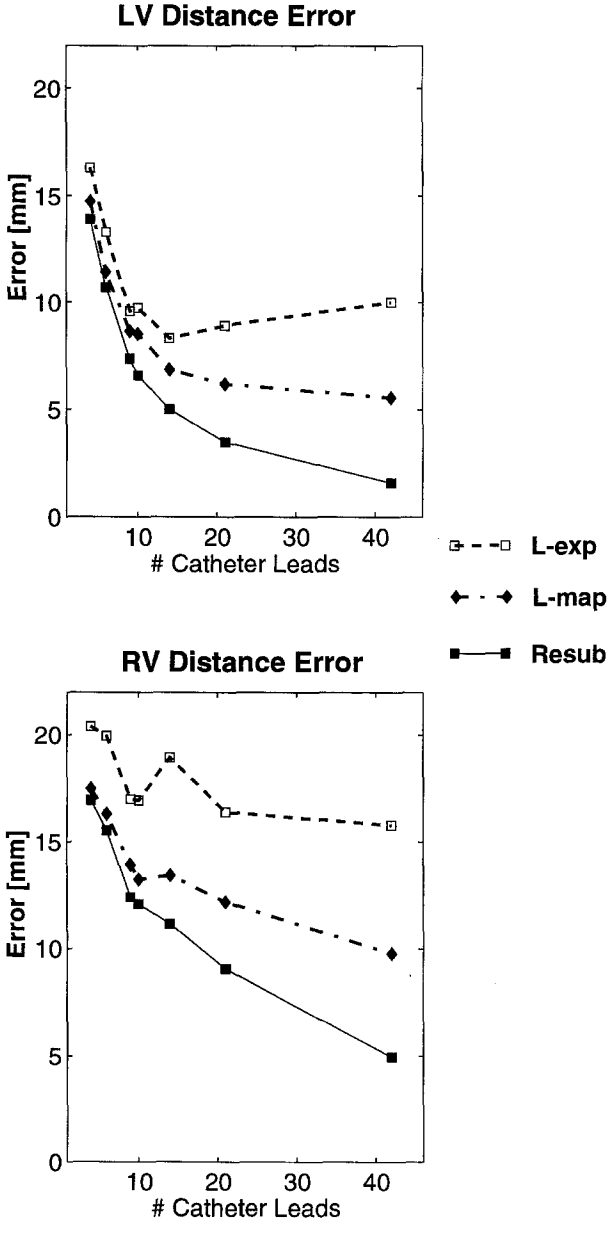

Fig. 8. Mean error plots of linear distance error (mm) for three different training protocols after separating beats paced from the left (n = 106) and right (n = 47) ventricles. (Top) Ectopic epicardial pacing sites in the left ventricle. (Bottom) Ectopic epicardial pacing sites in the right ventricle.

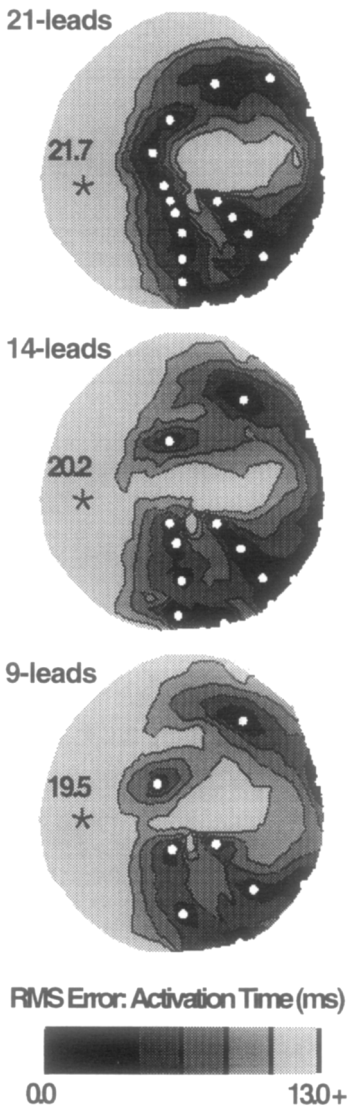

Fig. 9. Iso-error maps for mean RMS error with various leadsets using the L-EXP protocol. Leads in the subset are shown in white. Isochrones are displayed every 2.17 msec. Note that the lightest colored region includes all errors above 13 msec, with the location of the maximum error marked by an asterisk (*) and labeled.

that lay along the major coronary veins: the coronary sinus and great cardiac, left ventricular posterior, and middle cardiac veins. The parameters then available for manipulation were the number and locations of leads selected from this original set. Based on a simple assumption that regular spacing would provide the best overall results, we selected and tested six subsets. A somewhat surprising finding was that by all statistical measures tested, results did not degrade sharply until the leadset contained fewer than 10 sites. The iso-error maps demonstrate this point well as they show the region around each electrode in which a specific level of error would be expected; iso-area regions were elliptical in shape and seemed to align along the vessels, so that relatively few electrodes were required for adequate coverage. These results also suggest that such iso-error maps may prove useful in selecting optimal lead subsets (and thus catheter configurations and placement), a topic of future research.

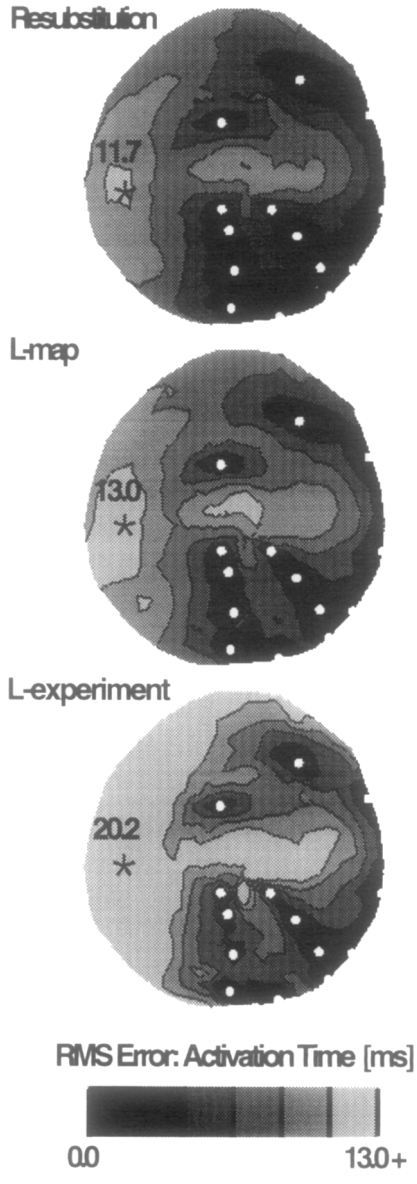

Fig. 10. Iso-error maps for mean RMS error with a fixed leadset (14 leads) using different training protocols. Layout is otherwise identical to that in Figure 9. Note that the bottom panel of this figure contains the same results as the middle panel in Figure 9.

Effect of Pacing Site

Our results showed better accuracy of estimation of beats paced from the left ventricle than the right, a finding which suggests several possibilities. One plausible explanation is that because there were many fewer beats paced from the right ventricle than the left (47 to 106), the database contained a more complete description of left than right ventricular activation. The limited number of beats available at the time of the study made matching left and right ventricular beats difficult. Another source of this difference in estimation accuracy may, however, lie in inherent differences in variability or complexity of activation in the right versus left ventricles. The thinner wall of the right ventricle could lead to more rapid excitation of the conduction system in this region and thus an earlier appearance of secondary wavefronts initiated in the subendocardium. Studies already underway will seek to reconcile this question by increasing the size of the database and exploring a more evenly distributed set of pacing sites, as well as simultaneous multiple pacing from both left and right ventricles.

Training Protocols

Another significant factor in estimation accuracy was the type of training protocol employed. In the case of RESUB training, all beats were included in the training portion of the database, then each was estimated from the resulting transformation. This is clearly the optimal and unrealistic case but is a measure of the best possible fit achievable for a given database (at least in the least squared error sense of the estimation algorithm). As such, it is a useful tool in examining the effect of selecting different composition of the database and will be used as such in subsequent studies directed at optimizing database selection.

In the L-MAP and L-EXP protocols, one beat or one experiment worth of beats, respectively, was withheld from the training set and then used as the basis for testing. Hence, these cases reflected better the likely practical conditions under which such a method might be used. The L-MAP case might arise in the case of experimental cardiac mapping in which one or more more leads show intermittent failure. The overall configuration of the recording leads would be stable, but poor contact or other technical problems might corrupt different leads at different times. Our results suggest that a relatively small drop in accuracy results from the L-MAP protocol over the RESUB.

The L-EXP protocol most closely represents the anticipated clinical application of this method. Complete epicardial activation data from a previously recorded set of patients are the basis for a transformation matrix that is then applied to new cases in which activation times only from catheter electrodes are available. The results presented here show a much larger drop in accuracy under these conditions than for the L-MAP protocol. We note, however, that much of the data collected for this report was initially intended for other purposes and there was only moderate attention paid to reproducible sock electrode placement; in fact, there is no information available as to the degree of variation that would arise from, for example, placing the same sock twice on the same heart, an important topic of future studies. Given the many possible sources of variation between experiments, estimation accuracy was encouraging for the L-EXP protocol. Relative errors were below 17% in almost all cases, and earliest activation sites were estimated to within a mean of less than 12 mm when nine or more electrodes made up the subset.

Estimation of Epicardial Potentials

All results in this report use epicardial activation time as the quantity to estimate. An obvious question is whether this method would also permit estimation of epicardial potentials from catheter measurements. The choice of activation time rather than potentials was motivated by several considerations. It is well known that activation maps are simpler in their shape and configuration than potential maps and thus estimating activation time was a technically simpler task. Activation time is also known to be more stable from beat to beat than potentials, which are affected by many factors both within the heart and in the thorax (eg, body habitus, shape, and respiration). Activation times also do not changes appreciably when the heart is exposed to air, whereas epicardial potentials vary substantially depending on the conductivity of the surrounding medium (35). Finally, the dominant use of epicardial potentials in experimental and clinical practice is to extract from them activation times; by having to extract only from the small subset of measured leads and then estimating activation time at other sites directly, one avoids a layer of indirection and thus a possible source of error.

Clinical Application of Estimation

While the main goal of this study was to establish the feasibility of this technique, it is clearly appro-

priate to discuss its application to clinical conditions. The two requirements of the method that seem most relevant are the need to have a database of complete epicardial activation maps and to record catheter potentials from a (more modest) number of sites in the patient. Our studies did not attempt to optimize in any way the composition of the database used to create the estimator; these are complex questions that are the topic of current and future research. Whatever the outcome of these studies, there will be a need for recording epicardial activation maps from human subjects. We envision that such recordings will be possible as a by-product of other open-chest surgeries, which occur for a variety of reasons. The additional burden of recording epicardial signals from various pacing sites will be justified if experimental studies can show the benefits of the catheter-based approach. One particularly relevant scenarios is bypass surgery in cases with previous myocardial infarcts as this will provide data from hearts with disease similar to that often found in arrhythmia patients. While increasingly rare in practice, surgeries to treat arrhythmias that are epicardial in origin, which some studies suggest arise in a substantial number of cases (11,12,14), would also provide a natural opportunity to acquire epicardial data for both immediate and future clinical use. An important aspect of such acquisition will be the need for coordination between investigators who contribute to a shared pool of data. We reiterate that extensive animal experiments will provide much of the groundwork for determining the best number and type of activation maps for creating estimators. Minimizing the number of human recordings will be an important component of this process.

The second requirement for the clinical application of estimation of activation times is recording venous electrograms from the patient under examination. Here, too, subsequent research will seek to establish the smallest number of appropriately placed leads necessary for adequate reconstruction of activation maps. The catheters used for this study are now in clinical practice throughout the world and subsequent generations with even finer, more flexible composition have already appeared. Inserting multiple catheters simultaneously in a single patient is already quite feasible and does not increase patient risk substantially. It is also not absolutely necessary to obtain simultaneous recordings from all catheters provided that the arrhythmia is stable enough to be repeated. Multielectrode catheters can already reduce the total duration of recording substantially over present single-electrode catheter approaches. The estimation technique described here will further shorten this time and provide more information than is currently available by any percutaneous means.

Limitations of the Study

One weakness of the study is the relatively small number of experiments (6) on which the results are based. However, these six experiments did yield 153 beats that made up the activation time database, paced from a wide variety of sites. Moreover, the estimation performed just as well for the single experiment that contained data from an infarcted heart as it did for cases of normal, healthy hearts. Even when the five noninfarct experiments provided the training data, the average values for correlation and relative error for the remaining, infarcted heart were essentially the same as for other experiments.

Other limitations in the study—the imbalance between right and left ventricular pacing, the effect of sock placement, and the relatively sparse application to postinfarct hearts with abnormal conduction—are functions of the preliminary nature of the study and the fact that we were able to utilize existing experimental data. These important questions are all topics of ongoing research.

Conclusions

This study represents the first attempt that we know of to estimate complete epicardial distributions of any physical quantity from lead subsets based on coronary venous catheters. In fact, use of such a small number of leads, from any locations, as the basis for complete epicardial mapping has never to our knowledge been reported. Developing this technique into a clinically viable imaging modality would have profound benefits for cardiac electrophysiology. It would convert a highly invasive, expensive, and painful surgical procedure into a relatively noninvasive examination that could be performed in a catheter laboratory. Moreover, the method itself is not bound to the epicardium but could also serve to reconstruct endocardial activation maps with fewer electrodes or with more detail than currently possible.

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