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Report of the first virtual visualization of the reconstructed electrocardiographic display symposium

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Abstract In August 2004, a group of scientists and clinicians with a deep interest in electrocardiography met to discuss the present and future of the electrocardiogram as an imaging modality. Motivated by a set of challenges to the field, they each presented and discussed their ideas about the basic electrophysiology, the computational approaches required, and the clinical state of the art and where it might go in the future. In this paper, we present a summary of these presentations and discussions, starting with a statement of the challenges and a motivating case study that illustrates the inadequacies of electrocardiography as it is current practiced. Following this introduction are overviews of the present state of the inverse problem of electrocardiography and the underlying assumptions of this form of simulation and modeling. We conclude with a summary of the needs that we feel must be addressed to achieve the full potential of electrically based imaging of the heart.

1. Introduction and background (RS and RM)

There has been great progress in the last several years in the simulation of the electric fields generated from the propagating electromotive surfaces (EMSs) of the heart. There followed realistic simulations of the projection of these electric fields through an inhomogeneous torso model to its surface as conventional 12 lead electrocardiograms (ECGs), vectorcardiograms (VCGs), and body surface potential maps generally referred to as the ECG forward model. The ECG inverse solution, which generates a complete image over time of the electric activity in a specific individual human's heart, has the potential to provide comprehensive information of normal and pathological electrophysiology. The ECG inverse solution is generally considered a scientific impossibility, because of the assumption that an infinite number of current generator clusters in the human torso could account for the same body surface ECG potentials; there could be no unique solution. More recently, the development of inverse imaging of isochrone and isopotential maps at the epicardium and endocardium in realistic inhomogeneous torso and animal models have shown good correlation between inverse predicted and observed potentials. This was accomplished by the intelligent use of anatomical and electrophysiological constraints on the mathematical inverse solutions—a direct challenge to the "no unique solution" idea. These advances have prompted many of us who have investigated this area to accept the challenge. We have generated this ad hoc workshop on the potential of

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collaboration for the construction of a detailed inverse ECG image of the propagating EMS of a specific individual's heart: both excitation and recovery.

The workshop took place on August 26 and 27 in Halle, Belgium, with the authors of this report as participants. The goal was to use a loose framework of presentations on topics from the inverse problem and, more generally, the future of electrocardiography, to spark discussion and debate among the participants. This report is a summary of those presentations and discussion.

2. The challenge to electrocardiography (FK)

Several challenges have to be met to achieve our final goal, which is to extract the maximum amount of ECG information available from body surface potentials. There are several steps involved in the overall procedure, each of which needs optimal solutions:

1. Hard ECG-independent validation information to arrive at the "true" diagnosis. That information has to be assessed on the basis of imaging techniques, electrophysiology, pathology, postmortem, and so on. Although some clinical entities can be established with reasonable certainty (eg, left ventricular hypertrophy [LVH]), others are more fuzzy (diffuse multiple old myocardial infarction [MI]). Because assignment of patients to one or another clear-cut category may not always be possible, a further break down in subentities will be required; moreover, combining subentities may be necessary, and such combinations will, in turn, define a new subentity. For instance, in the large group of MI patients, the following breakdown is needed: new acute MI vs old MI; one lesion vs multiple lesions, male vs female, location of MI, age groups, and so on.
2. As a direct consequence of challenge [1], very large numbers of patients are needed because of the number of classes. Statistical procedures (in particular multivariate techniques) require a certain ratio between the number of diagnostic criteria-classification variables and the number of subjects involved in a particular entity. According to Pipberger, that number is 20; that is, if the statistical analysis returns 15 classifiers for a given diagnosis, the study population needs to include at least 300 patients and 300 healthy (normal) subjects. Again, in MI, we can arrive at as many as 15 subgroups by taking as parameters the location within the coronary arteries, the type of MI (acute, old, Q wave vs non–Q wave), the size, single vs multiple, with or without LVH or LV remodeling, and so on. If we stratify further by including sex (multiplying the number of subgroups by 2) and age (again, multiplication by 5 if we consider 5 age groups), we may end up with 150 subgroups, increasing the number of patients 10-fold.
3. It is a truism to declare that if one wants all the surface ECG information, one needs to make sure to collect as much as possible the surface potential data. That can only be achieved by sampling the total ECG information both in time and in space. Whether this requires 100, 200, or more electrodes is just one aspect of the problem: sampling rate and processing of data (baseline, averaging, and so on) are other aspects. In this context, acquiring the information by wired electrodes or wireless electrodes is just a (challenging) technicality. A practical spin-off of this point is the approach of selecting a limited set of "optimal" leads, which poses the problem of one comprehensive lead set for all entities or specific lead sets for each large group.
4. The statistical analysis of these huge amounts of data is probably the least challenging aspect of all. Many classification techniques are available and can be tested and compared. Training and testing sets for the determination of the validity and repeatability of the model have further impact on the size of the study population. Regardless of the chosen statistical methods used for classification purposes, it is crucial to strictly adhere to ECG-independent information for the constitution of the various clinical entities. A faulty and absurd protocol for the discrimination of MIs from normals is the following: using the presence of Q waves for binary group assignment [2], classes are created. Multivariate discriminant analysis is then performed to select in a stepwise manner a set (the number of selected variables depending on the sample sizes) of optimal classifiers. The thus obtained ECG measurements are linearly combined to calculate a discriminant function: that function, in turn, computes for each subject the (posterior) probability of belonging to 1 of the 2 classes. Given the experimental design described above, 100% yield (not a single case misclassified) is difficult to conceive.

If and when all these challenges are properly tackled and yield satisfying solutions will we be able to come close to our goal(s) of extracting all available information from the ECG (limits of electrocardiology) to produce the best clinical model for assigning correctly each patient to the diagnostic entity to which he or she belongs.

New progress in inverse heart modeling (eg, the multidipole model of Ron Selvester and Joe Solomon) and in more and more sophisticated imaging techniques such as fast computed tomography (CT) and magnetic resonance imaging (MRI) reported in this workshop have generated a few thoughts (dreams?) on future developments that I would like to share here:

1. Epicardial potentials and isochrone distributions are local in nature and show patterns that are much more complex and detailed than body surface potentials.

They also more directly reflects underlying time-varying myocardial characteristics. The interpretation of those numerous islets of potentials derived from hundreds of electrograms is extremely difficult, and the constraints set for the computation of an inverse solution are very severe; because of the overdetermination of the data matrix, which precludes any unique solution, several assumptions (anatomical, physiological, on the propagation of activation fronts, etc) are necessary to increase the stability of the solution. The problem of torso-heart geometry further complicates matters as the matrix of transfer coefficients relating heart surface to body surface is derived from MRI (or other anatomical) measurements. Ron suggests that wireless 3-dimensional ultrasound microtransducer system might alleviate part of the difficulties.

2. Whether reconstructed from inverse solutions applied to body surface data or from direct epicardial measurements, the very high resolution inherent to the proximity of the sources produces too many details, "noise," and large numbers of sinks and peaks. These surface patterns become smoother and much less complex as one "looks" at them from increasing distances; by the time one reaches the body surface, no more than a few poles remain visible. One could, of course, address the problem by the use of filtering (mathematical or physical filters) or by subtraction techniques, which achieve some kind of filtering by decreasing unnecessary variability.

   From that observation, it seems reasonable to suggest that because calculations can be produced for various depths from epicardium to body surface, selecting, for instance, the layer of interest at 1 cm above the epicardium may provide an acceptable compromise between conservation of information and reduction in complexity of the epicardial distribution, and at the same time, provide electrical images directly related to the underlying anatomy (see Fig. 1).

   This aspect is of major interest as it would allow ECG imaging to compete with other widely accepted imaging techniques in that it is also based on the anatomy. Although no direct relation can be established between surface potentials and underlying anatomical sites, potentials generated at a small distance from the epicardial surface will provide that information. The reason is that the more one moves away from the sources, the more each measurement is the composite resultant of a larger area (solid angle effect).

3. Technically, if we could achieve wireless recording of potentials, and maybe develop a wireless 3-dimensional ultrasound microtransducer system for anatomical data, we would be in a position to build a database of sufficient size and diversity to submit to statistical analysis and, hopefully, to useful interpretation.

4. The eventual design of a new practical lead system will necessarily rest on a totally new approach: leads (and their labels) will be directly derived from their anatomical position on the epicardial surface (new reference system), for example, left and right coronary, circumflex artery, septum, right ventricle, and so on. This will of course call for the design of new measurements and criteria for diagnostic purposes and perhaps for improved performance.

   At this stage, we will be confronted with all the problems that I described in the previous pages (the challenge to electrocardiography). On the other hand, I am not too optimistic about the future of electrocardiography if we pursue the present course, which too often, consists of squeezing out from the commonly used leads (plus a few additional ones) the last bits of information. We have to invent a totally new direction; it may not work but it could. That should be reason enough to try.

   Let me indulge in a little brainstorming here about what is probably unfeasible and certainly shocking to clinicians and nonclinicians alike.

   It is obvious that direct measurement of potentials, because they vary in time, on the surface of the heart would be ideal. It would certainly solve a great deal of problems and eliminate the need for an inverse solution (though not that of a matrix relating the heart-surface potentials to the body surface).

   So, do we "cut them up" and wrap a "sock" (as they use in Salt Lake City) studded with hundreds of electrodes around the heart? Chances are that neither the patient nor the investigator would be overly pleased with this technique. In this era of "buttonhole surgery," is it more conceivable (ethically) to introduce a catheter into the pericardium and inject a few cubic centimeters of harmless fluid? My guess is "yes" (more on the procedure in "Heart

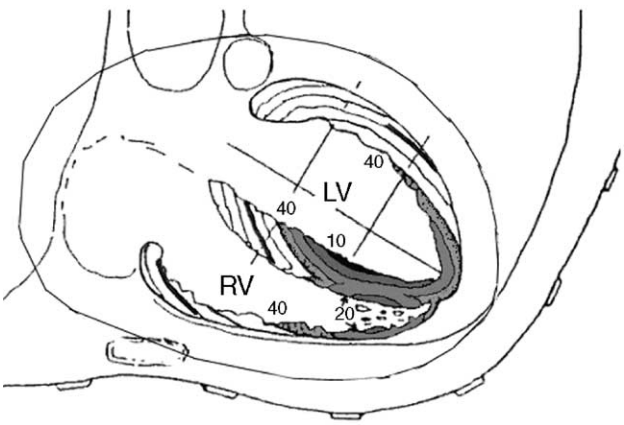

Fig. 1. Illustration of a transverse slice through the heart and torso with a surface defined arbitrarily at 1 cm from the epicardial surface.

Disease" by Braunwald, 1992, p 1481, Saunders). Now, let us take this a step further (and this is where we are on our way to hitting the fan!) Suppose that we introduce in this solution a few hundred tiny round pellets (say 0.05 mm in diameter of conducting material that is also radio-opaque). This would allow us to pinpoint their positions relative to the coronary vessels, valves, septum, and the like (if combined to echo or, possibly, angio). After the recording, which has to be wireless, the pericardial liquid is aspirated and the pericardial cavity rinsed until all pellets are expelled.

3. Case report (GW)

The case of Reggie Lewis provides dramatic evidence of the inadequacies of current cardiac evaluations, because access to the best medical care in the world did not prevent the untimely death of a young otherwise healthy athlete. (Reggie Lewis was a star basketball player for the Boston Celtics who had syncope during a game.) He received extensive cardiovascular evaluation at 3 leading academic medical centers with 3 contrasting diagnostic conclusions, ranging from normal heart with "neurocardiogenic syncope" to severe cardiomyopathy. The same electro-, echo-, and nucleo-cardiographic tests at the 3 centers had different interpretations. Autopsy after exercise-induced ventricular fibrillation revealed severe nonischemic cardiomyopathy.

- Currently, new diagnostic methods such as MRI and CT are providing 3-dimensional images of normal and pathological cardiac anatomy and function with startling resolution.
- Rather than integrating these multiple modalities, clinicians have simply added MRI and CT as additional individual tests whereas proliferating new electro-, echo-, and nucleo-cardiographic methods.
- Cardiac function is driven and coordinated by electrical events that can only be detected through electrocardiography, nonarrhythmic electrophysiology.
- Our mission then is to identify the steps that can help evolve electrocardiography into an integrated multimodal imaging method that can provide the normal and pathological cardiac electrical information in concert with anatomical and functional information to improve patient care.

4. General discussion session

GW The clinician prefers not to view cardiac electrical signals represented by ECG waveforms that require imaginative interpretation, but rather cross-sectional, anatomical views that indicate the pathophysiological origin of those signals, for example, the region of altered spread of activation or ischemia-induced hypokinesis.

FK The clinician does not want to even see the electrical data at all but wants to see the dead area in the anatomy; he/she does not want to see spread of activation per se but rather a simple indicator of type, location, and extent of problems.

PR The clinician wants to see information not only on the surface of the heart but throughout the volume. Is it possible for an inverse solution to provide this information?

RM The inverse solution has no generalized formulation that provides volumetric information in a unique way. However, with suitable constraints, it is not out of the question to imagine inverse formulations that could provide such information for specific aspects of cardiac activity, for example, determine an ischemic zone under certain conditions of changes in membrane potential.

FK The epicardial information, either measured or computed, is often too difficult to interpret with all its details; to simplify the display of this information, one might imagine computing the potentials at some distance, 1 to 2 cm, from the epicardial surface. The essential features would be preserved this way, but the levels of noise and distracting details would be reduced and diagnostic efficiency improved.

PR But why not filter the signals and achieve the same end, yet without losing the spatial resolution that will come from this approach?

CZ Can we picture this as working with a microscope at different magnification? Giving up resolution to get a better overview of the state of the heart?

FK Yes, exactly.

FK One goal that would offer new versatility to electrocardiography would be to develop wireless approaches, one that included anatomical imaging in the same process, perhaps by means of ultrasound.

GW Suppose that one could take away the body surface, that is, one could position electrodes on the surface of the epicardium. What would one do with that information?

FK Being that close to the surface, I would know where I am with respect to the underlying heart anatomy; what I don't really know is what the ECG signal would look like from that location but I think it might be useful.

RS I expect from a review of current epicardial potential maps and waveforms from individual leads we could get a pretty good estimate of what ECG waveform 1 cm out from that epicardial lead would look like.

FK Can one actually have wireless electrodes?

AvO While it is conceivable, the cost and challenges are enormous and I think that if we can come up with

some new approach that requires the use of electrodes, then we can sell it, otherwise not. The main point of interest is the extraction of more useful information from recorded ECG signals as such.

RS Jerri Liebman and the group at Cleveland has done a good job with dry electrodes to get excellent signal quality; it seems we can develop an electrode jacket that can solve these practical problem. So electrode technology is not really a serious limitation.

FK Another approach to improving electrocardiography would be to give leads a clearer link to underlying anatomy. Whether these leads lie on the body surface or somewhere the heart, they could identify specifically the electrical activity from a particular part of the heart. Leads would no longer reflect activity along certain lines or vector directions in space but rather be associated with some part of the heart. It should be possible, mathematically, to expand the lead voltage, which is a composite from various sites, into its components and quantify the contribution of each electrode site to that voltage.

RS The deterministic torso perturbation inverse that Joe Solomon and I reported years ago looked directly at this idea. It was a 17 multidipolar heart segment model: 5 for the RV, 12 for the LV with 3 orthogonal (xyz) dipoles at the centroid of each of the 17 segments (51 dipoles total) and 64 torso electrodes. A subject-specific impedance matrix between these 51 heart dipoles and the 64 torso electrodes was generated from injecting a calibrated signal sequentially at each of the 64 torso electrodes and in turn measuring the voltage at each of the other 63. In a series of baboon studies, it did an excellent job of inverse projection of body surface potentials back to each of the 17 segments of the heart that generated them. In an experimental infarct involving 3 of the 12 segments of the LV, the correlation of the % of each of the segments infarcted was within the margin of error of the quantitative planometric pathoanatomic estimation of infarct (Pearson $r = 0.86$) (ref, and check this #, rs).

GW To what extent does one see local vs remote information on either the body surface or the heart surface? This seems to be the question we need to address so that we can increase our ability to obtain local information.

FK I would guess something like 30% local information from the body surface and perhaps 60% from the heart surface.

AvO I think the question is too vague. One has to define what local information one means before there is a sensible answer.

RS Perhaps thinking of the problem in terms of solid angles would be a useful approximation. As we get closer to the heart the solid angle for a given region of the heart is large and hence provide larger signal. The relative differences in solid angles for different parts of the heart also becomes larger when we are closer to the heart, the potential varying inversely as the square of the distance from the local area to the surface electrode. This drives an improved ability to differentiate local from remote information. It is the basis for the construction of a potential map I cm outside the epicardial surface proposed by Fred earlier (Fig. 2).

AvO Yes, the question is not well enough specified as Galen states it; it is clear that as one gets closer, the accuracy increases. Ron's approach is excellent and one sees that remote information is very small in comparison to proximal information. The situation is hopeless from a single lead.

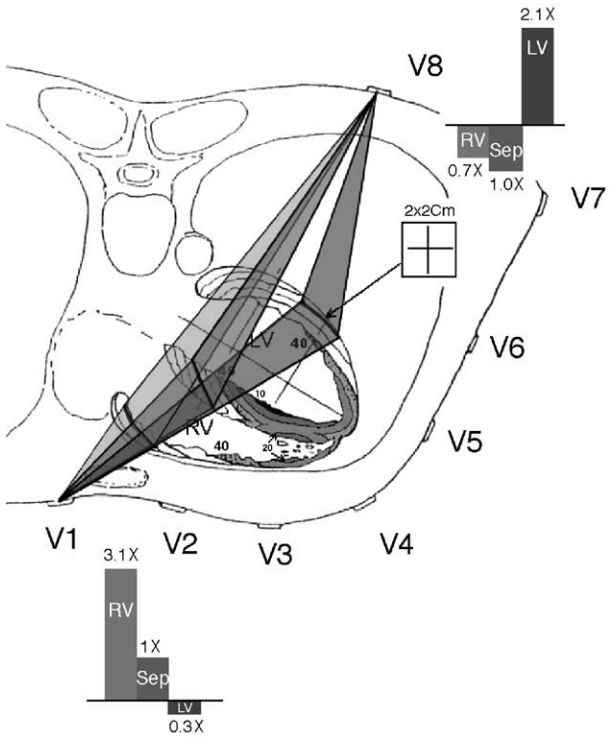

Fig. 2. Transverse plane view of the human thorax. The solid angle from 4 cm^2 of the propagating EMSs in the right ventricle, septum, and left ventricle at 60 milliseconds into the QRS illustrated here projected to V_1 and V_8 electrodes on the surface of the thorax. The relative voltage projected from each of the 3 active surfaces to lead V_1 and V_8 varying as the square of the distance from that surface to the specific electrode is shown in the bar graphs adjacent to the electrode. Note that the relative magnitude of the voltage from each region is referenced to the septum (as 1×). Thus, the relative projection of the base of the right ventricle to V1 is approximately 10 times that from the free wall of the left ventricle. Conversely, the relative projection of the free wall of the left ventricle to V_8 is 3 times that of the base of the right ventricle.

CZ Are there comparisons between normal and diseased cases that show the power of the epicardial imaging?

RM Yes, we have data like this for PTCA cases in which one can localize the region of ischemia only coarsely from the body surface but with much more precision after computing an inverse solution. A special feature of data from patients undergoing angioplasty is that one can record patient-specific controls and then during the various stages of the intervention. In our context, this allowed us to look at change in body surface potential distribution and explicit difference maps.

AvO Difference data like this are always best but we rarely have this kind if information; patients arrive sick and we have to treat them. In fact, being able to use their normal ECG record prior to any sin of a cardiac event would matter more than anything we can do with any sort of presently available diagnostic techniques.

RS This emphasizes the need for a databank of high quality ECGs of every citizen taken in young adulthood (and updated every 10 years), carried as a wallet sized electronic data card, ID confirmed with iris image.

AvO I fully agree!

FK What are the best physical quantities to display for the clinician? Potential is what we measure so should it be the quality we display and/or compute from an inverse solution?

AvO Voltage has too many problems, one must interpret it and determine what it might mean; activation time is a much more useful quantity. If one tries to determine activation from the BS, the accuracy is note useful; there is some literature about this but it is totally useless. To determine activation times reliably in the heart, one has to do a full inverse solution and this is very tractable at least for the epicardial and endocardial surfaces.

RM Although activation time is sensible for interpreting the spread of activation, it is not so useful for changes that affect repolarization and especially the effects of myocardial ischemia. For this, we will need potentials.

FK My concern is different: what do we offer to the end user? Will it be easier for him/her to accept isochrones, or a map of voltages, or of time signals (scalars) the clinician is used to seeing?

GW I don't think the clinician cares about the scalar ECG very much; it is becoming irrelevant. Today's young cardiologists tend to lack the imagination to accurately interpret an ECG—they need something they can see directly. They just memorize the meaning of the waveforms rather than understanding the normal or abnormal anatomy or physiology they represent. In contrast, Ron Selvester is a master at imagining the cardiac activation sequence from the ECG. The modern clinician, including the cardiac electrophysiologist, cannot do this and is not likely to learn how. They will have to see the data as an image. If it were not for the board exams, our current cardiology fellows would not "learn to read an ECG" at all; if there is no unique information on the ECG then let's move it into a museum; if there is, then let's figure out how to market it.

FK Anatomical images on which the information extracted from the data is displayed in a way that is easy to grasp; for example, drawing the heart with an area showing loss of tissue would represent an infarct and could be viewed in connection with the infarct-related artery.

PR I have seen the way clinicians work and when they get the full report with ECGs, they don't look at the data, they look at the summary that someone has prepared for them.

GW That is right, but they make lots and lots of errors working this way. In daily rounds, cardiac fellows cannot really explain what things mean. As an example, when there is an infarct in a patient with heart failure they cannot picture how big the infarct is because they cannot interpret the ECG. Even when the ECG looks essentially normal only when they get the MRI do they notice there is not much scar and finally begin to think about what is really going on. Then they start to imagine some other causes other than infarction for the "ischemic cardiomyopathy." The heart might be ischemic but not dead, chronic ischemia can often be the cause of heart failure, rather than infarcted tissue.

PR What about nuclear scans; can they not tell you this information?

GW They can indicate uptake but they are not as good as MRI; nuclear scans can look abnormal but it may not be infarcted.

PR What about the uniqueness of inverse solution?

AvO The inverse is unique to the epicardial surface but one needs another inverse solution after that to get more information and the formulation of that inverse depends on the information one wishes to determine. Some people claim they have solved it all and they have gotten close but it involves a great amount of work and those situations for which they have done it are very limited. There is in theory a unique solution in terms of potentials but one needs complete information of geometry and perfectly clean data; any lack of this information will spoil the fun. Then one has to get more specific and ask focused questions and find ways to include prior information that we know from electrophysiology; This is feasible now, but not without a lot of energy. There are so many sources of error that can spoil the fun. Having said that, one

can always do something better than just stare at the ECG for lack of something better to do. It is amazing that any voltage criterion approach can work; the amplitudes vary so much naturally that is makes a hard threshold very challenging; it is amazing how well one can do given the variation that is simply present in the data. The success one can achieve is very surprising given the lousy criteria that are used.

RS Adrian, a quite cogent argument for the very potent electrophysiological and anatomical constraints of this system that we need to get a lot better at using. The torso perturbation inverse, involving 17 heart segment ×3 xyz multiple dipoles mentioned earlier, is a mathematically deterministic (unique) inverse involving mural myocardium. It needs the forward propagation model to make any sense of the output of these regional segment dipoles. Also required are very precise anatomical data of the torso, and electrode location as well as precise information of the location of the centroids of the 17 heart segments.

AvO We also have to use the time domain information and with all this, one can improve detection. We are very close to this point, but it is not clear if this will have a great impact on clinical electrocardiography. But we can bring in elements to make the inverse robust so at least it does not supply "wrong" information. A smooth, dull image is still valuable, especially if we add in the temporal information.

RS Yes; the time information helps a great deal; we used to look at time dependent body-surface potential 3D perspective plots generated by Bob Pearson, of high resolution, clean 1 ms data shown as a movie. For example, there was clear appearance of a mound in the deep valley of later QRS, over the anterior chest above V_1, and V_2, that grew as the QRS died down and emerged a positive mound of early repolarization. Later repolarization slowly recapitulated the QRS shapes of peaks and valleys at a lower amplitude and a little more anterior in normals. Often in the early P-Q segment we could see a short lived local dimple or pit in the

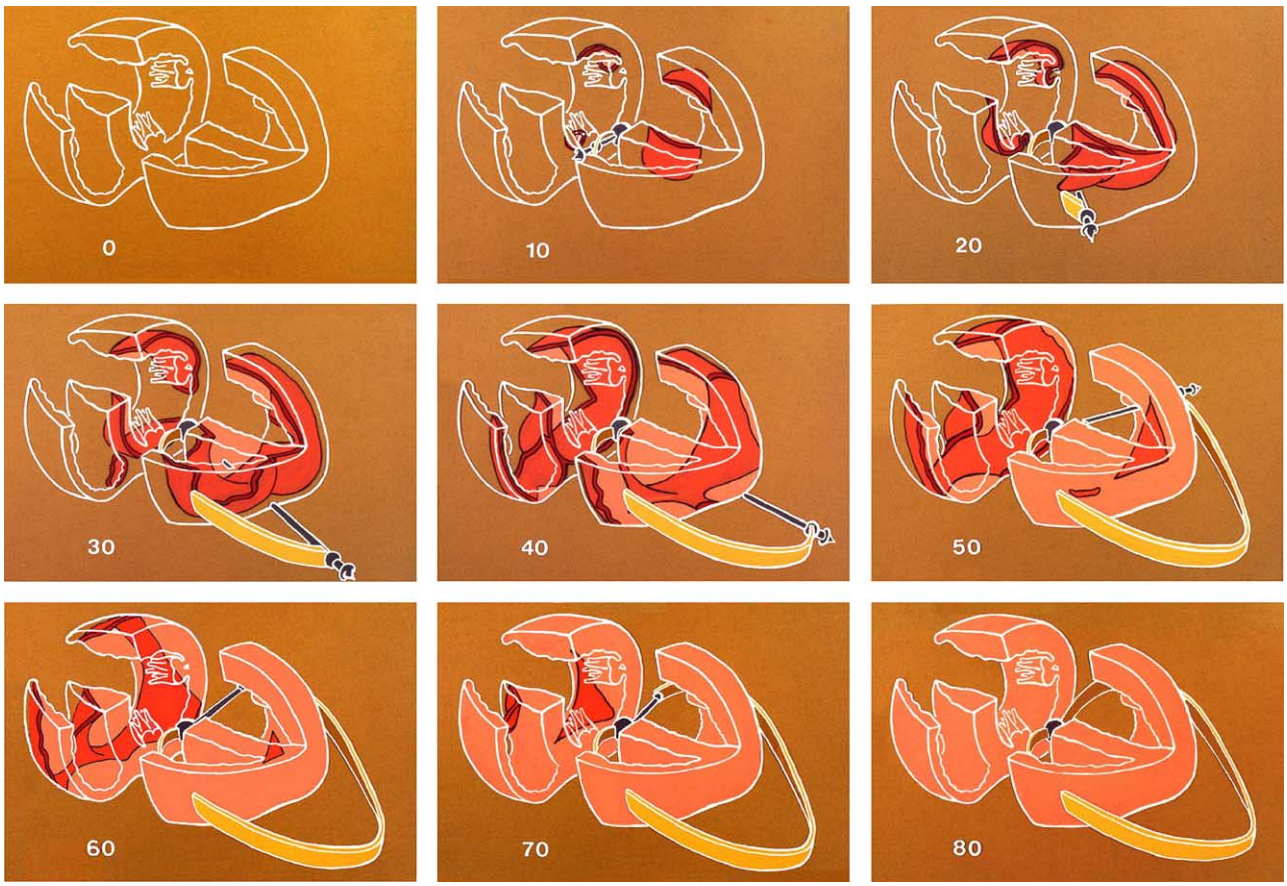

Fig. 3. Ten-millisecond images of normal activation in a normal human heart with a propagating EMS shown in red. The origin of the QRS VCG generated by it is shown in blue and the evolving QRS vector in yellow.

broad shallow basin that timed out consistent with proximal His depolarization.

5. Lessons learned from forward modeling of activation (RS)

A response to the challenge of inverse computation of the propagating EMS (the Fred challenge)

1. The fact that no heart will function without an orderly wave of excitation and recovery is a fundamental constraint on any inverse "ECG imaging method ... for the construction of an image of the ... propagating EMS(s) of the heart."—An important tool here is a high-resolution computer simulation of propagation.
2. The location of the start of that propagating EMS in conducted beats is limited to a few endocardial regions. These initiate a rapid spread throughout the Purkinje network to the ventricular endocardium. Both are very potent constraints. The inverse models of both endocardial potential and isochrone maps

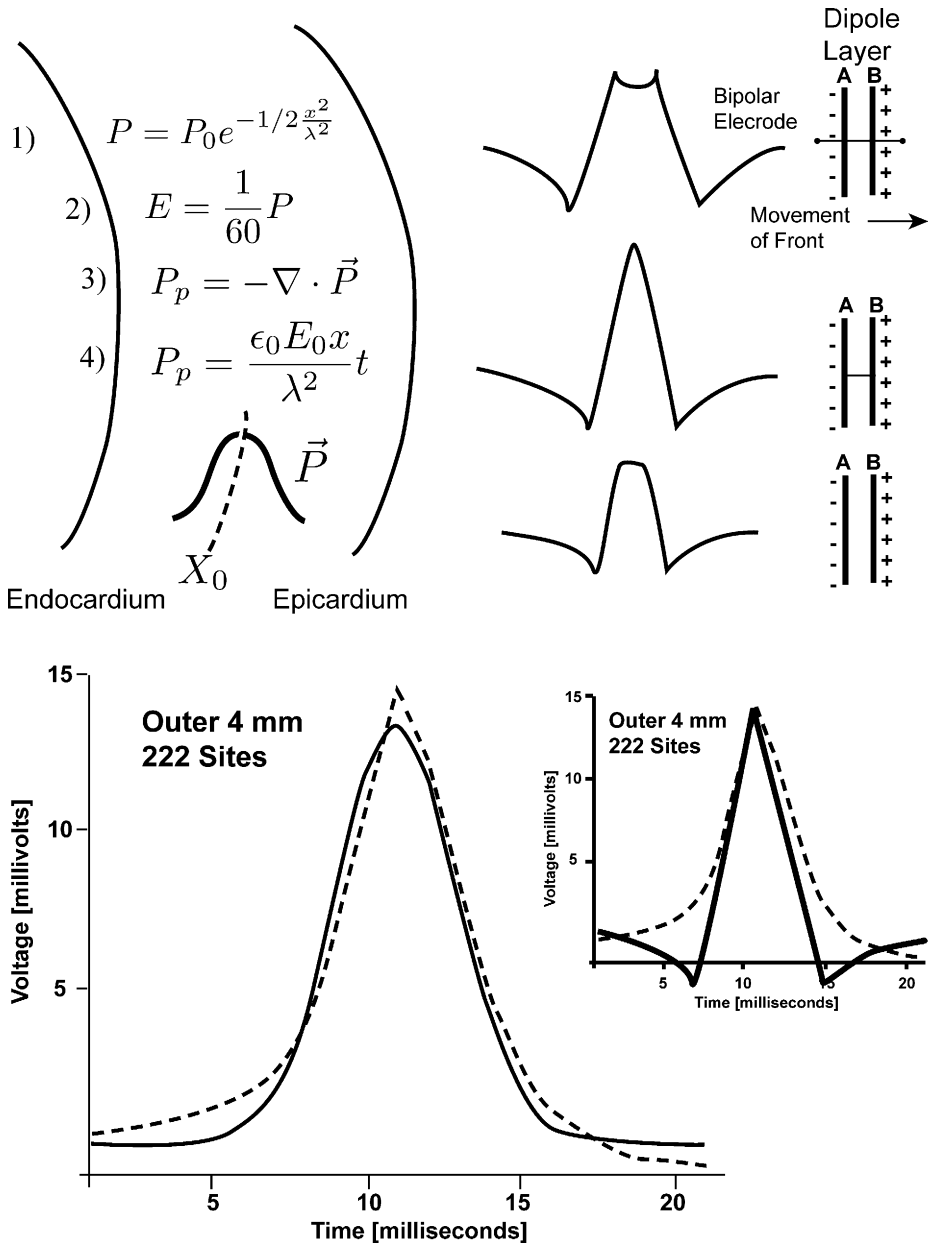

Fig. 4. Left upper panel: normally distributed microscopic dipole model of the propagating EMS. Right upper panel: intramural electrograms with 2, 1, and 0.5 mm of electrode separation, recording a uniform dipole layer model of the propagating EMS with 1 mm of separation. Lower panel: comparison of these 2 models with the average of 222 intramural electrograms recorded from the dog's left ventricle by bipolar electrodes with a 1-mm interelectrode separation.

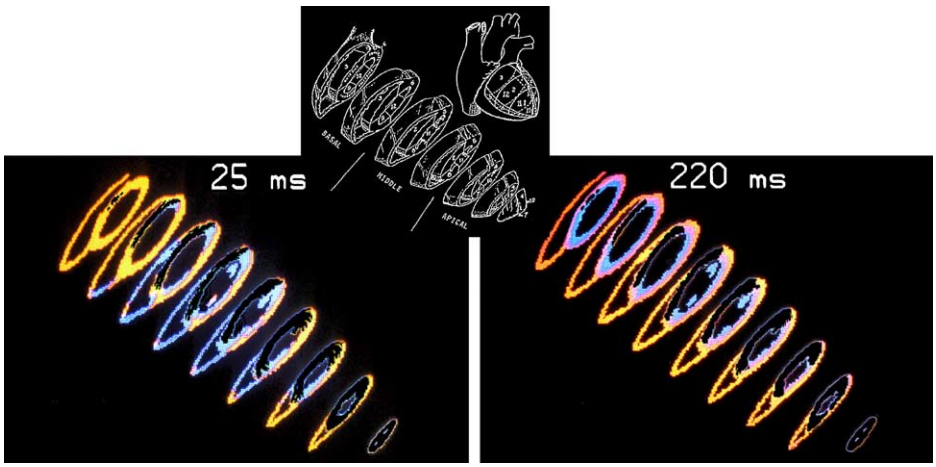

Fig. 5. Anterior view of the undersurface of bread-loaf cross sections of a normal human heart. Lower left panel: 25 milliseconds into the QRS, depolarized myocardium is in blue and resting in yellow, the boundary between the 2 is the propagating wave front. A large anterior myocardial infarct (see arrows) is outlined as an inactive region (the black area in this figure) throughout both depolarization and repolarization.

may be first order approximation here, constrained by models of propagation, and by inverse epicardial potential maps and isochrone maps.

3. In analyzing causes of instability in our inverse multidipole heart model, Joe Solomon found that variation in torso-heart geometry (distance and boundary effects) was by far the most critical. For generating this G matrix, MRI would be the gold standard here. Is a wireless 3-dimensional ultrasound microtransducer system in the wings?

I have included this set of snapshot images of the propagating EMS in the normal human ventricle with the QRS VCG it generated (see Fig. 3) as draft suggestions for consideration of possible implementation of the Fred Challenge. Fig. 3 illustrates bread-loaf cross sections of a 1-mm^3 digitized human heart with a simulated V Depol-Repol that outlines a large old anterior infarct.

5.1. Source models

Ideal double layers do not generate signals that match experiments. An EMS of distributed microdipoles 2.5 mm wide does match experiments (Fig. 4). One has to incorporate measured signals as part of the source description or only use idealized models at a distance from the measurement site(s).

CZ We assume these models are purely deterministic but what would effect of stochastic variation be? Why don't we include such variation in the formulation of source models?

RS Because we do not see signs of stochastic behavior in the measurements.

CZ But in sinus beats, there will be beat-to-beat variability that goes back to stochastic variation. In the future, we should simulate a more stochastic process in realistic source models.

RS I think this is a second order effect that will come after success with the 1st, currently under discussion. This kind of stochastic variation is swamped out by the signal averaging used to get the very clean high-resolution signals needed.

5.2. Display of model results (RS)

GW Ron's computer simulations have shown that infarcts that extend transmurally can produce a decrease in the QRS duration, because electrical activation occurs only through the remaining viable myocardium. Myocardial ischemia, when it is most severe, has the opposite effect on QRS duration because it slows electrical propagation. The recently reported (AHJ—Nov 2004) substudy of the SHOCK trial of cardiogenic shock during acute MI showed that prolonged QRS duration predicted improved outcome with surgical coronary bypass grafting (Fig. 5).

AvO I expect this is a valid observation, and the explanation may be valid, but not in all circumstances.

FK In patients with anterior ischemia, results show early repolarization over the sternum. Does the model replicate this behavior?

RS Yes.

AvO The more general point is that an event on the body surface can come from a summation of effects from multiple parts of the heart, not just the most proximal segment of the heart. Also, many things go on in the heart that do not show up in the VCG.

5.3. Role of early activation sites (RS)

Results of the model suggest that the activation sequence will ultimately depend most on the sites of early activation than many other features of the model.

AvO Yes, we found the same thing with ECGSim. When we used the earliest activation based on the inverse solution, we did not get as good match between forward computed and measured data as we would like. We then adjusted the initial pacing sites based on the Durrer activation sequence and some amount of experimentation, which led to much better results.

One must not see the formal nonuniqueness of many inverse solution formulations as a hard limitation; with enough constraints coming from the physiology, a problem may have a unique or nearly unique solution. In fact, many of these constraints are well known and fairly simple to imagine because they do not necessarily require incorporation of all features of, for example, anisotropic tissue structure. The situation may become different when one wishes to detect pathophysiological activation sequences; here, the constraints are more subtle and may require more detail in the forward model.

What are some useful constraints that we can place on the inverse problem to improve the accuracy and achieve some degree of uniqueness?

RS One compound 3 part set of constraints: this is a propagated phenomenon and we have to include this information in the model: (a) A fan of a limited number (probably 7-10) of start points in the LV and 2 to 4 in the RV inserting into (b) the peripheral endocardial Purkinje network with the spread of activation through this network at 3.5× that of (c) normal across fiber mural conduction, swamping out any longitudinal, along fiber propagation.

AvO The model that underlies ECGSim does this already.

RM But does your model constrain in any way the propagation that can arise, that is, will it work for all abnormal activation sequence like these that arise from ectopic pacing and reentry?

AvO No, I cannot restrict the activation or else I could not simulate pathology.

RS ECGSim is an important first of the 3 part set of propagation constraints. When we build the subendocardial Purkinje and intramural propagation behavior as constraints in the inverse models we can simulate focal pathology: (a) in the mural myocardium, that is, single or multiple infarcts, diffuse fibrosis/myopathy, RVH, and LVH; (b) proximal defects in the His-Purkinje, that is, RBBB, LBBB, LAFB, LIFB; (c) when detailed anatomy of fiber orientation is built that into the model (as done by RM, Taccardi et al [ref] and by Yorum Rudy et al [ref]) we get at ectopic pacing and reentry of ventricular rhythms. Theoretically, if we get a good simulation and image display of these abnormal activation sequences, these will show the same local single and multiple infarcts and diffuse fibrosis/myopathies.

PR All forward models have propagation.

RM This is partially true but (almost) none of the forward models that include propagation have associated inverse problems.

GW Observation of the interaction between Ron and his simulation colleague, Bill Olson; indicates how the specific knowledge of anatomy of the endocardial insertions of the mitral papillary muscles serves to constrain the forward solution.

PR But there is so much variation in the initial sites of activation; how do we know which ones to take in the model?

RS There is an iterative approach that might approach a unique solution; all we had to do was move His-Purkinje insertion sites and initial activation around to get the forward solution to reproduce the ECG we had from measurements. Perhaps, in the example Galen cites, the papillary muscle insertion can give us anatomical information we need to determine this information. They may provide the outer bounds of the His-Purkinje insertion sites into the peripheral Purkinje network on the endocardium. We did not have an automatic way to set the sites of initial activation and had to do it manually. But if we could link information like this to individual anatomy in some way, then perhaps we could constrain activation from objective cardiac anatomical measurements.

GW We will be doing the experiment for this idea. We will use cardiac MRI data from the Glasgow Western Infirmary MALT study to identify the mitral anterior and posterior papillary muscle insertion sites in the Olson/Selvester left ventricular activation simulation model. We will then run the activation and compare the resulting QRS waveforms to those recorded from each individual to determine similarities achieved and differences remaining. We will also use MRI cardiac spatial anatomical orientation to determine its contribution to an individual's QRS complex.

RS And one could also run an activation inverse solution to see if earliest activation does wander (vary from subject to subject) in the same way as the MRI suggests.

CZ How do you synchronize the signal from different patients? What about lead location variability?

GW We will compare the simulation result to the patients own ECG.

FK But will varying other parameters also bring about the same results? How unique are the settings that arise?

AvO When we did our inverse solutions with patients, the only way we could get normal looking sequences was by regularizing to reduce spatial noise in the inverse.

RS But even when smoothing, why did it work? It does not sound like the inverse solution included this fundamental behavior of activation.

AvO Even with regularization constraints, we could never get good early activation with our simulations; we could never get the septal pattern as seen in Durrer's paper. However, if we set starting points based on the Durrer paper and froze the location and timing of that point as we computed the rest of the inverse, we got good results. If we varied the start location for this early activation instant we could identify the best start candidate based on correlation. These results are what are in ECGSim. So it was a combination of an inverse solution and this additional constraint based on a fixed location and timing for early activation. Applying this constraint generally helped the inverse solution stability; without this, we could not get robust results. The errors went down clearly over those reported in the original paper by applying this process.

RM This is a perfect example of using additional constraints in a smart way.

GW It is interesting to speculate that earliest activation sites might be constrained by the myocardial anatomy, in this case of the papillary muscles.

RS We did not try to move the sites based on papillary muscle anatomy; we just moved them to make the ECG fit between simulated and measured; we will have to see if the anatomy can be used to improve matches (and constraints) to the start points in future studies.

AvO ECGSim allows you to alter these parameters to see what the effect of earlier activation might be.

GW Then we could use the MRI data based on identification of papillary muscle anatomy to set the earliest site(s) of activation. We could see what the effect of this variation would be in ECGSim.

AvO One could do this, but how would it be helpful and what clinical questions could it answer? One often does not appreciate the difficulty of the inverse problem. We can match the measured ECG data, this is not a problem, but the source solution may still be garbage that one cannot interpret. I have now started a process in which I fixed the first point such that of all points, it gives the best forward solution; then I can identify another key location in activation of the RV and try all those initiation points to see what the best forward solution is. I can continue this to add a few more points and get nice results. Even though the implicit propagation is uniform in this case, the results suggest that I can simulate this through a series of fixed activation sites and times.

RS So this means that after all my zealous promoting, Adriaan is finally really hearing me!

AvO Yes, at least a bit.

PR We are talking about propagation of excitation and we all agree that this is a truly propagating phenomenon. This raises a question I have had for some time—is repolarization also a propagating phenomenon?

RS No, not according to the physical definition of propagation, that is, of a behavior that goes from one cell triggering the next cell. Since it is tied by individual action potentials to a propagating depolarization it might be called an indirect or entrained propagation.

RS Clinicians making clinical diagnoses of cardiac pathology from the 12 lead ECG have been doing an empirical form of inverse solutions forever! I think we can use fewer electrodes than 200 if we have the individual anatomy correct and very good ECG data. We would also have to know in detail how the volume conductor was affecting the local heart signals as seen on the body surface ECG, that is, transfer impedances from heart to surface.

FK If one is able to fit the body surface distribution, then one can also fit the epicardial distribution, right?

GW If ECGSim could simulate an individual's normal ECGs from their own anatomy, then it could potentially also simulate abnormalities that might occur.

RS As long as one did not break any other physiological behavior.

GW Then one could generate a complete library of potential abnormal ECGs that would show what that ECG might look like.

AvO Yes, this is not an easy task but it would be possible given the current forward solution technology.

6. Task-specific source models: subendocardial ischemia (Rob)

6.1. Study goals

The goal of this study is to improve understanding of the mechanisms of subendocardial ischemia and to improve diagnostic results of transient ischemia, for example, from stress tests or during anesthesia.

6.2. Motivating background

The results of the study of Li et al [1] show subendocardial ischemia causing elevation of ST-segment potentials over the vessel-specific endocardial perfusion bed; at the same time, epicardial potentials show depression over the same region for both left anterior descending coronary artery and left circumflex coronary artery lesions. The regions of epicardial ST-segment depression lie over the lateral boundary of the perfusion bed and hence in a common region for both vessels. Li et al used a relatively simple model of the heart to approximate the ST-segment potentials so we set out to develop a highly realistic model that included anisotropy.

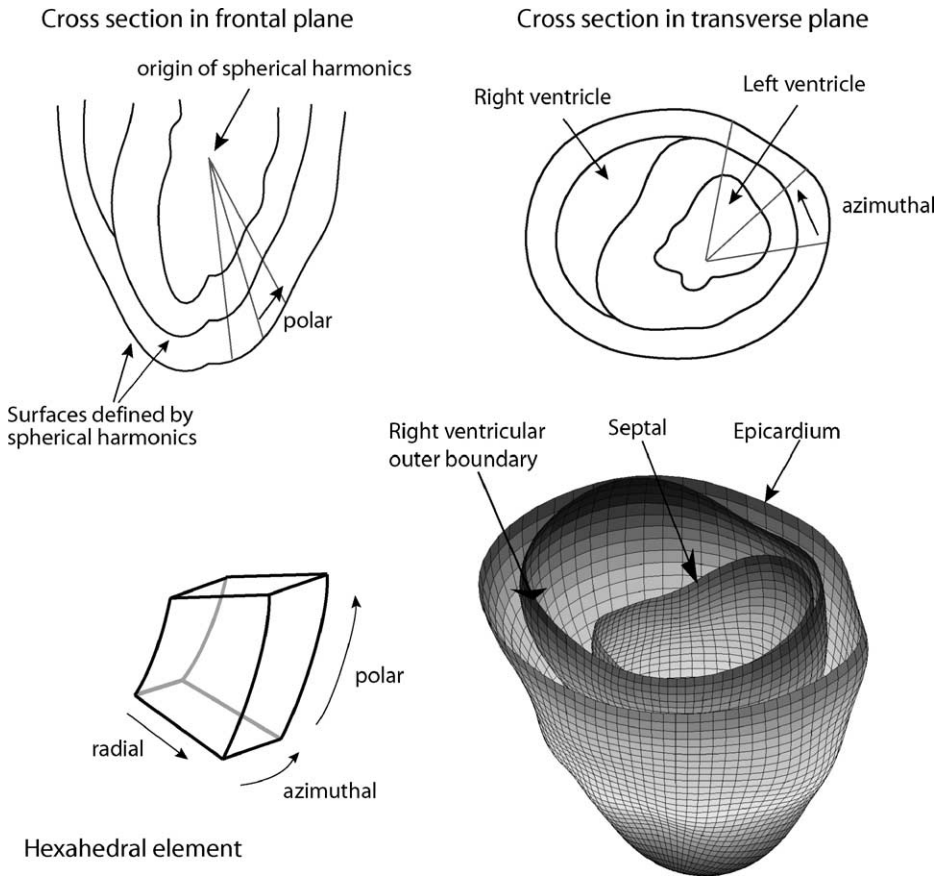

Fig. 6. Geometric model of geometric model of the heart based on Auckland heart. We resampled the original Auckland points and fitted them to spherical harmonic functions, and from this, created a mesh suitable for finite element computations of the ST-segment potentials.

6.3. Approach

The approach used was bidomain modeling of a whole heart [2] based on the Auckland geometry [3]. We created a simple model of ischemia by assigning depressed ST-segment potential to predetermined ischemia zone; we also varied the transmural extent of the ischemic zone to simulate varying degrees of subendocardial ischemia [4].

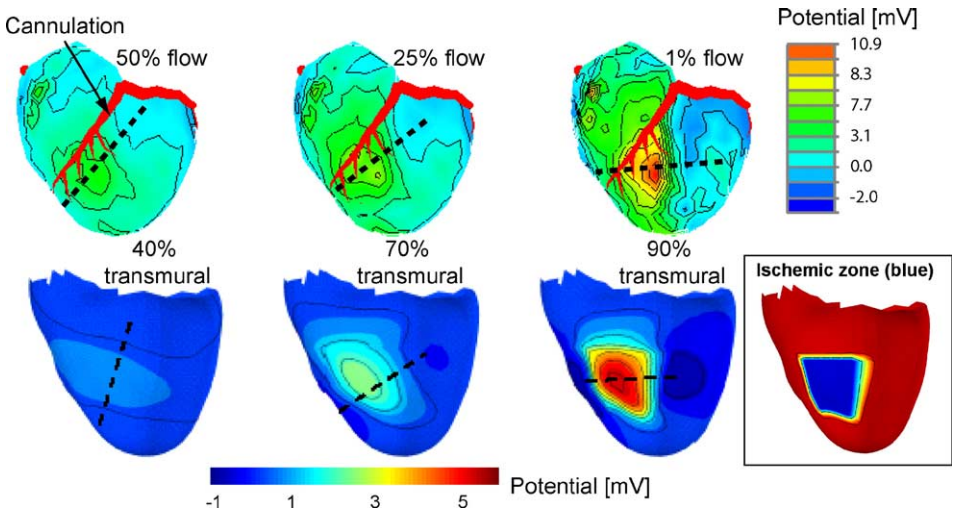

Fig. 7. Results of experiments and simulation of ST-segment potentials in the case of subendocardial ischemia of varying degree. Upper panel shows the results from experiments with progressive reduction in blood flow through a cannula in the left anterior descending coronary artery. The lower row contains approximately equivalent simulations in which we varied the transmural extent of the ischemia and computed the resulting epicardial potentials. The rightmost panel showed the ischemic zone as projected on the anterior view of the heart model.

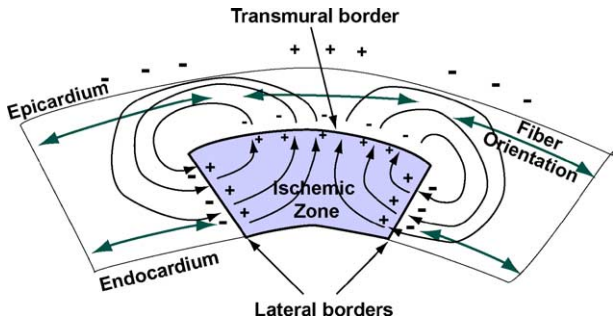

Fig. 8. Schematic diagram of the proposed mechanism for the epicardial potentials resulting from subendocardial ischemia. The potential difference that arises on the lateral boundaries of the ischemic zone is larger than that at the transmural border, as indicated by the larger "+" and "–" signs. The reason for these differences is the relationship between the direction of current flowing across the border and the local fiber orientation.

GW The shape of the ischemic zone is typically like a wedge or cone with more lateral extent at the endocardial side, narrowing down to the minimal extent at the epicardium. The model geometry shown here does not reflect this and probably should (Fig. 6).

RM Correct, and we will change this and see if the simulation results change as a result.

AvO One way to picture the bidomain is as the region in the north of the Netherlands, where the water and land are closely intertwined; at fine resolution, one is there in the water or on the land but at a slight coarser resolution, one can pick a point (or small region) which has both a water component and a land component. Thus, water and land are both present throughout the region and their parameters (eg, temperature or salinity) become continuous variables. In the heart, the 2 regions are intracellular extracellular and they have parameters of electric potential and conductivity that vary continuously throughout the region.

6.4. Results

The study shows that with ischemia of less than 70% extent, there is a slight elevation of ST-segment potentials and 2 depressions on either side of the ischemic zone. For more than 70% of transmural extent, the elevation becomes prominent and resembles the well known response to transmural ischemia (Fig. 7).

GW Can we picture this ischemia of less than 70% as an "endocardial game" that produces ST depression in leads with their positive poles over the left ventricle, that is replaced by a dominating "epicardial game" when the ischemia becomes more transmural-subepicardial? Then the potentials might be expected to show a gradual change in the transition from an endocardial game to a mix of endocardial and epicardial games?

RM In a sense, yes, one can picture it this way. When the ischemia is limited to the subendocardium, the primary sources come from the transmural boundaries. But as the extent of the ischemia extends across the myocardium, the lateral boundaries become more and more important. This change is the result of alignment of the ischemia zone and the local myocardial fibers; where the ischemic boundary is orthogonal to the fiber direction, the resulting extracellular current source is larger than when ischemic boundary and fibers are parallel.

Experimental results also support these simulations: when we varied the blood flow rate in the cannula feeding the coronary artery in question (left anterior descending coronary artery), we saw results that qualitatively mimicked the simulations. Potentials change in the same way as did the rotation of a line constructed to join the central maximum with symmetric depressions (Fig. 8).

GW The model suggests that there is a minimum on either side of the central maximum; why does this not appear in the experimental results and why do we not see this in patients, or even in the Li and Li results?

RM We believe this arises because of the location of the ischemic zone relative to the septum and right ventricle, which we believe can obscure one of the minima. It is essentially hidden or short-circuited by the highly conductive blood mass of the RV.

6.5. Discussion

These forward simulation studies were fairly unusual in that they did not seek to mimic existing experimental data because they were an attempt to capture the physiological response of the heart to ischemia. Interpretation of the results has led to a new hypothesis about the very nature of the electrocardiographic response to ischemia.

The long-term goal of these studies is to use the same model parameterized in appropriate values such as the location and extent of subendocardial ischemia. It is not clear whether such a formulation will lead to a unique result, but it appears to be a good candidate as long as we can formulate enough physiological constraints.

7. Reflections on the T wave (AvO)

The following points summarize the origins of the T wave and thus provide a basis for its clinical interpretation [5,6]:

- The T wave describes the equivalent double layer source model for the entire depolarization and repolarization phase of the cardiac cycle. The local source strength of the double layer is the local transmembrane potential. For the solution of the

forward problem, a model of the volume conduction effects has to be used. The results are expressed by a transfer coefficient matrix in which sources are currents, the medium is linear, and superposition is permitted.
- When transmembrane potentials at all myocytes are equal, the external field is zero, there is no current, and hence no ECG signal.
- A double layer that contains all active sources is perfectly equivalent and can become the basis for a forward/inverse solution pair.

The root-mean-squared curve is a very useful tool with which to identify fiducials in the time course of the ECG; it also provides good way to mark isoelectric points, which may form the basis for baseline correction.

IQRST is the integral of signals over some or all of the beat. These have meaning if associated with their start and end point. One can define primary and secondary T waves that depend on either activation sequence or variation in repolarization time among action potentials.

The propagation of the actual process of repolarization may take the same or even less time than that of depolarization because the action potential duration is not constant. The T wave merely looks longer because the repolarization takes longer to play out. This may be likened to the bow and stern waves from a boat; they both go by at the same speed, but the waves that result are much sharper from the bow than the stern.

8. Giving new meaning to old leads (GW)

8.1. Background

After Galen learned from his Swedish colleagues that they routinely display the 6 limb leads in their orderly sequence from aVL to III, he began searching for a lead to fill the gap between these and the orderly sequence of chest leads from V_1 to V_6. This quest resulted in the 1994 paper in the J-ECG on the "panoramic sequence of ECG leads" (Anderson ST, 1994 #4). During this process, in 1994, Fred sent Galen a letter along with a cardboard cutout he termed *a contraption* with which to identify leads in space and illustrate the gaps in coverage by the sequences provided by the 12 standard leads. Fred asked for a reply from Galen about his interpretation of lead coverage, and this is Galen's reply:

> It is fascinating that lead V_4R fills the gap between the rightward inferior view of lead III and the rightward superior view of lead V_1. Fred's 3-D contraption provides an excellent perspective of these views of the cardiac electrical activity. However, I wonder how the view from V_4R compares from those of -aVL that is spatially adjacent to III, and $-V_6$ that is spatially adjacent to V_1.
>
> A clinical motivation for this inquiry is the problem with practical consideration of the term *contiguous leads* in the ECG standard routinely used when evaluating individuals with symptoms suggesting acute MI. Which leads are really spatially contiguous, and should consideration of lead contiguity be included in the best metric used for detection of such a critical clinical condition?
>
> Other aspects of this ECG standard are considerations of only ST-segment elevation rather than "deviation" and the threshold value required. Pentti and I are currently on an AHA committee to consider these ECG standards.

AvO Any standard that is based on absolute threshold values is doomed to fail because of the large standard deviation in the ECG amplitudes of healthy subjects. One cannot simply measure amplitudes and hope to separate patients reliably into groups.

PR Changing ECG standards is a slow and frustrating process.

GW The process of changing ECG standards might be accelerated by results of experimental studies that test consensus hypotheses generated by an ad hoc group such as ours. Clinical medicine needs new ECG standards, and I anticipate a dynamic process for considering changes over time driven by multimodal anatomical and functional image-based information.

AvO Creating new "pseudo-leads" will not solve this problem. We will make more meaningful improvements by tweaking the existing signal information and scrutinizing the possible link between the features used and the underlying electrophysiology.

GW Fred's past studies have identified the surface electrode sites that provide capability beyond that from the 12 standard electrode sites for ECG diagnosis of many pathophysiological problems.

Fig. 9. Workshop group, from left to right: Judith and Fred Kornreich, Galen Wagner, Rob MacLeod, Ron Selvester, Pentti and Farida Rautaharju, Ingeborg and Christoph Zywietz, Marilyn Wagner, and Adriaan van Oosterom.

We are currently testing the value of such recording using cardiac MRI as "gold standard" in the MALT (Magnetic Anatomic and eLectrical Technology) study based at the Glasgow Western Infirmary. Consecutive patients with symptoms suggestive of an acute MI received serial MRI and ECG studies during the following year. Many substudies are in process, and participation is open to other investigators to either design additional substudies or contribute additional patients. Body surface maps provide ECG data from multiple recording sites.

RM There are large amounts of body surface potential map data available at the CVRTI but not with MRI on the patients.

AvO It is very important to obtain accurate electrode location information from these patients [7].

RS Very important, I'd say essential.

AvO Yes, exactly!

9. Summary

Starting from the challenge that launched the workshop (Fig. 9), the following points stood out as essential for the future success of electrocardiography:

1. We must establish electrocardiography as a true functional imaging modality in terms of the acquisition, interpretation, and presentation of data.
2. Electrocardiography must work in concert with other imaging modalities, especially those that generate anatomical information; there is a natural synergy with these modalities rather than a competition. A much neglected and easily implementable improvement of the diagnostic accuracy derived from the precordial leads would be to relate electrode position to the actual position of the patient's heart rather than to his/her ribs.
3. We must develop new ways to examine the functional relationships between cardiac anatomy and physiology; this will require detailed 3-dimensional anatomical imaging of the heart and patient-specific models with which to couple electrocardiographic information.
4. Visualization of the results of electrocardiographic studies must advance beyond the current state of signal-based display. Three-dimensional anatomical information, either schematic or patient-specific, provides the natural substrates for this display, a display that is capable of integrating information from direct measurements by multiple means, for example, endocardial and epicardial catheter-based records combined with computed values from forward and inverse solutions.
5. Forward problem formulations must become more specific to the questions of interest; the general-purpose inverse solution will remain a challenging goal, and specificity will expand the type and degree of constraints that apply and thus lead to more accurate and useful solutions.
6. Inverse methods should try to incorporate much more of the knowledge about the electrophysiology of the heart as obtained through invasive electrophysiological measurements. A straightforward example is the inclusion of the propagating nature of the basic processes.
7. Patient specific models are likely to be advantageous or even essential for electrocardiographic inverse solutions. Research into the relationships between geometric model accuracy and solution quality will be essential to answer these questions.

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