Multielectrode Venous Catheter Mapping as a High Quality Constraint for Electrocardiographic Inverse Solution

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Abstract: A persistent challenge in solving inverse problems in electrocardiography is the application of suitable constraints to the calculation of cardiac sources. Whether one formulates the inverse problem in terms of epicardial potentials or activation wavefronts, the problem is physically ill-posed and hence results in numerically unstable computations. Suitable physiological constraints applied with appropriate weighting can recover useful inverse solutions. However, it is often difficult to determine the best possible constraints and their optimal weighting. We have recently begun to use multielectrode catheters as a means of mapping epicardial signals in animal models. To accommodate the sparse sampling of this venous catheter based approach, we have applied statistical signal processing methods to estimate complete epicardial maps of activation time and epicardial potentials. Such measurements—and the estimated maps from them—also have the potential to provide high quality constraints for electrocardiographic inverse problems because they provide direct—albeit sparse—access to the desired solution. In this presentation we describe several approaches we have applied to extract useful constraints from sparsely sampled epicardial signals as well as a training set of epicardial maps, and use them to improve the quality of computed inverse solutions. Results suggest that combining various information sources provides valuable constraint information. Such a multimodal approach to cardiac mapping is clinically and technically viable and offers a possible means to overcome a major remaining limitation of inverse electrocardiography. **Key words:** Electrocardiography, body surface potential mapping, inverse solutions, catheter mapping.

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The broad goal of all electrocardiographic examination is to reveal information about the heart from whatever sources of electrical information are available and using whatever methods of interpreting the measured signals which may be appropriate. By combining both measurement and interpretation modalities, it may be possible to substantially improve overall information content and diagnostic performance. For example, clinicians already combine body-surface electrocardiograms (ECGs) with catheter based electrical measurements to improve localization of ectopic activation or reentrant arrhythmia (1-3).

Recent advances in catheter technology allow the use of multiple venous catheters, each containing up to 16 electrodes, to map regions of the epicardial surface of the heart (4-7). In previous studies, we showed that signals from such catheters were equivalent to those recorded from nearby sites on the heart surface (8,9) and that it was also possible to estimate high resolution activation maps of the complete epicardium from a sparse set of venous catheter measurements (9,10). Figure 1 shows an example of these results for a beat paced from the epicardium of the left ventricle.

One important limitation of the estimation approaches we have described is that it recovers activation times but not electric potentials. While activation time is an excellent source of information for detecting abnormalities in the sequence of the spread of cardiac excitation, it cannot reveal, for example, changes in repolarization that may be the underlying cause of reentry, shifts in TQ or ST segment potentials that arise during ischemia, or QRS morphology changes that follow infarction. Nevertheless, catheters do provide this information in their time signal morphology, at least at a sparse set of locations. The challenge was then to investigate means by which one could use venous catheter based measurements to improve recovery of electric potentials on the heart surface.

There are a number of approaches that we considered to make use of several potential information sources using appropriate signal processing techniques, to recover epicardial potentials. Perhaps the most obvious one was to simply extend the estimation approach we used for activation time to electric potential. Additional motivation for such a scheme came from the fact that the estimation method originated in body surface potential mapping, ie, estimation of body surface potentials from sparse lead sets (11-13). However, there are additional sources of electrocardiographic information that we wished to include under the hypothesis that they contribute unique features to the complete image of electrical activity on the epicardium.

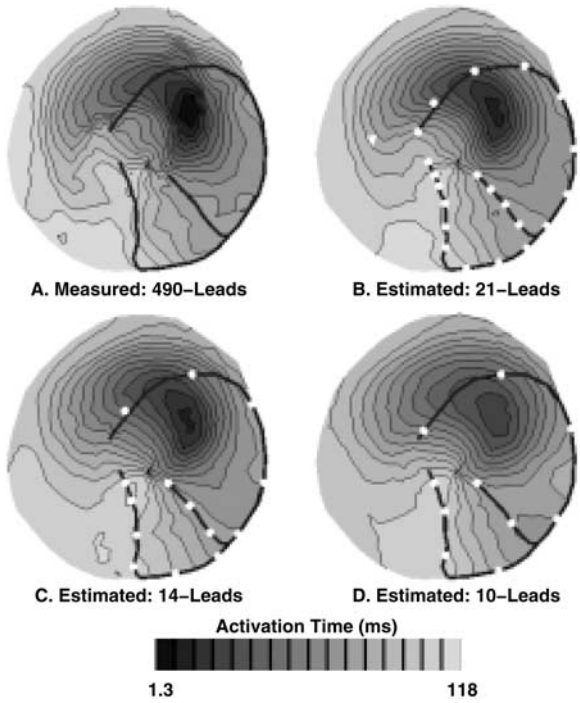

Fig. 1. Polar projections of the original and statistically estimated isochrone maps of activation for an epicardial pacing site in the left ventricle. The locations of the selected measurement leads are indicated by the white dots on the heavy black lines. Isochrones are displayed every 7.3 ms. (A) Original. (B) Estimation from 21-leads (CC = 0.99; RMSE = 4.2 ms, RE = 4.87%; LDist = 6.94). (C) Estimation from 14-leads (CC = 0.97; RMSE = 6.32 ms; RE = 7.33%; LDist = 6.94). (D) Estimation from 10-leads (CC = 0.95; RMSE = 8.35; RE = 9.68%; LDist = 5.02).

Body surface potentials, although attenuated and distorted compared to their cardiac sources, also provide a useful electrocardiographic information source, and computed inverse solutions provide a quantitative means of recovering this information. Due to attenuation and spatial smoothing that occurs in the thorax, however, the inverse problem of electrocardiography is ill-posed (14,16) and the forward matrix is badly conditioned, so that even small disturbances in the measurements lead to amplification of error in the inverse solution. As a result, one needs to apply additional constraints on the solution to produce useful results.

To provide the most complete information available, for the initial research reported here we used the high resolution body surface potential maps simulated from canine epicardial potentials available from our experiments. To link body surface

information with epicardial potential estimation, we used several different inverse solution approaches, including standard deterministic methods in the Tikhonov framework (14-16), as well as Bayesian statistical approaches which are well known in other types of inverse problems and have recently enjoyed renewed interest in electrocardiography (17-20). These statistical methods often produce better results than deterministic approaches; however, they depend heavily on the choice of parameters. The challenge remains to identify these parameters from any available information. In this study, we assume 3 different information sources: 1) Torso measurements and the forward model, 2) Sparse epicardial measurements (through venous catheters), and 3) Training sets of the complete epicardial maps. The goal was to study the use of these information sources to get the most out of them and to evaluate the benefits and costs of each. Thus, in addition to applying the epicardial estimation procedure, Tikhonov regularization, and statistical approaches separately, we also developed augmented approaches that made joint use of the information sources in various combinations, using appropriate mathematical methodologies, in an attempt to take advantage of the strengths of each.

The hypothesis that guided this research thus became *that a combination of measured epicardial information and inverse calculation can improve the quality of predicted epicardial potentials, versus either epicardial estimation or inverse solution alone*. To test this hypothesis, we applied these methods to data recorded in experiments using the isolated heart/torso tank preparation developed at the CVRI (21). We show here initial results of this study, which do, indeed, support the hypothesis that combining information sources can lead to improvements compared to either approach alone.

Materials and Methods

Experiments

All data for this research came from experiments using 2 different preparations of canine hearts. In the *in situ* case, the heart remained in the animal, exposed through a mid-sternal opening and suspended in a pericardial cradle. In the *isolated heart*, we used a preparation described previously (21-25) consisting of an isolated dog heart suspended in a torso-shaped electrolytic tank.

In both *in situ* and isolated heart cases, we applied a bipolar hook electrode to the right atrium and stimulated it at frequencies beginning just above the intrinsic rate of the isolated heart. Transmural multielectrode needles provided ectopic pacing from sites throughout the depth of the left and right ventricular walls. Regular monitoring of blood gases ensured that perfusion was adequate and pH was normal between interventions.

Signal Acquisition and Processing

In each of preparations described above, we recorded epicardial potentials simultaneously from 490 epicardial sock electrodes contained in a flexible array attached to a nylon stocking fitted over the ventricles. We recorded all channels from the sock electrodes using our custom built acquisition system, which permitted simultaneous recording of up to 1024 channels at a sampling rate of 1000 Hz with adjustable gain and each channel buffered by sample-and-hold circuitry, as described previously (21,25).

Signal pre-processing consisted of gain correction of all channels, windowing of single beats of interest, then linear baseline adjusting of each signal using customized software. In cases of poor electrode contact or otherwise inadequate signal quality of the epicardial signals, we applied wave-equation based interpolation (26) to reconstruct the electrogram.

Epicardial Estimation Procedure

The procedure for estimation of epicardial potentials followed closely one that we have described previously (9,10) with the modification that we used all potentials recorded throughout the QRS rather than just the single activation map for each beat. For this method, we used sparse epicardial measurements and a training set of complete maps, but not the torso potentials and the forward model. The idea of this form of statistical estimation is to quantify the relationship between a small subset of leads and all the remaining sites in a more complete mapping of the heart.

From the training set, the first step of the estimation process consists of separating a subset of known (or selected) leads from the unknown leads and then determining the best linear prediction between the two. With such a predictor in place, it is then possible to apply it to a new set of measured values for which the complete map is not available to estimate the complete map from a sparse set of multi-electrode venous catheter measurements. The method we used for finding the predictor is

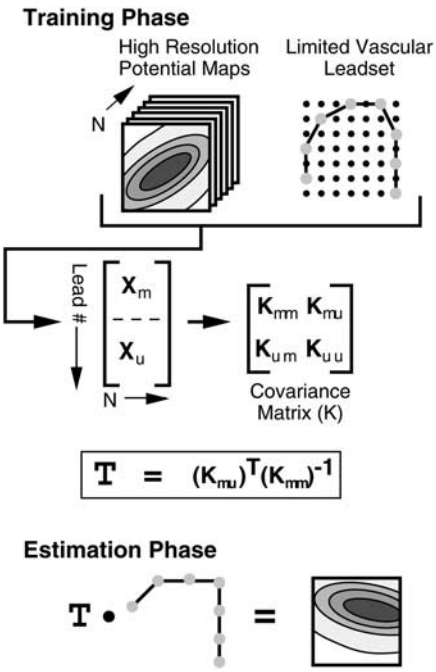

Fig. 2. Training and estimation phases of the statistical estimation method. The *training phase* produces a transform matrix, T derived from the covariance of the training data. The *estimation phase* then requires only a matrix multiplication of each measured subset of lead values by T.

from Lux et al. (13) and is illustrated schematically in Figure 2. This technique requires the calculation of mean and the covariance matrix of the training data set and then matrix manipulations of its submatrices. The predictor is then a matrix which when multiplied by a vector of sparse measured potentials produces the estimate.

The training set for the results presented here consisted of epicardial maps from 16 ventricularly paced beats gathered from 2 different experiments. We selected beats paced from a variety of sites and experiments that included both control beats and those following acute infarction by coronary ethanol injection, so as to have a varied set of activation sequences and potentials. Because the target application was venous catheter measurements, the selected subset of leads consisted of epicardial sock leads that lay over the coronary sinus, great cardiac vein, left ventricular posterior vein, and middle cardiac vein. Determining the optimal location and placement of these sites is the topic of other research (10) and for this study we simply selected 42 sites spread evenly across all the veins.

We refer to estimation based only on sparse epicardial measurements and the epicardial training data as *epicardial estimation*.

The relationship between pacing site in the training data and the type of beat (sinus rhythm or ectopic, and in the latter case the location of the ectopic focus) under study, has a significant effect on the results. In this work, the training set came from 2 experiments with beats paced from left and right ventricular sites. The test beats came from similarly paced beats but from entirely different experiments with different animals. In this way, we tried to simulate the realistic situation of the training and test measurements coming from different patients. To be able to test the specific effect of pacing site, we also subdivided the training sets according to the pacing site of the beats they included. For example, one training set consisted of entirely left ventricularly paced beats while another contained a balanced mix of left and right ventricularly paced beats, a factor that previous studies showed can alter estimation performance (10).

Inverse Solution Approaches

The other methods tested all include use of torso surface measurements as an information source. Our approach to using this information involves solving an inverse problem, which in turn requires a forward solution, ie, a mathematical representation of the relationship between epicardial potentials and those on the torso surface.

Forward solution. The forward solution contains implicit information about the geometry of the epicardium and the body surface, as well the conductivity of the intervening volume conductor. We computed all the forward solutions for these studies from a geometry that included the epicardial sock electrodes and the torso tank model. The sock location came from measurements of heart position from a single experiment and the resulting geometric model consisted of 490 heart nodes (976 triangles), 771 torso tank nodes (1254 triangles) with a homogeneous volume between. To compute the forward solution matrix, we used a boundary element formulation based on the method of Barr et al. (27) modified to use linear elements (28). The result of the forward solution in this type of problem is a matrix, A, that linearly transforms the epicardial potentials to the torso potentials.

Augmented Inverse Solution

The classical inverse problem of electrocardiography uses only torso potentials and the forward model to estimate the epicardial potentials, with additional deterministic constraints to deal with the

ill posed nature of the problem. However, if one wants to use statistical constraints, there is an additional need for information regarding statistical characteristic of the solution. To study the use of these information sources in inverse solutions, we developed several augmented inverse solution approaches for determining epicardial potentials. Each approach used some or all of these information sources to supply either direct input to the desired solution or a constraint that could fit into an inverse solution scheme.

Subtraction of measured leads. This method uses the torso potentials along with the forward model and the sparse epicardial measurements but not the training set. In this approach, we subtracted the contribution of the measured epicardial potentials from torso potentials to obtain an augmented input vector and a reduced inverse problem:

$$\tilde{y} = y - A_m \tilde{x}_m = A_u x_u + n \,, \quad (1)$$

where $A = [A_m\ A_u]$ is the forward solution matrix, with A_m and A_u the sub-matrices that multiply the measured and unmeasured epicardial leads respectively, while y are the body surface potentials, $\tilde{x}_m$ are the measured subset of epicardial potentials, x_u are the unknown epicardial potentials, and n is a noise vector associated with measurement errors.

The task then became solving for x_u using a standard scheme, for instance, zero-order Tikhonov regularization (14). We called this the *subtraction approach*.

Combined estimation. In the Epicardial Estimation Procedure section, we described an *epicardial estimation method* to perform estimation of complete epicardial maps from lead subsets. We can use a similar approach to estimate the epicardial potentials at all leads from an augmented measurement matrix defined as a combination of the sparse epicardial measurements and the torso measurements. In addition to these measurements and the forward model, this method also requires a training set of the complete epicardial maps and the measurement noise variances both at the sparse epicardial and torso leads to define the mean and the covariance of the augmented measurement matrix in terms of the statistics obtained from the training set. These statistical parameters are then used to create the transfer matrix that relates the augmented data matrix to the unknown epicardial potentials.

We refer to this method, which uses all of the available information, ie, the torso measurements and the sparse epicardial measurements, the forward model, and the epicardial training set as the combined estimation.

Bayesian approach. The Bayesian inverse approach requires *a priori* information about the mean and covariance of the epicardial potentials, information not available from measured body surface measurements. We hypothesized, however, that we could extract these parameters from the sparse epicardial measurements and/or a training database.

The Bayesian Maximum a Posteriori (MAP) approach we used to compute the inverse solution maximizes the posterior distribution function of the epicardial potentials, based on the conditional probability distribution function (pdf) of the torso potentials conditioned upon the epicardial potentials, and the prior pdf of the epicardial potentials. This prior pdf represents our statistical knowledge about the epicardial potentials and can be fully represented by the mean vector and the covariance matrix assuming that the epicardial potentials have a multivariate Gaussian distribution.

We treated this problem in two different ways: in the first approach, we assumed epicardial potentials were stationary in time with zero mean, and used the same covariance matrix for all time instants. In the second approach, which was part of the hybrid method we describe in the next section, we assumed that the mean vector changed in time. The first method, recently studied by van Oosterom (18,19), uses the torso potentials and the forward model along with the training set but not the sparse epicardial measurements. We denote results of this approach as the MAP solution.

Hybrid approach. The hybrid approach first used the epicardial estimation to estimate the unmeasured epicardial potentials. Then we used these estimated potentials along with the measured sparse epicardial measurements as an estimate of the time varying mean in the prior pdf. We determined the covariance matrix from the epicardial measurement noise variance and the covariance of the estimation error (29,30). This method also uses all of the available information sources, ie, the torso measurements and the forward model, the sparse epicardial measurements, and the epicardial training set.

Validation

We simulated sparse epicardial measurements and the torso measurements from the canine epicardial potentials recorded according to the protocol presented in the Experiments Section. We added normally distributed zero mean i.i.d. noise to 42 selected leads on the heart surface to simulate

sparse epicardial measurements. To simulate the torso measurements, we multiplied the epicardial potentials with the forward matrix, and added noise that was also zero mean and i.i.d.

In all cases, we knew the true epicardial potentials and thus could compare them with each of the estimated values. Comparison consisted of qualitative analysis of the epicardial maps as well as instant by instant calculations of relative error. To gauge performance under a variety of conditions, we used test beats from a range of ventricular pacing sites.

Results

We present here initial findings of epicardial estimation and augmented inverse solution approaches to the problem of determining epicardial potentials from sparsely sampled lead subsets and/or body surface potentials. All results came from different time instants of the same left ventricularly paced beat and highlight different aspects of the approaches. For those methods that require a training set, we first used a training set composed of LV paced beats, then a training set that included both RV and LV paced beats. Statistical measures provided an overview of relative performance of each approach.

The first sequence of isopotential maps in Figure 3 shows an expanding area of excited tissue (negative potential) to illustrate the relative fidelity of each estimation or inverse approach. At 23 ms after stimulation (Fig. 3A), none of the methods captured all the spatial detail of the original map, shown in the upper left-hand corner of each set. At this time instant, estimation based only on epicardial potentials performed slightly better than the others in terms of localizing the pacing site. Combined estimation and hybrid MAP methods also were successful in localizing the pacing site of the test data, while the Subtraction and MAP solutions were overly smooth and less accurate.

In Figure 3B, at 38 ms after stimulus, the MAP solution began to capture the larger area of activation (negative potentials) and also the positive region with a maxima between the left anterior descending artery and the activation wave front. The combined estimation and hybrid MAP solutions better captured the closely spaced contours of the activation wave front and the positive region between the wave front and the left anterior descending artery than the epicardial estimation. Nevertheless, all three of the solutions that make use of

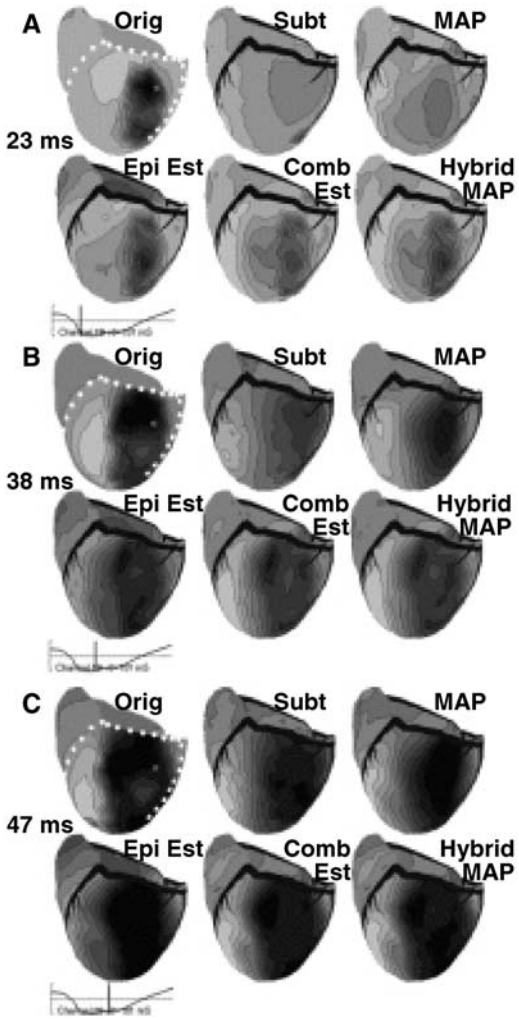

Fig. 3. Estimated and inverse computed epicardial potentials for a left ventricularly paced beat using a left ventricular training set. The top, left-hand image in each panel contains the original measured potentials and labels on the others identify the method used to compute them. A, B, and C show the potentials at 23, 38, and 47 ms after stimulus, respectively. Isopotential contours are evenly and identically spaced in each map between the maximum and minimum of the measured map. Dark regions correspond to the more negative potentials and light regions to the more positive. Circles in the measured map identify the select subset leads; the other images show coronary arteries. The view is of the left lateral side of the heart.

sparse epicardial measurements performed better than subtraction or MAP.

At 47 ms, in Figure 3C, all methods captured the broad expanse of activated tissue (negative region) but the subtraction and MAP solutions were overly smooth, resulting in an erroneous spread in the isopotential lines of the activation wave front, es-

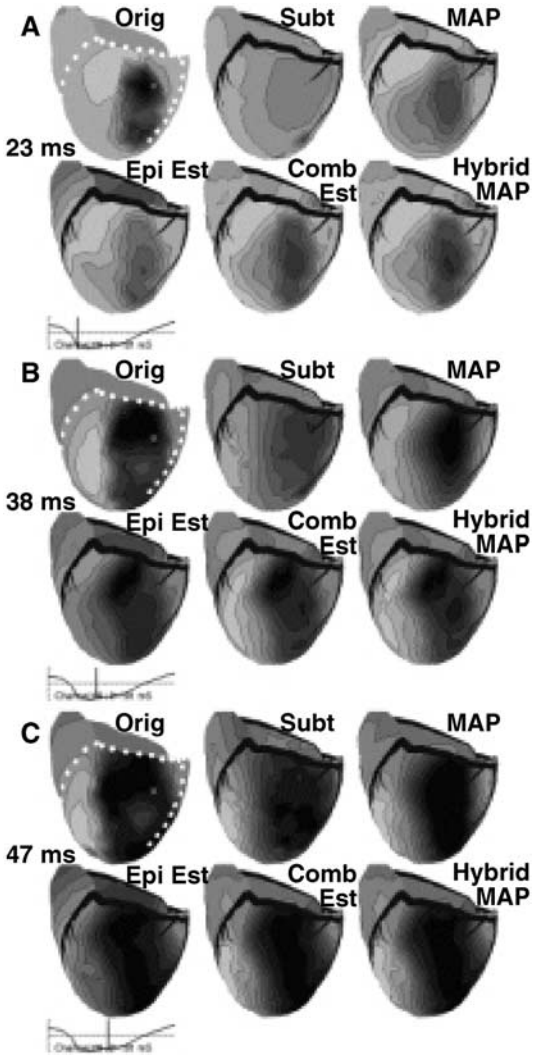

Fig. 4. Estimated and inverse computed epicardial potentials for a left ventricularly paced beat using a training set containing a mixture of left and right ventricularly paced beats. Composition is otherwise identical to that in the previous figure.

pecially the portion of it moving across the anterior surface toward the right ventricle. Here again, the combined estimation and hybrid MAP solutions reproduced the contours of the wave front with the best fidelity to the original.

In Figure 4, we show the same original data but solutions were based on a training set containing both left and right ventricularly paced beats. In this case, all solutions that use the training dataset were better able to capture the positive region to the left of the left anterior descending artery than with the left ventricularly paced training set. Within this set of results, the combined estimation, MAP, and hybrid approaches generally performed better than the others. Note that the subtraction approach results did not change from the case of the left ventricularly paced training set as they did not depend on any training data. Another difference compared to the results of the left ventricular only training set was that in the mixed training, the epicardial estimation, which did not use the torso measurements and the forward model, seemed to perform somewhat more poorly than the other two estimation based approaches (combined estimation and hybrid MAP), especially at the earlier time instances.

Table 1 shows relative error (RE) between the original measurements and the computed epicardial potentials averaged over the QRS interval for both LV-paced and mixed training sets. The average RE and the standard deviation was the same for the subtraction method, since it did not use the training set. Among the methods that use the training set, average RE in the MAP estimation (no sparse epicardial potentials) was slightly larger with the mixed training set compared to LV-paced case. The 2 methods that used all of the available information, combined estimation and hybrid-MAP methods, showed a slight decrease in the average RE for the mixed training set over LV only pacing of the training set. Average RE for the epicardial estimation method stayed the same, but the standard deviation was slightly smaller with the mixed training set. Of particular interest was the finding that estimation based only on epicardial potentials performed worst and the subtraction approach performed best, at least based on average relative error. However, there were, periods during the QRS complex in which the other inverse methods showed lower error than the subtraction approach, especially during the first half of the QRS. The fact that visual comparison of the maps did not support such a uniform superiority of the subtraction approach also illustrates the known insensitivity of global

Table 1. Average of RE Over the QRS interval (mean ± std)

	Subtr	MAP	Epi Estim.	Hybrid MAP	Comb. Estim.
LV Training	0.46 ± 0.13	0.55 ± 0.08	0.94 ± 0.20	0.52 ± 0.08	0.51 ± 0.08
Mixed Training	0.46 ± 0.13	0.59 ± 0.10	0.94 ± 0.15	0.47 ± 0.09	0.48 ± 0.08

statistical metrics for spatio-temporal distributions such as potential maps.

Discussion

The rationale for this study was the desire to recover potential distribution over the epicardial surface and not just activation time, in as noninvasive a manner as possible. Potentials offer additional information by reconstructing the signal morphology, the analysis of which that can be valuable in detecting ischemic changes, infarctions, and abnormalities in recovery that might suggest the underlying cause for arrhythmias. Thus, the goal of cardiac mapping should be to detect spatial distributions of both potentials and activation (and perhaps even recovery) times to gain a complete insight into the underlying electrophysiology.

Just as the goal of electrocardiography is to obtain multiple types of information, several types of data can be useful. The surface electrocardiogram is the most easily obtained electrical signal from the body, and many studies suggest that specific lead locations can provide information relevant to different aspects of physiology. The more recent addition of catheter based access to the heart has enabled not only improved diagnosis with modest additional invasiveness and risk, but also novel therapeutic opportunities. In addition to body surface and catheter recordings, training datasets of epicardial maps have also been used to obtain statistical prior information on the epicardial potentials. Hence, this study is a logical extension of the progression in that it seeks to jointly incorporate body surface, catheter, and training set based information to gain additional insight into cardiac function. Our hypothesis was that through a combination of signals from previous epicardial recordings, venous catheters and the body surface, together with appropriate mathematical methods, one could reconstruct complete epicardial potential maps more accurately than from any source alone.

The results we present are preliminary and based on a very small sampling of the data available to us. Thus, we can make only tentative observations that must withstand considerable additional validation prior to their acceptance. The first general finding we observed is that all combination approaches, ie, those that used both measured epicardial signals from even a small subset of leads and some form of inverse solution, performed at least as well as, and often much better than, traditional inverse solutions based only on body surface potentials. Our results also suggest that methods that made use of both the training set and a measured subset of potentials performed better than those based only on the training data. This finding supports a continued effort to develop and refine catheter based mapping approaches and bring them into clinical practice.

We also observed a general finding that approaches that included an explicit inverse solution tended to produce smoother solutions than those that employed only estimation. This is not surprising as inverse techniques, especially those based on the Tikhonov formal and standard smoothness constraints, do tend to err on the side of over-smoothing the solution. By combining inverse solutions with estimation, however, there is now a new source of constraints and thus the expectation of more accurate trade-offs between smoothness and instability of the inverse solution. One of the most promising directions may be to provide enough information through estimation and limited lead measurements to derive statistical priors that are accurate enough to support the use of statistical techniques like MAP. Van Oosterom (18) has shown that these methods yield excellent results, provided the statistical characteristics of the epicardial potentials are known well enough.

Among the many questions still to address within the context of this combined approach are selection of training data, optimization of limited lead number and location, the relationship between type of activation sequence and proper choice of all solution parameters, implementing an expectation-maximization type algorithm to estimate statistical characteristics and the inverse solution simultaneously in an iterative fashion, and, of course, whether there is one combination approach that outperforms all others.

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